The impact of DAA treatment on HIV/HCV co-infected individuals across Europe

Analyses of co-infection data from a European cohort study

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Declaration

I, Sarah Amele, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

With the introduction of safe and highly efficacious direct-acting antivirals (DAAs), elimination of HCV has become more viable. The World Health Organisation set the targets of reducing HCV incidence and mortality by 2030 to achieve this goal. To meet these goals, increased consideration is required of those most at risk of HCV, such as people living with HIV (PLWH) due to the shared routes of transmission. Data from the EuroSIDA study has been used to investigate the epidemiological characteristics of HIV/HCV co-infected individuals in Europe, with a specific focus on regional differences in DAA effectiveness and treatment outcomes.

My findings show that there were major gaps at all stages of the HCV continuum of care among PLWH for all regions in 2015, with only 78% of anti-HCV positive individuals receiving a HCV-RNA test, 47% of those HCV-RNA positive starting HCV treatment and 23% achieving SVR. By 2017 there were improvements in the transition of individuals through stages after improved access to DAAs, as 83% of individuals who were anti-HCV positive were HCV-RNA tested, 61% of those HCV-RNA positive received treatment, and 42% achieved SVR. Among individuals treated with DAAs who had a known treatment response, 91.5% achieved SVR12. There was no evidence of regional differences, indicating high rates of SVR12 can be achieved across all European regions in real-world settings. The proportion of individuals who were reinfected within 24 months of achieving SVR was 7.7% among HIV/HCV co-infected individuals, with evidence of regional differences. There was also evidence to suggest that the odds of individuals being reinfected decreased over time.

The findings from these studies highlight the effectiveness of DAAs and their positive impact on the outcomes of HIV/HCV co-infected individuals. However, to achieve the goal of HCV elimination by 2030, improvements in HCV screening and access to DAAs is urgently required.

Impact statement

Among HIV/HCV co-infected individuals, a large proportion are people who inject drugs (PWID) who face multiple forms of stigma and discrimination, impacting their access to equitable healthcare. To achieve the World Health Organisations (WHO) target of eliminating HCV by 2030, it is important to have accurate and up-to-date data on the changing epidemic, especially among groups that face structural barriers to care. This is necessary to inform decision-making and resource allocation to ensure all HCV-positive individuals are engaged in all stages of care. The analyses presented in this thesis provide a number of valuable findings that can be used by researchers, healthcare practitioners, and policymakers to ultimately optimise the health and wellbeing of this key population.

I established a standardised methodology for describing the cross-sectional HCV continuum of care, which highlighted gaps where interventions need to be targeted to ensure individuals achieve cure. This is also useful for policymakers to monitor the effectiveness of their response to the epidemic, and progress towards the WHO elimination targets. The method I developed has been used by national HIV cohort studies in Europe to evaluate the HCV epidemic among their population. I also explored a novel technique for describing the longitudinal continuum of care over time, which is the first time this methodology has been applied in the HCV context. This method provides further insight into how individuals transition through care over time, and also allows for exploration of retention in care. This is useful for researchers looking for meaningful ways to explore how individuals transition through care over time and can be used to complement the traditional cross-sectional approach.

I also presented data on the effectiveness and safety of DAA treatments in HIV/HCV co-infected individuals. This was one of the first studies to provide real-world data on the effectiveness of DAAs in Central-East and Eastern Europe. The findings can be

used by policy makers, healthcare practitioners, and advocates to support the treatment of all individuals with HCV, regardless of co-infection with HIV, which is in line with European treatment guidelines.

Preventing reinfection after cure is essential to achieving HCV elimination and was therefore explored in this thesis. The findings highlight the importance of healthcare providers continuing to engage, support, and frequently test individuals at high-risk of reinfection to identify and treat HCV early if it reoccurs. There was no evidence of higher reinfection of HCV among PWID, which can help reduce stigma around treating PWID.

The findings from this thesis have been disseminated to the public, researchers, and policy makers via peer-reviewed journals and international conference posters and orals. The findings were also able to reach a wider audience as the results have also been reported in articles targeted at communities affected by HIV.

Acknowledgements

This thesis is dedicated to my parents, for the countless sacrifices they made so I could be where I am today.

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Frequently used abbreviations

AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase aminotransferase
aOR	Adjusted odds ratio
APRI	Aspartate aminotransferase to platelet ratio index
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
cART	Combination antiretroviral therapy
CHIP	Center of Excellence for Health, Immunity and Infections
CI	Confidence interval
CoC	Continuum of care
CoDe	Cause of death
CVD	Cardiovascular disease
DAAs	Direct-acting antivirals
EACS	European AIDS Clinical Society
ESLD	End-stage liver disease
ESRD	End-stage renal disease
GEE	Generalised estimating equations
HAART	Highly active antiretroviral therapy
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIC	High-income country
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injecting drug use
IFN	Interferon
IQR	Interquartile range
LIC	Low-income country
LTFU	Loss to follow-up
MSM	Men who have sex with men
MTCT	Mother to child transmission

NNRTI	Non-nucleoside reverse transcriptase inhibitor
Non-ADI	Non-AIDS defining illness
NRTI	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PEG-IFN	Pegylated interferon
PI	Protease inhibitor
PLWH	People living with HIV
PMFU	Person months of Follow-Up
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
PYFU	Person years of Follow-Up
RBV	Ribavirin
RNA	Ribose nucleic acid
SVR	Sustained virological response
WHO	World Health Organisation

Chapter 1 Introduction

This chapter provides a comprehensive background of the epidemiology and biology of HIV and HCV at the start of my PhD in 2017.

1.1 HIV and AIDS

1.1.1 Epidemiology

Global disease burden is shifting from infectious illness to non-communicable diseases, however, HIV/AIDS is still one of the leading causes of death and disease burden globally (1,2). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017 report, 35 million people have died from AIDS-related illnesses, and more than 70 million individuals have been infected with HIV since the beginning of the epidemic (3). They also reported that in 2016 an estimated 36.7 [95% confidence interval (CI) = 30.8-42.9] million people were living with HIV worldwide, 2.1 [95% CI = 1.7-2.6] millions of whom are children under 15 (3).

Figure 1.1: Number of new HIV infections, by calendar year (4)

The global incidence of HIV reached its peak of 3.3 million new infections in 1997. This was followed by a period of sharp decline between 1997 and 2005, where the incidence decreased by approximately 4.8% per year (5). The number of AIDS-related deaths has fallen by 48% since its peak in 2005, from 1.9 million to 1.0 million (4). The decrease in HIV incidence and AIDS-related death is mainly attributed to the global upscale of antiretroviral therapy (ART) (4,5). In 2010, 7.7 million people living with HIV (PLWH) had access to ART and by June 2017, 20.9 million people were accessing treatment, however, around 43% of PLWH still do not have access to ART (4). While there has been a fall in HIV incidence, the decrease in the number of AIDS-related deaths means that there has been an increase in the number of people living with HIV.

In September 2000, world leaders met in the United Nations Headquarter in New York and adopted the United Nations Millennium Declaration (6). This was a commitment to a global partnership for development in areas such as health, poverty and education. It included specific targets that were to be achieved by 2015, which became known as the 8 Millennium Development Goals (MDGs) (7). Great progress was made towards goal number 6, to 'Combat HIV/AIDS and other diseases'; new HIV infections fell by 40% between 2000 and 2013, by June 2014 13.6 million PLWH were on ART (a huge increase from 800,000 in 2003) and 7.6 million AIDS-related deaths were averted (8). In November 2001 the Doha Declaration was adopted, which allowed developing countries to circumvent patent rights and manufacture generics, which provided better access to essential HIV medication (9). In 2011, UNAIDS set the goal to treat 15 million people by 2015, this target was achieved in March 2015, which was another great global accomplishment (10). Post-2015, the 17 Sustainable Development Goals (SDGs) were established by the UN to build on and complete what the MDGs did not achieve (11). Goal 3 'Ensure healthy lives and promote well-being for all at all ages' included the target to end the AIDS epidemic by 2030 (11). To do this, the 90-90-90 goals must be achieved by 2020 (12). This means that 90% of all PLWH are aware of their HIV status, 90% of all people diagnosed with HIV infection will receive ART and 90% of all people receiving ART will have viral suppression (12).

However, while the number of new HIV infections has been declining, the Fast-Track Target agreed upon by the United Nations General Assembly in 2016 required fewer than 500,000 new infections per year by 2020, and the current rate of decline does not seem fast enough to reach this target (Figure 1.1) (13).

While 53% of all PLWH had access to treatment in 2016, this varied depending on age group, as only 43% of children aged 0-14 had access to ART in comparison to 54% of adults aged 15+ (3). Women account for 51% of PLWH, with young women (aged 15-24) being twice as likely to acquire HIV as their male counterparts (14). However, due to higher treatment coverage and treatment adherence, AIDS-related death was 27% lower among women and girls (4). Yet, AIDS-related death is still the leading cause of death among 15-49 year old females (14).

The prevalence and incidence of HIV vary greatly by region, with HIV having a disproportionate impact on sub-Saharan Africa (Figure 1.2) (15). There were 25.5 million PLWH and 1.16 million new infections in Sub-Saharan Africa in 2016, meaning Sub-Saharan Africa accounted for 69% of the global prevalence and 64% of the global HIV incidence in 2016 (Figure 1.3) (4). Women and girls account for 59% of the total number of PLWH in this region, with 3 in every 4 new infections in Sub-Saharan Africa among 15-19 year olds occurring in females (14).

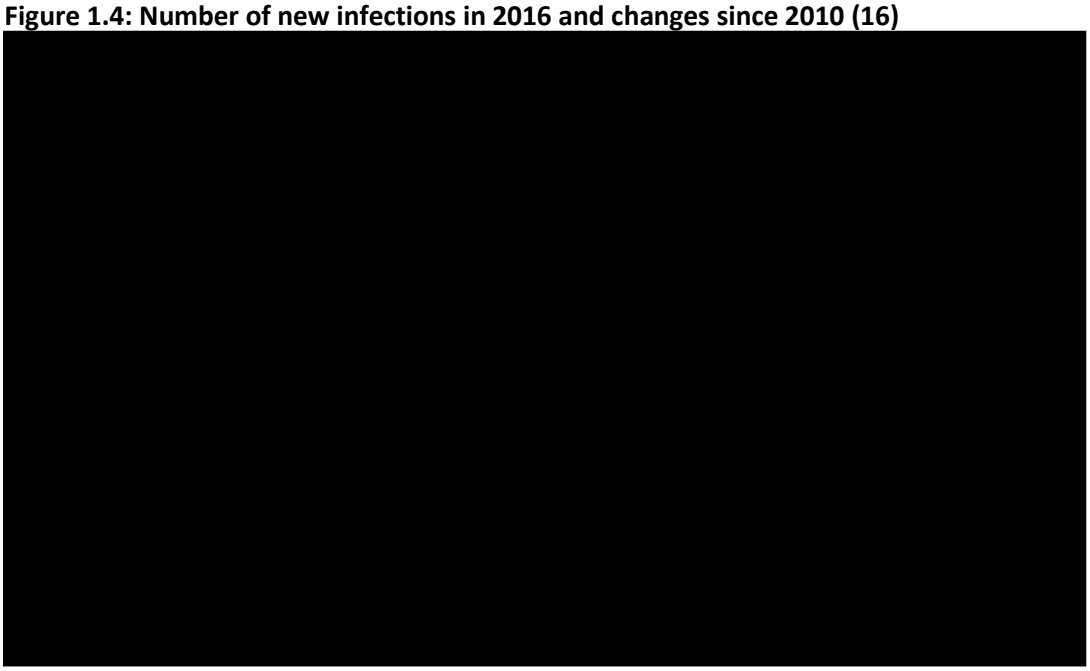
The main route of transmission varies by the prevalence of HIV. In settings where there is a high HIV prevalence, young women are at high risk of infection, with women aged 15-24 making up 26%, 22% and 17% of new HIV infections in 2016 in Eastern and Southern Africa, Western and Central Africa and the Caribbean, respectively (4). However, in lower prevalence settings, HIV infections occur mainly in key populations; people who inject drugs (PWID), sex workers, transgender people, prisoners, gay men and other men who have sex with men (MSM) (4). These key

populations made up 80% of new infections outside of Sub-Saharan in 2015 (4). While the proportion of HIV infections in key populations is much higher in the rest of the world, key populations still make up 25% of the prevalence in Sub-Saharan Africa (4).

Figure 1.2: Number of people living with HIV in 2016 (16)

Figure 1.3: Number of new infections over time, by region (4)

Figure 1.4: Number of new infections in 2016 and changes since 2010 (16)



European Epidemic

The number of people living with HIV in Europe is comparably lower than other regions (Figure 1.2) (4). However, while the number of new infections globally has been decreasing over time (Figure 1.1), the number of new HIV infections in Eastern Europe and Central Asia region has increased by 60% since 2010 (Figure 1.4) (4). There has also been a 38% increase in AIDS-related mortality in this region over the past 10 years, despite the decline in AIDS-related deaths globally (4).

In 2016, 160453 new HIV diagnoses were reported from 50 of the 53 countries in the WHO European Region (17). This number equates to a rate of 18.2 newly diagnosed infections per 100,000 population (17). However, the epidemic is not homogeneous across Europe, with the Eastern Region most affected (17). Of the 160453 newly HIV diagnosed in Europe, 128,079 (80%) were from the East, 103,438 (81%) of whom were reported in Russia (17). This means Russia accounted for 64% of the new HIV infections in Europe in 2016 (17). Russia also had one of the highest rates of new infections per 100000 population (70.6), followed by Ukraine (33.7), Belarus (25.2) and Moldova (20.5) (17). There were 26602 (17%) new infections in the West, and

5772 (3%) in the Centre. These numbers correspond to a rate of 50.2/100000 in the East, 6.2/100000 in the West, and 2.9/100000 in Central Europe, therefore the rate in the Eastern region is 8 times higher than the West and 17 times higher than the Centre (17).

The rate of new HIV infections in the WHO European Region was 12/100000 in 2007 and by 2016 the rate had increased 52% (17). The main driver of this increase is the 95% rise in the rate of new infections in the East, which was 25.7/100000 in 2007 and 50.2/100000 in 2016 (Figure 1.5) (17). However, there has been a surge in HIV tests performed for diagnostic purposes, increasing by 58% from 14077542 in 2007 to 22192146 in 2016 (based on 31 countries with data in both 2007 and 2016) (17). Countries in Eastern Europe tended to report higher testing rates, however, there was lots of variation across the Region and limited data (17).

Across the different regions, there is also variation in the main mode of transmission, which highlights the differences in the HIV epidemic in the region (17). The main route of transmission in Western and Central Europe is sex between men followed by heterosexual transmission, while the main route of transmission in Eastern Europe is heterosexual contact followed by injecting drug use, with sex between men only accounting for 3.7% of the new HIV infections (Table 1.1) (17). Across the WHO European region, there has been a 23% increase in the number of new diagnoses through heterosexual contact and a 10% increase in transmission through sex between men between 2007 and 2016 (17). There was a 40% decrease in transmission through injection drug use, however data from Russia as well as seven other countries (see footnote of Figure 1.6 for details) were not included in this analysis, which accounted for a large number of new diagnoses in this region (17).

The increasing HIV incidence in the Eastern Region is partly attributable to the collapse of the Soviet Union in the early 1990s (18). This led to increases in unemployment as well as other social and economic changes (18). These changes negatively impacted the health structure in the region and led to wider economic inequalities, which, in conjunction with a huge increase in injection drug use has fuelled the HIV epidemic in Eastern Europe (18). Therefore it is important that preventative measures are put in place to curb the spread of HIV in this region (19). While the main route of transmission is no longer injecting drug use, PWID still accounts for a large proportion of those newly infected. However, despite the evidence to suggest needle syringe exchange programmes and opioid substitution therapy (OST) can reduce HIV incidence (20), OST and other harm reduction services are not adequate as only 1% of injection drug users (IDUs) receive OST in Eastern Europe (21). Low rates of OST are partly due to harm reduction services being criminalised in certain countries. OST is illegal in Russia, despite having one of the highest rates of opioid use in the world, as well as increasing HIV rates (22,23). The government's punitive policies towards drug use means PWID are not freely able to access treatment and services and there have been huge human right violations (22). OST is also prohibited in Turkmenistan and Uzbekistan (22).

Table 1.1: New HIV diagnoses in WHO European Region, by region and EU/EEA (17)

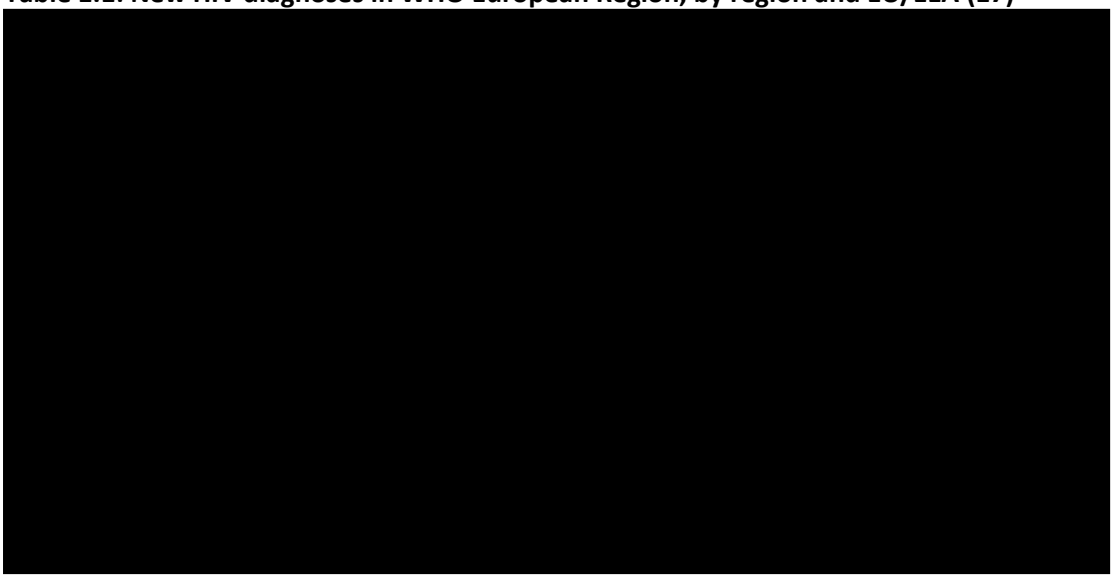


Figure 1.5: Rate of new HIV diagnoses by year of diagnosis in WHO European Region, by region and EU/EEA (17)

Figure 1.6: New HIV diagnosis in WHO European Region (2007-2016), by transmission mode (17)

1.1.2 History of HIV

AIDS was internationally recognised in the 1980s, however, the earliest case of AIDS was identified retrospectively from the medical records of a 25 year old sailor from Manchester who died of an AIDS-like illness in 1959 (24). Phylogenetic analysis was later used to identify the first recognised infection of HIV from a biopsy specimen from a female from Kinshasa, obtained in 1960 (25). This study estimated the first HIV infection to have occurred in 1921 (95% CI = 1908-1933) (25).

There are two types of HIV, HIV-1 and HIV-2, which differ based on their genome organisation and phylogenetic relationship with other primate lentiviruses (26). While HIV-1 and HIV-2 both originated from simian immunodeficiency virus (SIV), HIV-1 is thought to have originated from SIV in chimpanzees and gorillas while HIV-2 is genetically closer to the sooty mangabeys monkeys SIV (27,28). HIV-1 and HIV-2 both entered the human population through zoonotic (cross-species) transmission (26). This could have happened as a result of humans having direct exposure to animal blood as a result of hunting or eating chimpanzees, which was traditionally a subsistence activity in the regions (26). As a result of this practice, the prevalence of SIV antibodies in villages where bushmeat is hunted is 7.8% (29). This suggests that the SIV infection occurred in humans prior to the early 1900s, however, these isolated infections did not turn into epidemics (30). The social disruption in the region due to colonialism was paramount in creating conditions that promoted the epidemic spread of HIV (26,30). Colonial practices such as enslavement, labour camps, forced resettlements, and nonsterile vaccination alongside the practice of hunting bush meat, created prime conditions for the epidemic to spread (26,30).

HIV was estimated to have first been introduced to the US population in 1969 (31). However, the first case reports of what was later known as HIV infections were made in 1981, when five cases of a rare opportunistic lung infection known as *Pneumocystis carinii* pneumonia (PCP) (now known as *Pneumocystis jirovecii* pneumonia (PJP)) were found in young healthy men in Los Angeles (32). Around this time there were reports of a rare and aggressive cancer Kaposi's sarcoma (KP) in New York and California (33). These individuals were also found to be immunocompromised. At the time, the occurrence of these opportunist infections was rare and had very high mortality rates. The initial cases were found exclusively in young gay men, which meant there was speculation that their lifestyle was somehow responsible (34,35). However, by December of that year, there were reports of PCP in intravenous drug users (36), and by the following year, there were cases in people who received blood transfusions (37,38) and children of individuals from these risk groups (39). Around the same time, cases of PCP and KS were also being reported across Europe (40) in

countries such as the UK, Spain and France (41–43). There were also cases of a new fatal disease in Uganda known as ‘slim disease’ (44,45).

The term Acquired Immunodeficiency Syndrome (AIDS) was defined in 1982 by the CDC as ‘a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease.’, which allowed for monitoring and surveillance of the disease (46,47). By September 1982, there were on average 1-2 new cases being reported every day in the US (46).

HIV was identified in 1983 by a French team at the Pasteur Institute led by Luc Montagnier and Françoise Barré-Sinoussi (48). What they named Lymphadenopathy Associated Virus (LAV) was isolated in an individual at risk from AIDS. A year later in 1984, a new retrovirus named Human T-cell Lymphotropic Virus 3 (HTLV-III) was discovered in the US by Robert Gallo’s lab at the National Institute of Health (NIH) (49). It later transpired that LAV and HTLV-III were the same virus, and likely to be the cause of AIDS (50). However this led to a lengthy controversy between the team at the Pasteur Institute and the NIH team, as the team in Paris had sent their sample to the NIH group before Gallo’s publication, however, Gallo was cleared of all suspicions of misconduct (51). In 1991, Nature published a letter from Gallo, admitting that the virus he discovered actually came from a sample that had been contaminated by the French virus (52). In May 1986, LAV and HTLV-III were re-named Human Immunodeficiency Virus (HIV) by the International Committee on the Taxonomy of Viruses (53,54). This initial discovery of LAV/HTLV-III was actually HIV-1 (group M) virus, which is the more common strain and has a stronger association with progression to AIDS (26)(55) and what this PhD thesis will be focusing on. The HIV-2 virus was discovered slightly later in 1986 (56). HIV-2 is less infectious, spreads at a slower rate, has slower progression to serious symptoms and is mainly found in West Africa (57,58).

1.1.3 Pathogenesis of HIV infection

Lentiviruses, from the Latin lentus for 'slow' viruses, are characterised by having a long incubation period (the interval between infection and the development of serious symptoms) and can cause a wide range of pathologies in humans and animals (59–61). According to the International Committee on the Taxonomy of Viruses (ICTV), there are ten species of lentivirus, eight of which are found in animals, and two of which are found in humans, HIV-1 and HIV-2 (62). The lentivirus genus belongs to the retrovirus family, which are a class of viruses that store their genetic information in ribonucleic acid (RNA), as opposed to human genes which are made of a related molecule called deoxyribonucleic acid (DNA) (63). Retroviruses are unique, as they contain the enzyme reverse transcriptase which is used to convert the RNA into viral DNA through the process of reverse transcription (63).

The HIV-1 particle has a spherical shape and a diameter of about 120 nanometers (nm) (64). It is surrounded by a viral envelope, which protects the internal components of the virion and contains proteins that interact with host cell surface proteins, leading to the fusion of the viral membrane and cell membrane (64,65). The HIV core is encased in a cone-shaped protein shell called the capsid that protects the virus from the host's immune system (66). The HIV core contains two copies of the single-stranded HIV RNA genome, reverse transcriptase, integrase and other viral proteins (66,67).

The primary function of the immune system is to defend the body from pathogens, which are organisms such as viruses and bacteria that can cause diseases (68). Molecules on pathogens called antigens allow the immune system to differentiate pathogens from the body's own cells and tissues and react (68). B-cells mainly produce antibodies against specific antigens while T-cells are crucial in coordinating the immune response to antigens and stimulating the production of antibodies (68–70). HIV prefers to infect cells with a CD4+ receptor (which are molecules on the

surface of the cell) to which the virus can bind, such as macrophages and T-lymphocytes, which are both types of white blood cells (57,71). HIV also makes use of chemokine co-receptors (CCR5 and CXCR4) during the binding process, which are found on CD4-expressing cells (e.g. T-helper lymphocytes, thymocytes, dendritic cells and macrophages), therefore the main target cells of HIV are CD4+ T-cells and macrophages (72). As HIV primarily infects and replicates within CD4 cells and destroys them, the number of CD4 cells depletes as the infection progresses (69). The damage HIV causes to the immune system makes it less capable of carrying out an effective immune response, leading to an increased susceptibility to opportunistic pathogens (73). There are a small number of individuals (known as elite controllers) who are infected with HIV but are able to remain healthy and maintain a normal CD4 cell count for over 20 years, this is due to their strong cellular immune response (74,75).

Figure 1.7: The HIV replication cycle (67)

The HIV replication cycle describes the stages the virus undergoes from first contact with the host cell to the production of new infectious particles that can then infect other target cells, this process is shown in Figure 1.7 (64). The HIV virion binds to the target cell using the HIV surface glycoprotein gp120 and the CD4 receptors on the surface of the cell (66)(71). It then fuses to the cell membrane using co-receptors CXCR4 or CCR5. CXCR4 is mainly expressed on CD4+ T-cells, whereas CCR5 is also expressed on macrophages. The gp120 protein on the surface of the virus can have a preference for a type of co-receptor, which determines whether it is an (R5-) m-tropic, (X4-) t-tropic or (R5X4-) dual-tropic virus (55). Initial infection is usually via an m-tropic virus with a broadening of receptor usage later in the infection, which leads to strains that can utilise CXCR4 co-receptors and progression to AIDS (57)

The viral core enters the host cell cytoplasm and 'uncoats', releasing RNA and replication enzymes. Once inside the host cell cytoplasm, the enzyme reverse transcriptase converts each of the two copies of HIV RNA to one DNA copy through reverse transcription (67). The DNA genome is then transported into the host cell's nucleus and using the viral integrase enzyme it is combined with the host DNA (27). This process is known as integration and allows the virus to use the host cell's genetic machinery to make new viruses (67). At this stage, the cell is latently infected and does not produce the virus until it is activated. On activation, the DNA is then transcribed into a new strand of RNA called messenger RNA. These are then carried outside the nucleus into the cytoplasm of the cell, where the HIV protease and host protease enzymes translate them into small pieces of functional protein which are used to build the HIV virion. Once the HIV-RNA and other virus building blocks gather, core proteins form a new capsid around them. The capsid then buds from the cells surface, creating a new HIV virus that can mature and infect other cells.

1.1.4 Transmission

Transmission occurs from the mucosal membrane or blood being directly exposed to infected bodily fluids (76). While HIV is present in most bodily fluids including blood, semen, cervical secretions, breast milk, sweat, tears, and saliva, this does not mean the virus can be transmitted through all these fluids, as the concentration of the virus varies considerably depending on location (58,76). As the concentrations are undetectable in bodily fluids such as sweat, tears and saliva, it is not possible for transmission to occur through casual or social contact (76,77). In 1983 CDC ruled out transmission by casual contact, food, water, air or surfaces (78). The largest concentrations of HIV are found in blood, semen and cervical secretions, making them the most infectious (76). Transmission can occur either horizontally through sexual contact and blood to blood contact or vertically from mother to child (67).

Latent HIV reservoirs (cells that are infected with HIV but not actively producing the virus) in blood and lymphoid tissue are established early on in the infection (79). Evidence of postintegration latency in resting CD4 T cells was established in 1995 (80). While ART can reduce the level of HIV in the blood, it cannot eradicate latent reservoirs (79). However, taking ART as prescribed can reduce the viral load to the point of viral suppression (less than 200 copies of HIV per ml of plasma) or an undetectable viral load (a test cannot detect the virus) (81). Keeping HIV suppressed or undetectable has many health benefits, it can also eliminate the risk of transmission (82,83). The risk of transmission varies greatly depending on the amount of virus in the body at the time of exposure, as the higher an individual's viral load is, the more likely they are to transmit the virus onwards (84).

1.1.4.1 Sexual transmission

Sexual transmission is the most common route of transmission worldwide (76). There are behaviour and biological factors associated with sexual transmission, such as the type and frequency of sexual contact, the use of condoms, circumcision (men), and

AIDS status (85). However, the strongest risk factor associated with sexual transmission is the viral load of the infected partner (85). As gender and route of sex have been shown to affect the risk of transmission, the sexual transmission risk group is generally split into heterosexuals and men who have sex with men (MSM) (86).

The HPTN 052 trial was carried out across 9 countries and enrolled 1763 couples between 2007 and 2010 (87). The study results showed that early initiation of ART could reduce the risk of onward transmission by 96% among serodiscordant couples (87). However, more recent studies show that PLWH who take ART and are virally suppressed have effectively no risk of transmitting HIV to their HIV-negative sexual partners (83). These studies provide evidence of the effectiveness of the Treatment as Prevention (TasP) strategy, which is now being used as a public health intervention to reduce the spread of HIV (88,89). Pre-exposure prophylaxis (PrEP) can help to prevent HIV infection in individuals who are HIV-negative but at high risk of becoming infected. The FDA approved PrEP (Truvada) for HIV negative individuals in 2012 (90). Truvada can be taken orally once daily or on-demand in MSM, and is a combination of emtricitabine and tenofovir disoproxil fumarate (90,91). The PROUD study was an open-label randomised trial carried out across 13 sexual health clinics in England to explore the effectiveness of PrEP in a real-world setting, among HIV-negative MSM at high risk of HIV (92). Results from the PROUD study showed that when PrEP is adhered to, the chance of HIV transmission is reduced by 85% in MSM in a real-life setting (92). They also did not find any evidence to suggest that the use of PrEP would increase the risk of other sexually transmitted infections (92).

Anal sex is associated with the greatest risk for HIV infection or transmitting HIV, as the lining of the rectum is thinner than vaginal tissue, allowing the virus to enter the bloodstream (84,93). In 2015 the CDC reported that 67% of new HIV infections in the US were among gay and bisexual men (93). Gay and bisexual HIV positive men are also at an increased risk of acquiring other sexually transmitted diseases such as syphilis, gonorrhoea, chlamydia and lymphogranuloma venereum (76). Having

multiple sexual partners (without condom use) can also increase the risk of getting HIV (94). The majority of HIV cases globally are not due to homosexual transmission, however, the connection between homosexuality and HIV since the beginning of the epidemic has contributed towards stigma and discrimination towards MSM (95). Homophobia and criminalisation of homosexuality in many countries can increase vulnerability to infection and make the development of effective public health interventions more difficult (95).

While sexual contact between men is the major transmission risk in high-income countries (HIC), heterosexual sex is responsible for the majority of the transmission in middle and low-income countries (LIC) (76). Women have a higher risk of infection than men during heterosexual contact, as the vagina is more prone to erosions and has more mucous area than male genitalia (96). In 2016, the number of new infections was 44% higher in young women aged 15-24 than men in the same age group (4). HIV also disproportionately affects women and adolescent girls as they are more vulnerable to violence and violations of their sexual and reproductive rights (97). In 2006, a randomised controlled trial in South Africa, which included 3274 uncircumcised men aged 18-24, showed that male circumcision reduced the risk of female to male HIV transmission by 60% (98). The World Health Organization encourages the use of male circumcision as a preventative tool in countries/regions where there is a high HIV burden due to heterosexual transmission with a low prevalence of male circumcision (99).

1.1.4.2 Blood-to-blood

HIV can be transmitted through infected blood or blood products, this could be through sharing or re-use of contaminated needles and syringes, through blood transfusion or healthcare workers contact with infected blood (76,100). In the early stages of the HIV epidemic blood products were not screened for HIV. A number of individuals, such as those with haemophilia who require a blood coagulant factor, those in need of a blood transfusion, or organ or tissue replacement were exposed

to infected blood products and contracted HIV (101). Approximately 90% of all individuals receiving a blood component from an HIV positive individual (who does not take viral suppressive ART) will contract the virus (102). However, since the licencing of the first HIV antibody screening test in 1985, blood products are routinely screened for HIV (103). In 1983 the CDC published recommended precautions for healthcare workers and allied health professionals to reduce the risk of HIV transmission (104). Also, due to universal screening of blood products, this mode of transmission has almost been eliminated in HIC (76).

The re-use or sharing of syringes or needles amongst people who inject drugs is the most common source of blood-to-blood transmission. Globally there are 12.7 million people who inject drugs, 13% of whom are HIV positive (105). The prevalence of HIV is estimated to be 28 times higher in PWID than in the rest of the adult populations (105). The current global policy on drug use focuses on prohibition and criminalisation, which can fuel HIV transmission as these frameworks mean PWID are less likely to access HIV prevention services, testing, treatment or healthcare (76,106). Harm reduction strategies aim to reduce the health, social and economic harms of drug use without requiring people to stop using drugs, which helps to reduce HIV transmission among PWID as they are less marginalised and are able to engage with health services (106). However as mentioned earlier, there are a number of countries with punitive policies towards drug use, where harm reduction services are illegal (22). Of the 158 countries where injecting drug use has been documented, 91 countries have a national policy on harm reduction, 90 have at least one needle-syringe exchange program and 80 provide opioid substitution therapy (106). The 2011 Political Declaration on HIV set out the aim to halve HIV transmission among PWID by 2015. However, this goal was missed by 80%, highlighting the lack of effective interventions among PWID, as harm reduction services are generally underfunded and lack political support (106,107).

1.1.4.3 Mother to child

Mother-to-child (vertical) transmission can happen *in utero,* during labour, delivery or breastfeeding (76). Almost all children with HIV are infected through vertical transmission (108). In 1985 the U.S. Public health service issued recommendations to help prevent mother to child transmission (109). In 1994 zidovudine was found to reduce vertical transmission from 25% to 8% (110,111). After zidovudine was found to be effective in reducing transmissions, there were a number of trials in LIC that were aimed at identifying shorter and cheaper regimens. However, as many of the control groups in these trials were given a placebo rather than the zidovudine regimen used in HIC, these trials were deemed unethical (112).

In most countries, it is recommended that pregnant women are tested for HIV, as the risk of transmitting HIV vertically can be reduced substantially if the mother is receiving ART (76,113). Globally there has been a 47% decline in new infections among children since 2010, which coincides with a 29% increase in the coverage of ART among pregnant women living with HIV (4). However there were still 160000 new HIV infections in children in 2016, and 23% of pregnant women did not have access to ART (4). Also, vertical transmission is more prevalent in LIC than the HIC, where the transmission rates are almost zero (76).

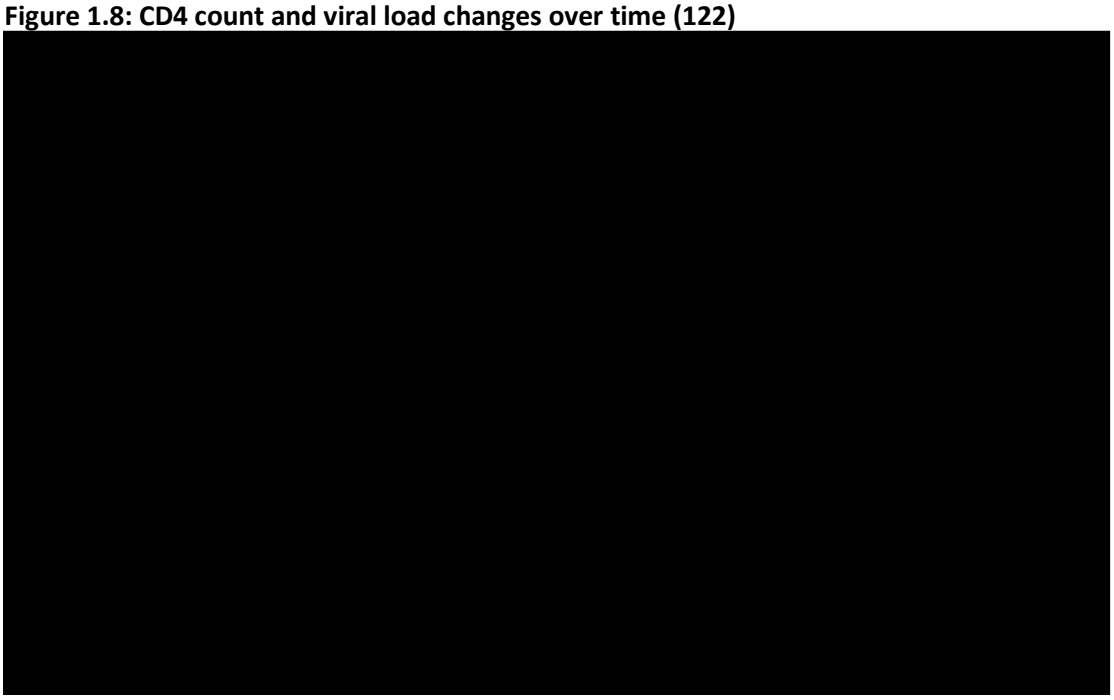
Transmission rates can vary from 15-45% without intervention, however, the rate of transmission drops below 5% with effective interventions during pregnancy, labour, delivery and breastfeeding (114). Symptomatic women with a high viral load and suppressed immune system have the highest risk of transmitting HIV through breastfeeding (115). The 2013 WHO guidelines recommended that ART be provided during pregnancy and breastfeeding to women who are not eligible for ART, and that they only continue ART after breastfeeding if it is of benefit to their own health (option B) (116). The START (multicentre study, including 4685 PLWH) and TEMPRANO (carried out in Ivory Coast, including 2056 PLWH) trial findings published in 2015 highlighted the importance of starting HIV treatment in all PLWH, regardless

of their CD4 count however prior to this treatment was only recommended in individuals with a CD4 count >350 cell/mm^3 (117,118). Therefore in 2015, the WHO changed their guidelines to include the recommendation of option B+, that all pregnant and breastfeeding women are provided with lifelong HIV treatment irrespective of their CD4 cell count (116). It is also recommended that children exposed to HIV are tested by the time they reach 6-8 weeks old and again at the end of breastfeeding. Children that are diagnosed with HIV should also be treated immediately (119).

1.1.5 Clinical stages of disease progression

In the absence of HIV treatment, the progression of the HIV infection can be broadly split into three stages: 1) acute HIV infection, 2) asymptomatic stage, and 3) symptomatic stage. The natural history of HIV infection can be seen in Figure 1.8. The Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) have both developed classification systems to define the stage of HIV (see Table 1.2, Table 1.3, and Table 1.4) (120,121). While the CDC classification system also uses CD4 count as a marker of HIV progression, the WHO system only provides clinical descriptions associated with each stage, making it more applicable in settings where monitoring CD4 count may not be feasible.

Figure 1.8: CD4 count and viral load changes over time (122)



Primary stage

Seroconversion is the period of time when the immune system recognises the HIV virus and develops an antibody response (123). The time from infection to completion of seroconversion is known as primary or acute infection (124). During this stage, the body starts to produce antibodies to the virus which usually appear 4-6 weeks after initial infection, but it can take 1-3 months for seroconversion to occur (124,125). Prior to seroconversion, the individual is highly infectious, however, would not test antibody positive (seronegative) (126). Before seroconversion, HIV can be diagnosed by viral antigens such as p24 or detection of HIV-RNA in plasma (127). This early phase is also characterised by rapid viral replication, leading to more than one million copies per millilitre (copies/ml) (122,128). This coincides with a short-lived, but sometimes drastic decline in the CD4 count (123,124). It is estimated that 25-65% of individuals experience symptomatic primary HIV infection or seroconversion illness, which is caused by the body's immune response to the HIV virus (123). These symptoms can resemble influenza, infectious mononucleosis or aseptic meningitis, and last a median of 14 days (124,129). Few individuals experience more extreme symptoms which are normally seen later in the infection, such as pneumocystis pneumonia or oesophageal candidiasis (123,124). Individuals who experience more

severe symptoms can be more likely to experience faster disease progression (124). After seroconversion, the CD4 count will recover to some extent and the VL will steady, at a level known as the viral set-point (124).

Asymptomatic stage

After primary infection, there is a temporary recovery of CD4 cells, which marks the beginning of the asymptomatic, or chronic stage (130). Some individuals are known as long-term non-progressors and are able to suppress viral replication to below the limit of detection (50 cp/ml) without treatment (74,131). These individuals can survive for longer after infection without treatment and have certain characteristics such as beneficial anti-HIV immune response (124,132). Less than 1% of HIV positive individuals are known as elite controllers and can maintain healthy CD4 counts for 20-25 years (133). The asymptomatic period is also referred to as clinical latency as there is a lack of symptomatic disease (130). Viral replication still occurs during this stage, however, it is controlled by the response of the immune system (130,134). A healthy HIV-negative individual has around 500-1500 CD4 cells/mm^3, but eventually, the immune response to HIV begins to fail, and the CD4 count decreases (135). CD4 count is estimated to decline by 20-78 cells/mm^3 per year depending on HIV-RNA levels (135). Around 18-24 months before the symptomatic stage, the rate of decline increases 3 to 5 fold (136). The length of this stage is highly variable, and as the CD4 count decreases the patient becomes more at risk of minor infections(124). However, individuals can generally remain asymptomatic if their CD4 count remains above 350 cells/mm^3 (137).

Symptomatic stage (AIDS)

The last stage is the symptomatic stage, which develops after a median of 10 years after seroconversion (137). Immunodeficiency occurs when the body does not have enough immune cells or the cells do not work properly, which means individuals are

more susceptible to infections (68). An AIDS diagnosis can be based on laboratory evidence, such as a CD4 cell count of less than 200 cells/mm^3 in an HIV positive individual (120,121) or the development of an AIDS Defining Illness (ADI) which can develop regardless of the individuals CD4 count, for example, if an individual is HIV positive and develops one or more opportunistic infections (see Table 1.3 and Table 1.4 for the full list of AIDS-defining conditions according to the CDC and WHO, respectively (120,121)). Once the CD4 count reaches below 200 cells/mm^3, individuals become much more susceptible to developing an opportunistic infection (124). Prior to the introduction of ART, the median survival time following an AIDS diagnosis was 11.6 months [95% CI = 3.3 – 19.1 months] depending on the opportunistic infection (138). According to a meta-analysis by Poorolajal et al., in the absence of HIV treatment, most patients will die within 24 months of the onset of AIDS, whereas if the patient receives HIV treatment survival is >10 years, however, this varies according to the type of AIDS event (139). There is also evidence to suggest that depending on the condition, survival halves after a second AIDS-defining condition (140).

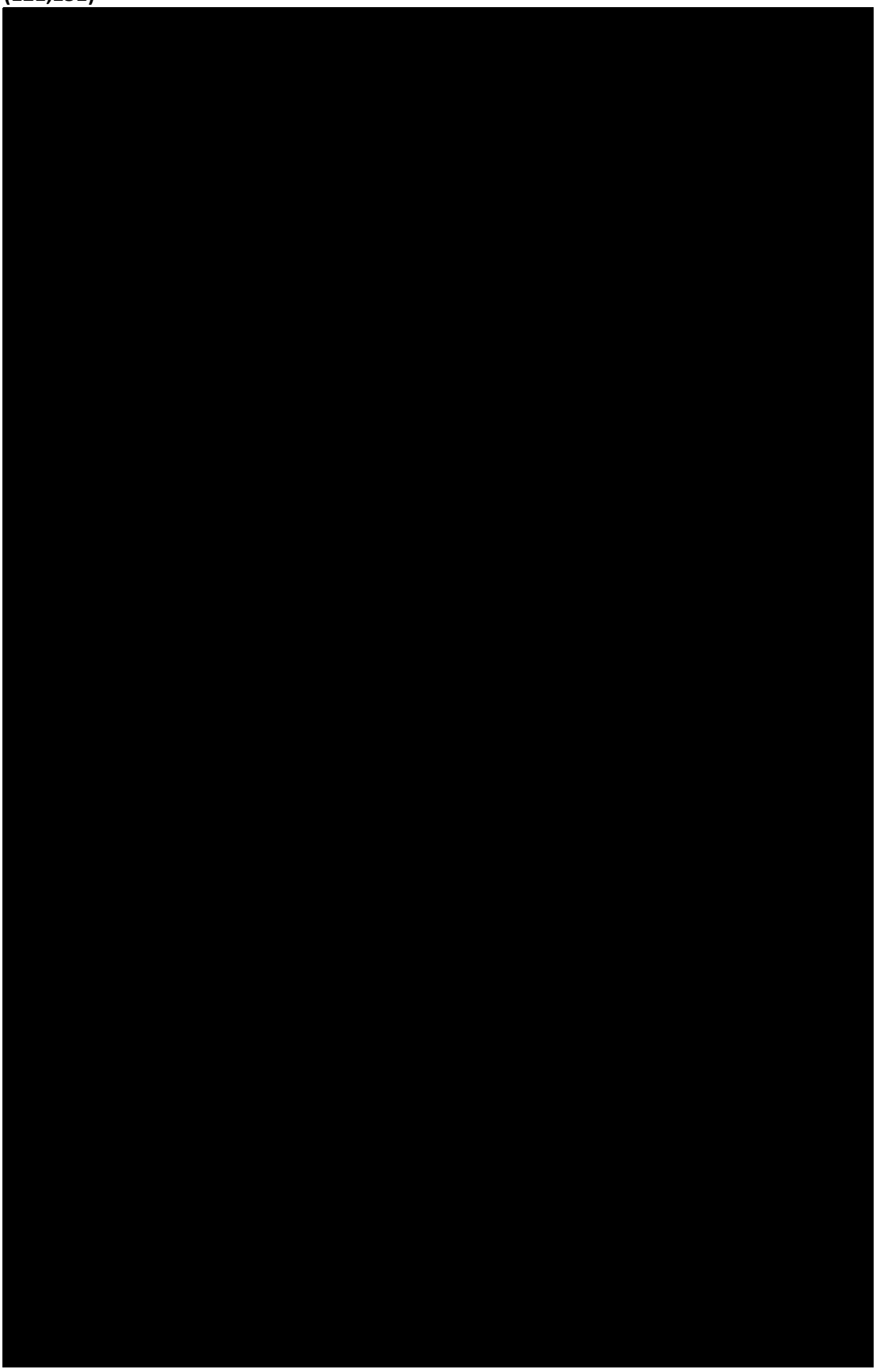
Factors that affect disease progressions:

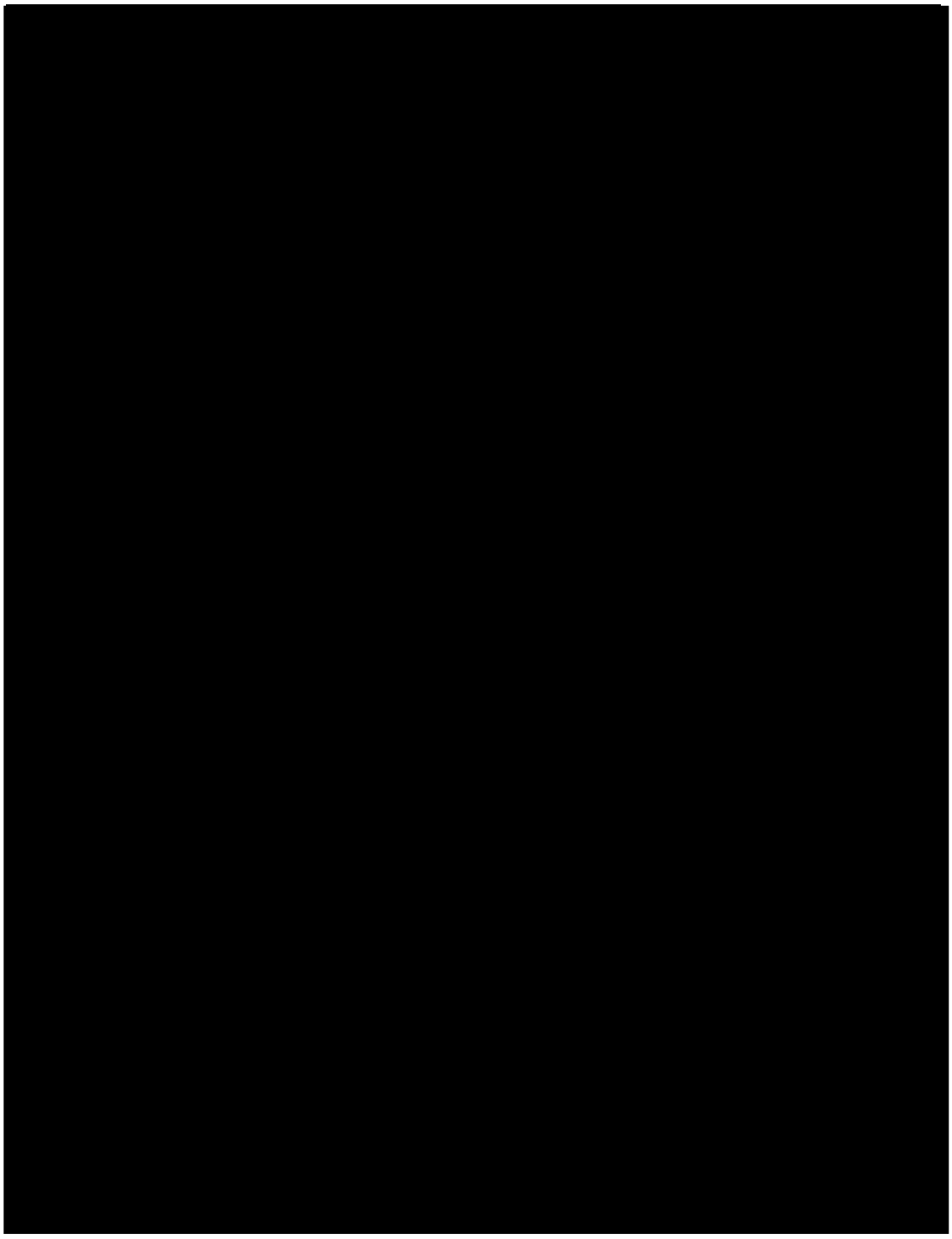
While the HIV infection progresses in stages, the time it takes for individuals to progress through the phases varies. These differences can be due to many different factors such as the individuals immune response, CD4 count, VL, genetic characteristics of the virus, age at seroconversion, ethnicity, and co-infection with other viruses (137,141–147). HIV-1 infected individuals' progress faster than those with HIV-2 (148). While gender is not thought to impact HIV progression, there can be differences in survival by sex in certain settings, such as among PWID (149). Despite all of these factors, disease progression is most impacted by whether the individual is on ART or not (150).

Table 1.2: CDC HIV infection stage based on age-specific CD4+ count or percentage of total lymphocytes (120)

Table 1.3: CDC list of AIDS-defining illnesses (120)

Table 1.4: WHO clinical staging of HIV disease in adults, adolescents, and children (121,151)





1.1.6 Treatment of HIV

Antiretroviral therapy (ART) treats HIV by inhibiting the replication of the HIV virus (152). The first drug approved by the FDA to treat HIV was Zidovudine which is also known as azidothymidine, or AZT (153). AZT is a nucleoside reverse transcriptase inhibitor (NRTI) and was approved in March 1987, 6 years after the first AIDS reports

in the USA (154). AZT was initially developed in 1964 as a potential cancer treatment, however, in 1985, AZT was tested and found to be a potent inhibitor of HIV (155). A randomised controlled trial with 145 patients on AZT and 137 patients on the control arm showed AZT significantly reduced mortality, with only 1 death occurring in the treatment group compared to 19 in the placebo group (156). The Data Safety and Monitoring Board decided it was unethical to continue to withhold the drug from the placebo group and therefore stopped the trial early and offered AZT to those in the control group (157). While there were apparent clinical benefits in some patients, there were also adverse events (AEs), and significant drug toxicity (158). Further trials showed that the benefits of AZT were not sustained due to rapid development of resistance, with the lives of patients being prolonged by 6-18 months (159,160).

The emergence of HIV with resistance to AZT called for the development of more effective combination treatments to improve survival (161,162). By 1991, more drugs from the NRTI family were introduced, such as didanosine and zalcitabine which had fewer AEs (163). These drugs were also found to improve outcomes for patients who switch from AZT (164). Investigators began to study the use of multiple treatments to combat the virus, and taking AZT in combination with either didanosine or zalcitabine was found to significantly slow the progress to an AIDS-defining illness as opposed to taking AZT alone (165). However these improvements were short-lived, and there were still high rates of treatment failure and NRTI resistance (166). In 1995, the FDA approved the first protease inhibitor, saquinavir (167). The results from the first trial using three drugs from different classes, known as combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART), were presented at the XI International Conference on AIDS in Vancouver in 1996 (168). The results showed that combining multiple drugs from different drug classes into one regimen improved treatment benefits (168). The treatment guidelines recommended at least three ART drugs to be used in combination, from at least 2 different drug classes (169). This caused an immediate decline of 60-80% in the rate of AIDS-related deaths in countries that could afford treatment (170). A third class of drugs, non-

nucleoside reverse transcriptase inhibitors (NNRTI) were also approved in 1996, allowing further combinations of treatments to be used (169).

While NRTI, PI and NNRTI were the three main drug classes, there are now three more classes available, integrase inhibitors (INI), and CCR5 and fusion inhibitors which are both types of entry inhibitors (159). The different drug classes target different stages of the HIV viral replication process and can suppress viral loads and transmission (Figure 1.9). However, complications can arise due to toxicity as well as the development of resistant strains (66). HIV drugs from the same or different classes can have different genetic barriers, which refers to the number of mutations required to overcome the anti-HIV activity of the drug regimen (171). HIV drug resistance can be reduced through the use of affordable drugs with high barriers to the development of resistance (172).

The original HIV treatments had a high pill burden, strict food requirements (due to drug and food interactions) and high toxicity which resulted in lower adherence (173). However, newer antiretroviral drugs are more potent and have improved pharmacokinetic profiles which require less dosing, pills, lower toxicity and resistance (173). Currently, recommended first-line therapy consists of three HIV drugs, two NRTIs (referred to as the 'backbone'), with one PI, NNRTI, or INI (151). While HIV treatment has improved greatly since the approval of AZT in 1987, there is still no cure or vaccine, and the drugs used are only able to reduce viral replication, therefore requiring a lifetime commitment to treatment (152). While there is no feasible cure for HIV, there has been one individual who was cured of HIV after receiving a stem-cell transplant, with donor cells that did not express CCR5, for treatment of leukaemia (174). However, this is an aggressive, high-risk therapy that was used to treat cancer not HIV.

Changes to regulations in 1992 meant that drug approval could be based on a surrogate marker as opposed to a clinical outcome (175). The FDA created a new class of drugs, 'investigational new drug', which meant drug approval was accelerated by 2-3 years (176). These changes in the FDA and other regulatory bodies allowed experimental drugs to become more widespread (177). The earlier ART randomised controlled trials (RCTs) used clinical outcomes, with one of the first clinical trials by Fischl et al. being terminated after only 7 months due to the clear benefits of AZT (156,178). However, after the introduction of cART, clinical trials with death as the primary endpoint required a longer time and larger sample size for treatment effects to be detected (179). Since the introduction of advanced molecular diagnostic tests in the mid-1990s, more clinical trials use surrogate markers rather than clinical outcomes (154). While surrogate markers can reduce the cost and duration of clinical trials, they provide no direct information regarding the long-term outcomes of patients using ART (179). In addition to this, patients from RCTs are mostly unrepresentative of the patient population as there are normally strict inclusion/exclusion criteria for participating in trials, trial participants also have better treatment adherence and more frequent follow-up than patients in routine care (180–182). While RCTs are the gold standard, there are many large HIV observational follow-up studies that have been following patients since the beginning of the epidemic, which play an important role in assessing the long-term efficacy of HIV treatments (183).

Figure 1.9: How different ART drug classes affect the HIV lifecycle (184)

NRTI

NRTI drugs were the first class of ARTs licenced to treat HIV (185). NRTIs, nucleotide reverse transcriptase inhibitors (NtRTIs) and NNRTIs all target reverse transcriptase, which is the HIV enzyme used during the process of reverse transcription to convert single-stranded HIV RNA into double-strand HIV DNA (169). NRTIs and NtRTIs are structural analogues of cellular nucleosides or nucleotides, which are similar enough to be used by HIV reverse transcriptase when constructing viral DNA (186). However, flaws in the nucleoside analogues hinder the cells from completing reverse transcription and making more HIV (186). The 2016 WHO guidelines recommend a combination of two NRTI/NtRTI drugs; tenofovir (TDF) and either lamivudine (3TC) or emtricitabine (FTC), along with one NNRTI drug, efavirenz (EFV) as first-line treatment, as well as alternative regimens (151). Current guidelines from the British HIV Association and the European AIDS Clinical Society also propose the use of TDF and FTC as the most suitable NRTI backbone for first-line HIV treatment regimens (187,188).

While AZT was the first treatment to be licenced to treat HIV, it is rarely used today because of the side effects (158). However, in some countries, AZT is still used in

individuals with reduced treatment options or pregnant women (186,187). Other NRTI drugs that were developed after AZT are also not recommended for use anymore, as AE from extended NRTI use has been linked to mitochondrial dysfunction, manifesting as fatal liver damage, myopathy, cardiotoxicity, and peripheral neuropathy and lipodystrophy (158,187,189). Zalcitabine was associated with significant mitochondrial and hepatic toxicities and was withdrawn from the market in 2006 (190). Stavudine was also significantly associated with these side effects, and while its use has been reduced in Europe it has not been completely phased out yet (151,187). The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) collaboration provided evidence to suggest that abacavir is linked to myocardial infarction (MI) and TDF increases the risk of nephrotoxicity (191–194). A large FDA meta-analysis did not find an association between abacavir and MI (195). However, a meta-analysis of prospective studies on the association between TDF and kidney dysfunction found the magnitude of the effect did not necessarily warrant a change in first-line regimens when monitoring of the kidney is possible (196).

PI

PIs were introduced in 1995, they differ from NRTI and NNRTIs as they target the protease enzyme instead of reverse transcriptase (186). PIs bind to the protease enzyme, blocking the maturation step of the HIV life cycle, which results in the release of immature, non-infectious HIV viral particles that cannot infect other cells (197,198). The first licenced PI was saquinavir and soon after ritonavir and indinavir were also approved, however, there are now currently 10 PIs licenced for the treatment of HIV; saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, tipranavir, and darunavir. The arrival of PIs allowed for cART, dual-class therapy with three drugs (167). Earlier PIs had low bioavailability and high pill burden, which negatively affected treatment adherence (167). Ritonavir was found to be very effective, however it was not well tolerated (167). It was later found that small doses of ritonavir co-administered with other PIs could reduce the metabolism and improve the bioavailability and half-life of PIs, boosting the effectiveness (167). Cobicistat, a

pharmacoenhancer, is also able to boost PIs, however unlike ritonavir, it has no anti-HIV activity (199).

While PI monotherapy has not been recommended in any guidelines, it has gained popularity among patients with NRTI intolerance. Some studies provide evidence to support the efficacy of using lopinavir or darunavir boosted with ritonavir, and a UK analysis showed that PI monotherapy has large cost-saving potential (200–203). However, results of the PIVOT study (Protease Inhibitor monotherapy Versus Ongoing Triple Therapy) indicated that there were much higher rates of viral rebound over 3 years (PI monotherapy = 35% vs. cART = 3.2%) (204).

Side effects associated with PIs include gastrointestinal toxicity, particularly nausea and diarrhoea (166). More severe side effects can include hyperglycaemia and lipodystrophy, however newer PIs are better tolerated and have improved metabolic profiles (166,205).

NNRTI

NNRTIs are similar to NRTIs as they both interrupt the reverse transcription process of the HIV life-cycle (169,186). However, NNRTIs do this by binding to the reverse transcriptase enzyme and obstructing its ability to convert HIV-RNA to HIV-DNA (159,206). They are not effective against HIV-2 due to structural differences in the virus (207). NNRTIs were introduced shortly after PIs, with nevirapine approved by the FDA in 1996, delavirdine in 1997, and efavirenz the following year (159). Etravirine was approved in 2008, after the DUET-1 and DUET-2 RCTs (208). Etravirine was shown to be the only NNRTI to be clinically effective in patients with NNRTI and PI resistant HIV-1 (159).

NNRTIs are recommended by WHO as part of the first-line ART for adults alongside two NRTIs (151). Efavirenz is the recommended NNRTI, despite evidence to suggest there maybe be potential harmful side effects to the drug such as dizziness, headaches, and depression (151,207). NNRTIs generally have a low genetic barrier to resistance, which previously would lead to treatment failure (166,172). However, next generation NNRTIs, such as etravirine, have fewer side effects and a higher genetic barrier against resistance (209). Individuals with NNRTI resistance are less likely to achieve viral suppression, have worse health outcomes, and are more likely to discontinue treatment. While NNRTIs are an essential part of first-line ART, WHO has published guidelines recommending countries use different treatments if their level of NNRTI drug resistance is too high (172).

INI

Integrase inhibitors (INI), also known as integrase strand transfer inhibitors (InSTIs) are the newest class of HIV treatment (186). They work by targeting viral integrase and inhibiting the strand transfer of viral DNA, preventing the completed HIV DNA copy being integrated into the host DNA cell (209). The first INI licenced for use was raltegravir in 2007, since then two more INIs have been licenced; elvitegravir and dolutegravir (166,169). Treatment guidelines also recommend the use of an INI alongside two NRTIs as first-line ART therapy instead of a NNRTI (151). Elvitegravir requires boosting with cobicistat; both drugs are only available within the combination pill Stribild, which also includes tenofovir and emtricitabine. Dolutegravir does not require boosting and has a higher genetic barrier to resistance than both raltegravir and elvitegravir (166). Dolutegravir plus abacavir-lamivudine was the first treatment regimen to show superiority over two NRTIs and efavirenz (210).

Entry inhibitors

For HIV to enter a host cell the HIV gp120 glycoprotein binds to the CD4 receptor, then gp120 binds to either a CCR5 or CXCR4 co-receptor (209). Once HIV has attached to the CD4 receptor and co-receptor, the gp41 fusion peptide is exposed and inserts into the host cell membrane which initiates fusion, allowing the viral capsid can enter the cytoplasm (see Section 1.1.3 for more details on the HIV replication cycle) (209,211). Entry inhibitors prevent this initial stage of viral entry by preventing attachment, co-receptor binding, or fusion, therefore this class of HIV treatment is heterogeneous and can be split into multiple categories; attachment inhibitors, fusion inhibitors, and co-receptor inhibitors (166). Attachment inhibitors prevent the attachment gp120 and CD4, co-receptor inhibitors interfere with the interaction between co-receptors CCR5 or CXCR4 and gp120, and fusion inhibitors block gp41 from fusing with the host cell (166).

The only fusion inhibitor that is available for treatment is enfuvirtide (T-20), which was approved in 2003 and is effective in treatment experienced individuals (212,213). Enfuvirtide is infrequently used as it is injected parenterally twice daily, which can be cumbersome and problematic for long-term use (169). Maraviroc is a CCR5 antagonist which was approved for the treatment of treatment naïve and experienced individuals in 2007 (214). There are currently no CXCR4 antagonists or attachment inhibitors that have been approved, however there are a number of entry inhibitors that are in development (214).

1.2 HCV

1.2.1 History of HCV

There is historical evidence of hepatitis being around for thousands of years (215). In more recent years, large hepatitis epidemics occurred during military campaigns such as The American Civil War and World War 2 (215). However, it was not until 1968 that hepatitis B was discovered, and shortly after in 1973 that hepatitis A was discovered (216,217). Serological tests were developed soon after to detect both hepatitis A and B, however these tests did not account for all the cases of hepatitis in individuals with transfusion-associated hepatitis (218). In 1975, researchers believed that there was a third type of hepatitis, which was referred to as non-A and non-B hepatitis (NANBH). However, it was not until 1989 that the researchers at Chiron Corporation closely collaborated with the CDC and identified the hepatitis C virus (HCV) (219,220).

1.2.2 Epidemiology

Hepatitis C is a disease that primarily affects the liver, and is caused by HCV (221). Chronic HCV infection occurs when an individual maintains a state of viraemia for more than 6 months after onset as opposed to clearing the infection (spontaneously or through treatment), and occurs in approximately 75% of people infected with HCV (222–224). HCV is a major cause of chronic liver disease and leads to end-stage liver disease and hepatocellular carcinoma (HCC) in 20-40% of individuals (221,223). However, symptoms of chronic HCV can take decades to develop, therefore in the absence of widespread screening, the diagnosis of HCV tends to happen at late stages of the infection (225).

Chronic HCV infection is a major global health concern, with over 71 million people infected worldwide in 2015 (226). This translates to a global prevalence of 1.0%, however, only 20% of HCV infected individuals have been diagnosed (226,227).

According to the 2017 WHO Global Hepatitis Report, hepatitis C caused approximately 399000 deaths in 2015, mainly due to HCC and decompensated cirrhosis (227). While most studies suggest a decrease in the incidence of HCV since the second half of the twentieth century, there were still 1.75 million new HCV infections in 2015 (global incidence of 23.7 per 100000) (227). There were 843 000 individuals cured of HCV in 2015, therefore while the incidence is decreasing, the global prevalence is increasing as the number of individuals being cured or dying from HCV is lower than the number of new infections (227).

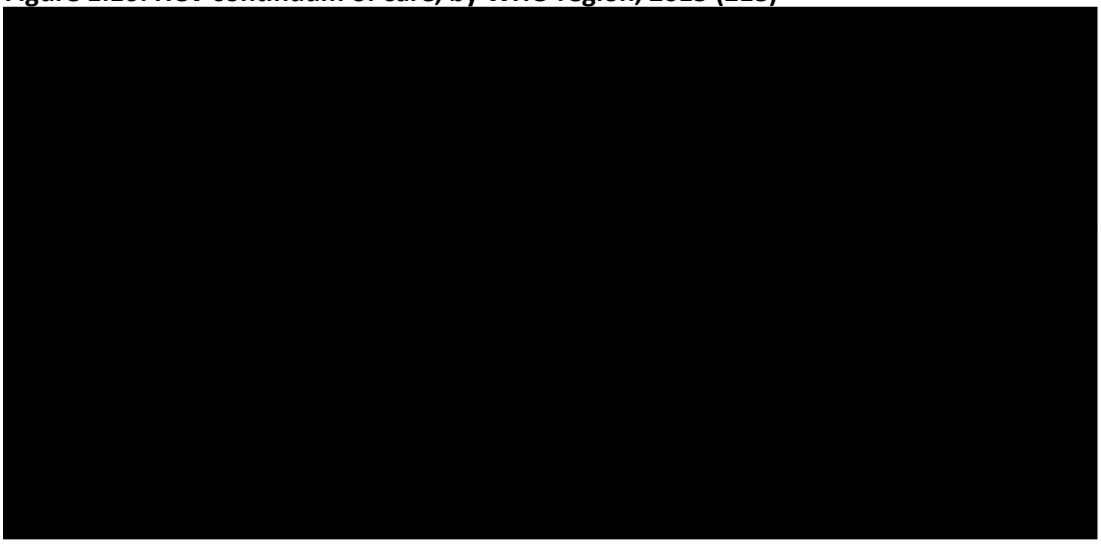
The introduction of highly effective direct-acting antivirals (DAAs) is a big step towards reducing the HCV epidemic, however, access to DAAs needs to be improved (228). The number of individuals who initiated DAA-based therapy increased from 1 million in 2015 to 1.5 million in 2016 (228). However, a small number of countries with large-scale elimination programs were mainly responsible for the increase in treatment uptake, as Egypt and Pakistan accounted for approximately half of the individuals on DAA (228). Globally, the cumulative number of individuals who have received HCV treatment was 5.4 million in 2015, however most of the individuals treated before 2015 received older treatment regimens (interferon-based) which were not as well tolerated and effective (227). It is projected that 80% of individuals who completed HCV treatment in 2015 achieved cure, however there were regional differences that reflect the difference in access to newer treatments (227).

The World Health Assembly's resolutions in 2010 and 2014 highlighted the global commitment to taking action against the HCV epidemic, as did the first World Hepatitis Summit in 2015 (227,229,230). In May 2016, the World Health Assembly endorsed the first Global Health Sector Strategy on viral hepatitis, which aims to eliminate viral hepatitis as a public health threat (231). By March 2017, 43 Member States reported having a national viral hepatitis elimination plan to WHO, with an additional 36 member states also reporting that national elimination plans were under development (227). The WHO set the aim of eliminating HCV as a major public

health threat by 2030, which requires 90% of individuals living with HCV being diagnosed, 80% of diagnosed individuals being treated with DAAs, 65% reduction in hepatitis C related deaths, and reducing new HCV infections by 80% (Figure 1.10) (227). In 2015, only 20% of HCV infected individuals have been diagnosed, and only 7% of diagnosed individuals have started HCV treatment (227). Reaching this ambitious goal requires a huge effort to increase testing, linkage to care and access to effective anti-viral therapy (227).

Widespread access to DAA therapy is a crucial part of the HCV elimination strategy, however the high cost of DAAs means that in most countries universal access to treatment is not feasible (232). In 2017, Lazarus et al. published a paper highlighting the challenges of global elimination, and instead suggested the WHO elimination strategy should be targeted at specific subpopulations (233). They believed it would be more pragmatic to aim for 'micro-elimination' as achieving elimination in a subpopulation would be much quicker and more efficient than attempting to achieve national elimination (233). This approach would also allow more targeted interventions that can be tailored to the needs of the specific subpopulation (233). Some of the target populations they suggest for micro-elimination are PLWH, people with haemophilia, people who have been incarcerated, MSM, and PWID (233). They also suggest micro-elimination could be targeted at certain settings such as hospitals or addiction centres, or geographical areas such as a city or region within a country (233).

Figure 1.10: HCV continuum of care, by WHO region, 2015 (218)



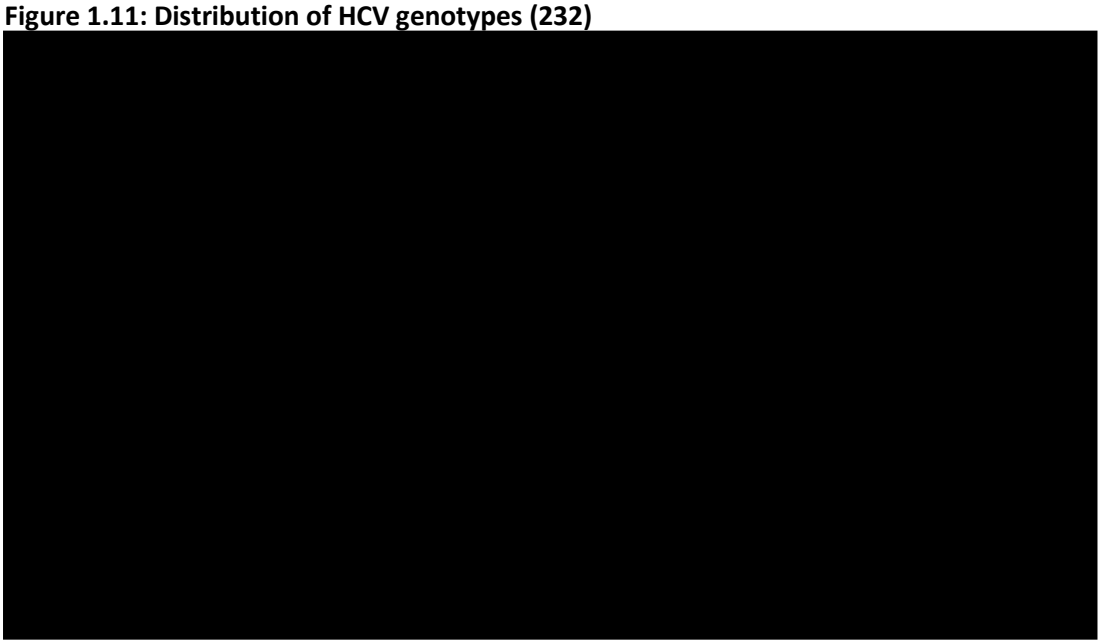
Globally, of those infected with HCV, 5.6 million (8%) are people who currently inject drugs (PWID) (227). As many infections are not diagnosed, unidentified PWID with HCV could cause the epidemic to spread rapidly within the community (232). While there is a high burden of HCV among PWID, there is low HCV treatment uptake (234,235). PWID are known to face barriers when accessing care, therefore adaptive prevention, care and treatment services free from stigma and discrimination are necessary to ensure their engagement with health services (227). A large proportion of individuals living with HCV are former injection drug users or were infected through unsafe health-care-related procedures (227). These individuals have better access to health care than current PWID (227). The risk of a mother with HCV transmitting the virus to her child is 4-8%, and there are no proven interventions to reduce the risk (236). Sexual transmission of HCV is infrequent in heterosexual couples (236). There are regional differences in the main route of HCV transmission, as the main route of transmission in the European Region is injection drug use, however, in the Eastern Mediterranean infection is mainly caused by unsafe healthcare injections (227). A large increase in timely diagnosis, adequate treatment options, improved infection prevention measures in healthcare, as well as improved awareness of HCV through public education is required to reduce the risk of HCV transmission (232).

The burden of HCV greatly varies by region, with the WHO Eastern Mediterranean Region having the highest prevalence at 2.3% (15 million infected) followed by the European Region with a prevalence of 1.5% (14 million infected). The Eastern Mediterranean and European Regions also had the highest rates of new infection in 2015 (incidence rate of 62.5 and 61.8 per 100000 individuals, respectively) (227).

While the prevalence of HCV in the WHO European Region is estimated to be 1.5%, there are major differences within regions and subgroups. A systematic review carried out by the European Centre for Disease Prevention and Control (ECDC) reported that the prevalence of HCV varied from 0.1% to 5.9% across EU/EEA countries (227,237). The rate of infection was lowest in Cyprus (0.1 cases per 100000 population) and highest in Latvia (76.1 cases per 100000) (238). In Europe, HCV was reported almost double the number of times in men than women, and the majority of cases (51.6%) were among 25-44-year-olds (238). Also, 15-80% of HCC events in Europe can be attributed to HCV (239). For the EU to reach the WHO goals by 2030, screening programs need to be increased, as finding and treating HCV early can prevent disease and transmission (239,240).

There are 7 main HCV genotypes and over 67 subtypes which vary based on the route of transmission and geographic regions (Figure 1.11) (232). Genotypes 1, 2, and 3 are distributed across most regions whereas genotype 4 is mainly found in the Middle East and Africa (232). Genotype 5, 6, and 7 are less widely spread and have been reported in South Africa, South East Asia, and Central Africa, respectively (232). There is some evidence to suggest that individuals with genotype 1 are more likely to spontaneously clear the infection, however if they remain HCV-RNA positive the disease progresses more aggressively than other genotypes (232). Genotype 3 is associated with hepatic steatosis, faster progression to fibrosis and a higher incidence of cirrhosis (232,241). While genotype 1 is the most common, non-genotype 1 HCV comprises of more than half of all HCV cases globally (242).

Figure 1.11: Distribution of HCV genotypes (232)



HCV co-infection with HIV is a major issue due to shared routes of transmission (243). In HIV/HCV co-infected populations with access to combination antiretroviral therapy (cART), liver-related death has become one of the leading causes of death (244,245). Of the 36.7 million PLWH globally, an estimated 2.3 million individuals have serological evidence of past or present HCV infection (anti-HCV positive) (227). Of these, 1.36 million are PWID, however, in regions where injection drug use is not the primary route of HIV, the prevalence of co-infection is lower (227,236). The burden of HIV/HCV co-infection is particularly high in Eastern Europe and Central Asia where injection drug use is the main mode of HIV transmission (246). Among HIV-positive individuals, the prevalence of HCV is highest in PWID (82.4%), followed by MSM (6.4%), however, the prevalence of HCV was much lower in HIV-positive individuals without high-risk behaviour (2.4%)

There is evidence to suggest that HIV/HCV co-infected individuals have poorer outcomes than individuals mono-infected with HCV (247,248). However, there is evidence to suggest that co-infected individuals on ART have a similar rate of liver fibrosis progression to HCV mono-infected individuals (247,248). The North American AIDS Cohort Collaboration on Research and Design found that HCV/HIV co-infected individuals who deferred ART therapy had an 85% greater risk of death compared

with those mono-infected with HIV (249). HIV/HCV co-infected individuals are less likely to spontaneously clear HCV, as following acute infection approximately 90% will develop chronic HCV (247). This increased risk of chronic infection is associated with HIV/HCV co-infected individuals having a higher HCV viral load, which is believed to be partly related to the decline in CD4 and CD8 T-cell response to HCV (247). HIV/HCV co-infected individuals are heterogeneous with complicated medical needs and are frequently socially disenfranchised (250).

While sexual transmission of HCV is infrequent in heterosexual couples, it is more common in HIV-positive men (236). This may be due to the sexual transmission or other exposure to blood or drug use (236). There have been several recent outbreaks of HCV among HIV-positive MSM, with one study showing the rate of HCV transmission increased from 0.9-2.2 infections per 1000 person-years in 1990 to 23.4-51.51 infections per 1000 person-years in 2007 (251). While the risk of MTCT is 4-8% in HCV mono-infected individuals, this increases to 10.8%-25% if the mother is co-infected with HIV and HCV (236).

1.2.3 Virology

HCV is a member of the *Hepacivirus* genus which belongs to the *Flaviviridae* family (232). The *Flaviviridae* viral family contains flavivirus, pestivirus, hepacivirus and pegivirus (252). HCV is a small positive strand enveloped RNA virus, however, the virus has not been definitively visualised as it is difficult to analyse the structure of the virus (252). The HCV particles have a spherical morphology, a density between 1.15-1.17 g/ml, and an average outer diameter of 55 nm (253). The viral particle includes the structural core protein (C), and the envelope glycoproteins E1 and E2 (232). The non-structural proteins include p7 ion channel, NS1, NS2 protease, NS3 serine protease and RNA helicase, NS4A polypeptide, NS4B and NS5A proteins and NS5B RNA-dependent RNA polymerase (254). The E1 and E2 proteins from the outer layer of the virion that encompasses the double-layer lipid envelope that surrounds

the viral nucleocapsid (252). The inner spherical nucleocapsid has a diameter of 30-35 nm and contains the genomic viral RNA and the HCV C protein (252,253). HCV has a half-life of only a few hours and production and clearance of an estimated 10^{12} virions per day (255).

The process of the HCV life cycle is complex and not fully understood yet (252). The main target cell of the HCV virus is hepatocytes, however other types of cells can be targeted such as B-cells and dendritic cells (254). The HCV virus attaches to the host cell through an interaction between the cell's surface and receptors on the host cell (Figure 1.12). The CD81 protein, which is found on the surface of many cells, is thought to be the receptor that binds to the virus (256). The cofactor scavenger receptor B type 1 (SR-B1) may also be involved in HCV viral entry as the CD81 receptor alone may not be sufficient (256). Other cellular factors such as claudine-1 and occludin have also been found to be involved in HCV entry into a host cell (257,258).

Once the viral envelope fuses with the receptors, the virus is internalised and the nucleocapsid is released into the cytoplasm (259). The coating of the virus then breaks down and the genomic RNA is released and used for translation and replication (259). The RNA genome is used for translation at the endoplasmic reticulum (260). The resulting single polyprotein precursor has a length of around 3000 amino acid residues and is eventually cleaved by cellular and viral protease into 10 viral proteins that are required for replication (260). The replication process is not well described but takes place in the 'replication complex' which contains non-structural and cellular proteins (259). NS5B is the key enzyme used during replication, however, other non-structural proteins are also important (261). The virus coating is made of protein-based capsomeres which are developed by ribosomes and released (262). Capsomeres assemble around the viral RNA to form a spherical shaped capsid which protects the virus's genetic material (262). The newly formed virus then travels to the cell's membrane and creates a bud (262). The plasma membrane encircles the virus and releases it, providing the virus with a protective lipid coat that it later uses

to attach to another cell (262). This process continues for hours until the cell dies (262).

Figure 1.12: HCV life cycle (252)

1.2.4 Transmission

HCV is a blood-borne virus and has been widely recognised as a parenterally transmitted infection (243). While HCV can be transmitted by sexual contact, it is mainly transmitted by direct blood-to-blood contact (263).

1.2.4.1 Blood-to-blood

Towards the end of the 20th century, HCV was transmitted on a large scale in many low- and middle-income countries (LMIC) due to unsafe health care practices and injecting drug use (264,265). Transmission occurred earlier in HIC, such a Japan, Italy and France, just after the Second World War (227).

Among the possible sources of health-care-associated HCV transmission, such as dialysis, surgery, and dental care, the Global Health Sector Strategy includes blood and injection safety as a core intervention (227). All blood donations should be screened for infection prior to use according to WHO recommendations (266). However, only 66% of blood donations are screened following basic quality procedures in LIC (compared to 99.5% in HIC) (266). Iatrogenic transmission still drives the epidemic in LMIC due to unsafe medical procedures and blood transfusions (267). Unsafe transfusions are not a major source of population-level transmission, however, it remains of particular concern in many LMIC, in settings where the prevalence of HCV is high and the quality of blood screening is inadequate (268,269).

Before the introduction of screening blood donations, approximately 10-20% of individuals who received multiple blood transfusions or blood products seroconverted to anti-HCV positive (270). Therefore, individuals with haemophilia and others in need of blood transfusions were at high risk of developing HCV infection (271). However, as people with haemophilia received clotting factors pooled from multiple donors, they were much more likely to be infected with HCV (and HIV) than individuals without haemophilia that received a blood transfusion (270). Tests to screen blood/blood products for HCV were made available in 1989, which lead to the reduction of HCV transmission through blood transfusion in HIC (272,273). If an enzyme-linked immunosorbent assay (ELISA) test is being used, the infection can be missed if the donor acquired HCV approximately 6 weeks prior to testing, as that is how long it takes for HCV antibodies to appear using an ELISA test (271). The nucleic acid amplification test (NAT) can detect the virus 1-2 weeks after infection; universal screening using NAT was introduced in the USA in 1999 (274,275). Since the introduction of these tests to screen blood, the risk of acquiring HCV through blood transfusion has reduced to approximately one in two million (275).

HCV infected individuals cannot give blood, and can only donate organs to those also infected with HCV (263). The waiting time for kidney transplants can be up to 5 years

in many parts of the USA, however, more than 500 high-quality kidneys are discarded annually (276). The Thinker Trial at the University of Pennsylvania aimed to examine the safety and efficacy of transplanting the kidneys of deceased HCV positive individuals into HCV negative individuals and then treating them with elbasvir + grazoprevir (276). All patients had detectable HCV-RNA after the transplant but were cured (SVR 12 weeks after completing treatment) (276).

There is a risk of HCV transmission for healthcare workers via injuries from sharp objects, or mucous membrane splash injuries, however the risk of transmission through this route is generally very low (275). The rate of transmission depends on the quantity of blood transferred, the concentration of virus in the blood, the depth of the inoculation, and the type of needle (hollow needles transmit more efficiently than solid needles) (270). The incidence of seroconversion after exposure to HCV is generally estimated to be <2%, however, estimates can range from 0-10% (252). Regardless, when a healthcare worker has been exposed to the infection, it is important to test the individual and follow-up with treatment when necessary (277).

While HCV transmission has been declining in Western Europe due to increased standards of blood safety and a decrease in the rates of needle/syringe sharing, there has been an increase in HCV prevalence in Eastern Europe, likely attributable to the increase in injection drug use (237,278). Injection drug use has become the predominant mode of HCV transmission (252). There is also evidence to suggest that the sharing of drug preparation equipment such as cookers, cotton filters, straws and other sniffing paraphernalia used during intranasal cocaine use may also cause transmission (271). However, the risk of transmission through these items is likely less than that for sharing needles and syringes (278). The prevalence of HCV in PWID has been estimated to be as high as 70%, however, there is considerable variation based on region, risk behaviour, and socioeconomic status (279). Harm reduction interventions including the distribution of sterile needles to individuals who inject drugs are inadequate (see Section 1.1.4.2 for more details on harm reduction) (227).

Considering the large population of PWID with HCV, it is important to scale up harm reduction services to reduce the risk of HCV transmission in PWID (227).

1.2.4.2 Mother to child

The advancements made in understanding HCV are not reflected in the pregnant population. The natural history of the virus in pregnant women and infants with HCV is not as well understood as it is in other chronic viral infections (243). Therefore, while there are clear guidelines in place to prevent the vertical transmission of HIV from mother to child, interventions in the HCV setting are not as developed (243). A systematic review found that the effect of the mode of delivery, labour management strategy or breastfeeding practices has not been clearly shown to reduce the risk of HCV transmission (280). The risk of vertical HCV transmission is 2-8% per pregnancy in mono-infected mothers, however, increased maternal viremia increases the risk of transmission (281). This risk of transmission has been found to be maybe two to four times higher in mothers co-infected with HIV (243,282). MTCT of HIV is also more frequent in mothers co-infected with HCV (283,284).

1.2.4.3 Sexual transmission

The risk of sexual transmission is generally low, however the risk may be higher if blood is present, such as menstrual bleeding or minor bleeding during anal sex, or when stimulants such as methamphetamine, mephedrone, or crystal meth are injected in a sexual context (252,285). In monogamous heterosexual couples where one partner has chronic HCV, the rate of transmission to the uninfected partner is very low (243). A large prospective cohort study of 895 serodiscordant monogamous heterosexual couples in Italy found the infection rate to be 0.25 per 1000 person-years (286). Also, increased transmission has not been associated with any particular sex acts among monogamous heterosexual couples, which makes for unambiguous messaging given to couples (243). HCV transmission among HIV positive MSM is becoming more common especially in large cities across Europe, Australia, and the US (287–290). The Swiss HIV cohort found that HCV infection incidence decreased in

PWID, remained stable in heterosexuals, but increased 18-fold in MSM between 1998 and 2011, which highlights the need for more work to improve HCV surveillance in HIV-positive MSM (289). Having a history of injecting recreational drugs in a sexual context has also been associated with HCV infection, which may explain the increase in HCV among HIV positive MSM (252).

1.2.5 HCV disease progression

HCV infection leads to acute hepatitis, and unless the virus is treated or the individual spontaneously clears the infection it can develop into chronic HCV, which can eventually progress to more serious diseases, such as liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (221,224,236,291). Chronic HCV is defined as the persistence of HCV-RNA for at least 6 months after the onset of infection (224). Persistent HCV infection relies on rapid replication of the virus, and an insufficient immune response (292). Chronic HCV is slow to progress, therefore many infected individuals do not develop liver-related complications for many years after infection (293). The speed of progression to liver-related complications varies greatly depending on a number of factors such as alcohol consumption and age at initial infection with HCV (293).

HCV-RNA can be detected from approximately 2 weeks after initial infection, however, seroconversion can take 6 weeks to occur; the development of detectable antibodies may be delayed or on rare occasions never occur in immunocompromised individuals, such as HIV positive individuals (294). As HCV antibodies are present even after clearing the infection, a NAT is necessary to detect the presence of the virus and confirm the individuals current HCV status (236). HCV viral load peaks soon after infection followed by a dip; in those that spontaneously clear HCV, the viral load continues to decrease until viraemia is no longer detectable (295).

Cirrhosis can be either compensated or decompensated; if cirrhosis presents with jaundice, ascites, or encephalopathy then it is considered to be decompensated (296). Decompensated cirrhosis is also associated with oesophageal and gastric varices, and can also lead to life-threatening conditions such as renal failure, sepsis, and bleeding in the gastrointestinal tract due to varices (236). Individuals with untreated chronic HCV have a 15-30% risk of developing cirrhosis within 20 years of acquiring the infection (236). Once an individual develops cirrhosis, the annual rate of HCC is 1-4% per year (297). Individuals who are male, over 55 years old or, with hazardous alcohol use have an increased risk of progression to HCC (267,293). HCV can also cause diseases outside of the liver such as cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance, type 2 diabetes, and skin disorders such as porphyria cutanea tarda and lichen planus (236).

While HCV mainly affects the liver, it can also lead to extrahepatic manifestations (EHM). Approximately 74% of people with HCV will develop a least one EHM, with age, sex and advanced liver fibrosis being the most common risk factors for clinical or biological EHM (298). Autoimmune and lymphoproliferative diseases such as cryoglobulinemia and lymphomas were found to be associated with HCV soon after the discovery of the virus (299). However, since then, there have been reports of HCV causing renal, metabolic cardiovascular, and central nervous system diseases (300). Some common EHMs are mixed cryoglobulinemia, some subtypes of B cell non-Hodgkin's lymphoma, membranoproliferative glomerulonephritis, porphyria cutanea tarda (PCT), and lichen planus (301).

Factors that affect disease progressions:

While the variation in disease progression may not be completely understood, there are a number of factors that have been identified as influencing the progression of HCV. Individuals who were <30 years old when they acquired the infection are 2-3 times less likely to progress to cirrhosis 20 years later (302). However, if an individual

acquired HCV after the age of 40-55, then their progression to liver injury is more rapid (252). Only 2% of immunocompetent subjects infected before age 20 progressed to cirrhosis in 20 years, compared to 63% of those infected after age 50 (303). Faster progression of fibrosis has also been found among individuals with liver transplants from older donors (304). Males with chronic HCV are reported to have faster progression to cirrhosis than females, also nearly 70% of liver transplant recipients for HCV were male (305,306). This difference could be partially explained by oestrogen altering hepatic fibrogenesis by inhibiting the activity of the hepatic stellate cell, which is a major cell involved in liver fibrosis (307). African Americans with chronic HCV have higher rates of HCC, lower response rates to interferon treatment and higher liver-related mortality than white individuals (307). However, African Americans are less likely to progress to cirrhosis, have lower alanine aminotransferase levels and lower activity on their biopsy scores, therefore the increased liver-related mortality could be due to racial disparities in the treatment of patients with HCV (307,308).

As mentioned before, not all individuals with acute HCV will become chronically infected. This progression is extremely variable and depends on a variety of factors. The immune response to HCV is important to determine the outcome of acute HCV and long-term disease progression HCV (243). There is genetic evidence to suggest that the interferon-λ3 and interferon- λ4 gene, formally known as interleukin-28B (IL28B), impacts the likelihood of the spontaneous clearance of HCV (309,310).

Being co-infected with HIV negatively impacts the course of HCV progression. Individuals who are HIV/HCV co-infected are less likely to spontaneously clear HCV, as following acute infection approximately 90% will develop chronic HCV (247). This increased risk of chronic infection is associated with HIV/HCV co-infected individuals having a higher HCV viral load, which is believed to be partly related to the decline in CD4 and CD8 T-cell response to HCV (247). HIV/HCV co-infected patients are also three times more likely to develop cirrhosis or liver decompensation than those HCV

mono-infected (311). In the absence of ART, co-infected individuals also have a faster progression to cirrhosis and liver disease, especially if their CD4 count is <200 cells/mm^3 (227,244,248). The effect of HCV on HIV is less clear. An analysis carried out among 2235 HIV positive individuals who were part of the Swiss HIV cohort study and started HAART between 1996 and 1997 found that in the first year of HIV treatment, individuals co-infected with HCV had smaller increases in their CD4 count than HCV seronegative individuals (312). However, the EuroSIDA Cohort Study did not find any evidence of HCV negatively impacting HIV disease progression (313).

Fibrosis Markers

Liver fibrosis occurs as a result of chronic damage to the liver. Tissue damage healing is considered the response to chronic liver injury, which causes excessive accumulation of extracellular matrix proteins (314). These proteins damage the liver by forming scars, which later develop into nodules that define cirrhosis and can lead to hepatic insufficiency (314). Figure 1.13 shows the natural history of the HCV mono-infection if left untreated. The risk of cirrhosis in untreated individuals with chronic HCV is 15-30% within 20 years (302). Once an individual has cirrhosis the risk of hepatocellular carcinoma (HCC) is 2-4% per year, although rates up to 7% have been reported in Japan (297). The yearly rate of decompensated cirrhosis among HCV positive individuals with cirrhosis is 4% (315). HCV is one of the leading causes of liver-related morbidity and mortality, therefore staging of fibrosis is vital for management and prognosis of individuals with HCV (316).

Figure 1.13: Natural history of chronic HCV (236,315)

Fibrosis staging is important for HCV infected individuals as it identifies those who are in need of enhanced monitoring and prioritisation of treatment before they develop decompensated cirrhosis (236). The METAVIR system is the most widely used biopsy-scoring method, which ranks fibrosis as F0 (no fibrosis), F1 (mild fibrosis), F2 (significant fibrosis), F3 (advanced fibrosis), or F4 (cirrhosis) (296,317). A liver biopsy is the gold standard test for measuring liver fibrosis, however, it is an invasive procedure that can cause pain (20%) or major complications (0.5%) (318). There is even a small risk of procedure-related mortality, with a mortality rate of 0.009-0.12% (319). The liver biopsy is considered to be an imperfect gold standard due to a number of issues with the accuracy of the liver biopsy (320). There is variability in the distribution of fibrosis across the liver; however biopsies only sample a very small part, and the length of the biopsy specimen is significantly associated with the accuracy (321). Bedossa et al. reported that using the METAVIR scoring system, 65% of biopsies 15mm in length were categorised correctly, while 75% were categorised correctly if the specimen was 25mm (321). Also, even when the optimal sample is achieved, there is still a small risk of inter and intra-observer bias (322).

The drawbacks of using liver biopsy to determine fibrosis stage have led to the development of non-invasive methods (316). Laboratory test results and an algorithm generated from factors that are associated with fibrosis such as age can be used as a non-invasive method for evaluating the stage of fibrosis (323). Non-invasive

markers are cost-effective, can be carried out at frequent intervals, and some have a high prognostic value, making them an appealing alternative to a liver biopsy (293,316). Due to the accessibility of the aspartate aminotransaminase (AST)/Platelet Ratio Index (APRI) ($APRI = \frac{\frac{AST\ level\ (IU/L)}{AST\ (Upper\ Limit\ of\ Normal)(IU/L)} X100}{Platelet\ Count\ (10^9/L)}$) and FIB-4 tests ($FIB4 = \frac{Age \times AST\ Level\ (IU/L)}{PLatelet\ Count\ (10^9/L) \times \sqrt{ALT\ (IU/L)}}$), they are recommended for the assessment of liver fibrosis and cirrhosis by WHO in resource limited settings (236). Compared to liver biopsy, a meta-analysis found that the APRI score cut-off of 2.0 for diagnosing cirrhosis has a sensitivity of 46% and a specificity of 91% (323). These tests are not able to accurately assess all stages of fibrosis or cirrhosis, for example, APRI has been validated for the diagnosis of significant fibrosis (≥F2) and cirrhosis (F4) (236,316). However FIB-4 test has only been evaluated for the diagnosis of fibrosis (≥F2) (236,316). The best non-invasive method for assessing the level of fibrosis and cirrhosis is the Fibroscan test, which is based on ultrasound technology using transient elastography to examine liver stiffness and assess the level of fibrosis and cirrhosis (236). The Fibroscan test has better diagnostic accuracy for detecting advanced fibrosis and cirrhosis than the APRI score and FIB-4, however there is a lack of validated cut-off values for all stages of fibrosis. Also, the cost of the equipment and need for regular recalibration and trained operators makes the Fibroscan less accessible in low-income settings (236).

1.2.6 Treatment of HCV

The main goal of treating HCV is achieving a sustained virological response (SVR) which indicates that HCV therapy has successfully cured the HCV infection (243,324). SVR is defined as an undetectable HCV-RNA at least 24 weeks (SVR24) after treatment completion of an interferon-based regimen or 12 weeks (SVR12) after treatment completion if on an interferon-free DAA regimen (311). Both SVR12 and SVR24 are acceptable endpoints approved by regulators in the USA and Europe given that their concordance is over 99% (325). Achieving SVR has been associated with significant improvement in mortality, liver histology, many other clinical outcomes in

comparison with individuals who do not achieve the same clinical milestone, as eradication of HCV reduces the progression of liver disease, liver-related and all-cause mortality (324,326–328). The rate of relapse after achieving SVR is very low, with 99% of individuals remaining infection-free 5 years after achieving SVR which suggests achieving SVR is indicative of curing HCV (324,329,330).

Interferon was originally found to treat HBV, a pilot study was later conducted in 1986 at the National Institutes of Health to test the effect of interferon on HCV (then NANBH) (331). The results of this study led to further trials with mid-sized control groups which confirmed the positive effect of interferon (332,333). Three million units of interferon were administered by subcutaneous injection 3 times a week, and while roughly one-third of patients responded to treatment, many relapsed which meant the SVR rate was approximately 6% (Figure 1.14) (332,333). Trials followed which aimed to establish the appropriate dose and treatment length, and increasing treatment length to 48 weeks raised SVR rates to 16% (334). Treating HCV with ribavirin was found to reduce alanine aminotransferase (ALT) levels, however, had no significant effect on HCV-RNA levels (335). Later ribavirin was found to improve SVR rates when combined with interferon (336). Pegylation was used to improve the half-life of interferon, and taking pegylated-interferon (PEG-IFN) once a week was found to be more effective than taking interferon 3 times a week (337). Studies showed taking PEG-IFN in combination with ribavirin was better than interferon plus ribavirin (338). A Cochrane review published in 2014 examined the difference between using PEG-IFN + ribavirin vs interferon + ribavirin (339). They found that PEG-IFN + ribavirin significantly increased the proportion of patients achieving SVR compared to those taking interferon + ribavirin (50.2% compared with 38.5%), however there was insufficient evidence to suggest PEG-IFN + ribavirin improved liver-related mortality in comparison to interferon + ribavirin (339). There was also evidence to suggest that taking PEG-IFN + ribavirin increased the risk of certain adverse events (339).

For many years HCV treatment was comprised of PEG-IFN and ribavirin for all genotypes and was taken for up to 48 weeks (243). PEG-IFN has a very poor side effect profile, can be difficult to tolerate and only results in SVR in 50% of patients. However, there is variation in SVR rates depending on HCV genotype, as those with genotype 1 do not respond as well to interferon as those with genotype 2 or 3 (254). Interferon-based regimens have even lower SVR rates and are more difficult to tolerate in individuals co-infected with HIV (248). Trials reported SVR rates between 27-44% depending on the HCV genotype in co-infected individuals treated with PEG-IFN (340–343), and a real-world study carried out in Spain found a similar result (31% - 33%) (344). Due to the lower odds of achieving SVR, and an increased number of adverse events (AEs), HIV/HCV co-infected individuals with milder levels of fibrosis were infrequently treated in the interferon era, preferring to wait for improved treatment options (345).

Figure 1.14: Development of HCV therapy (322)

However, the HCV treatment landscape has been revolutionised with the introduction of DAAs (243). Interferon was initially combined with DAAs, however now IFN-free combinations of DAAs are being used to treat HCV (346). During the interferon era, SVR rates were lower in co-infected individuals, however, treatment with DAAs leads to similar rates of SVR in mono and co-infected individuals (347). While DAAs can cure HCV, there is uncertainty about their ability to reduce the overall population burden of liver disease, as many individuals with chronic HCV are undiagnosed and transmission of HCV is increasing (348). There is a vaccine for other forms of viral hepatitis (hepatitis A, B, and E virus) however there is currently no HCV vaccine available (348). There are a number of vaccines under development, which would go a long way in controlling the HCV epidemic (348). Given the high cost of DAAs, an HCV vaccine could still be an important intervention to help reduce the transmission of HCV (349).

Major advances in the understanding of HCV virology led to a better understanding of the key HCV enzymes and the steps involved in the HCV lifecycle (350). Of the 10 viral proteins that are cleaved from the one polyprotein formed during the replication cycle, 4 have been found to be good targets for DAAs (351). DAAs are taken orally and treatment duration is usually between 8-12 weeks, however in some more complicated cases treatment duration can increase to 24 weeks (188). There are currently 13 different DAAs (351). All HCV infected individuals should be considered for treatment, however the regimen used depends on the HCV genotype, prior treatment history, pre-existing viral mutations, natural history and stage of disease, and evaluation of conditions that may affect therapy (352).

The first DAAs to be developed were NS3/4A protease inhibitors (PIs). NS3-dependent cleavage of the HCV polyprotein is necessary to form mature proteins, therefore, inhibiting NS3 protease activity can block RNA replication (353). The first generation PIs, boceprevir and telaprevir were taken with PEG-IFN and ribavirin and found to improve the response in individuals with genotype 1 (354,355). However,

boceprevir and telaprevir, are no longer recommended due to adverse events and low cure rates and have been discontinued as there are newer PIs that have superseded these drugs (236,351). PIs generally have a low resistance barrier (in monotherapy), multiple drug interactions, hepatic side effects, and are used in genotypes 1 and 4 (351). Second generation PIs are better tolerated and have improved efficacy. Two new PIs, voxilaprevir and glecaprevir, were recently approved and can be used to treat any genotype (351).

The amplification of the HCV genome by the RNA polymerase NS5B is a crucial step in the HCV life cycle (356). This enzyme can be inhibited by nucleos(t)ide and non-nucleos(t)ide analogues, therefore the NS5B drug class is further divided into nucleos(t)ide (NS5B-NI) and non-nucleos(t)ide inhibitors (NS5B-NNI) (356). NS5B-NIs work by providing false substrates for the polymerase leading to premature chain termination (356). Sofosbuvir, the only NS5B-NI currently available, has high efficacy, resistance barrier, tolerability and is pan-genotypic (351). NS5B-NNIs block the polymerase function by binding to four sites outside the catalytic site, which results in a lower barrier to resistance (351,356). The only NNI approved is dasabuvir, and while it is not as effective as sofosbuvir, it can be used as part of a multiple drug regimen with ritonavir-boosted paritaprevir (NS3/4A PI) and ombitasvir (NS5A inhibitor) against genotype 1 (356).

The membranous web is a specific subcellular structure that hosts HCV replication, translation, and processing of viral proteins (356). The NS5A protein is required for the formation of the membranous web, replication of HCV-RNA, and assembly of virions (356). NS5A inhibitors block HCV-RNA synthesis at the membranous web development stage and impair viral assembly by stopping the delivery of HCV genotypes to assembly sites (357). There are currently 6 approved NS5A inhibitors, and despite their high efficacy, pan-genotypic activity and little drug-drug interactions, problems can arise due to varying resistance barriers (351). While they

are highly potent drugs, in comparison to protease and polymerase inhibitors they are slower at preventing HCV-RNA synthesis (357).

Guidelines from the American Liver Association for the Study of Liver Diseases (AASLD) with the Infectious Disease Society of America (IDSA), the European Association for the Study of the Liver (EASL) and the European AIDS Clinical Society (EACS) have been published on the screening, treatment, and management of HCV patients (188,358,359). The WHO also published guidelines in 2016 which can be applied to any country, but is mainly targeted towards policy-makers in LMIC (236). All guidelines recommended that individuals with active HCV infection are considered for HCV treatment (188,236,358,359). EASL guidelines recommend considering all patients with HCV-associated chronic liver disease for treatment, and immediate HCV therapy for those with significant fibrosis or cirrhosis, extrahepatic manifestations, recurrence after liver transplant, and individuals with high-risk behaviours that are at risk of transmitting the virus (359). EASL also do not recommend treatment for patients with limited life expectancy, which is in line with the AASLD/IDSA guidelines (358,359). The WHO recommends the use of interferon-free regimens, however they recommend sofosbuvir + PEG-IFN + ribavirin as an alternative treatment option for individuals with genotype 3 and cirrhosis, and individuals with genotype 5 and 6 with or without cirrhosis (236).

HCV treatment uptake and efficacy were low during the interferon (IFN) era, especially among PWID and HIV positive MSM (278). The introduction of tolerable and highly-effective IFN-free DAAs has led to an increase in treatment uptake and cure, and may subsequently lead to a decrease in reinfection rates in high-risk groups by reducing the number of infectious individuals (278). Modelling studies suggest treating those at the highest risk of HCV transmission could reduce HCV incidence and prevalence (360,361). Studies among HIV positive individuals in Switzerland and the Netherlands both showed prompt and unrestricted access to HCV treatment can lead to a 50% reduction in HCV incidence (362,363). HIV and HCV treatment

guidelines recommend treatment of all HCV infected individuals (in particular, PWID and MSM) which could lead to a reduction in HCV transmission, however, not all countries in Europe are following these guidelines (364–367). A review of restrictions for reimbursement of DAA therapies between November 2016 and August 2017 in European countries (n=35) found that 6 (17%) countries, mainly in Eastern or Southern Europe, required abstinence from drug use or alcohol use (366). Also, 16 (46%) countries across all regions of Europe restricted DAAs to people with significant liver fibrosis (liver fibrosis ≥ METAVIR stage F2) (366). While the uptake of DAAs in Europe since 2014 has been increasing over time, there is still a significant difference in treatment uptake across the region, which is mainly due to the high cost of the drugs and limited access in certain patient groups (368). Also, the concerns around reinfection can prevent some clinicians from treating HCV in individuals from high-risk groups, mainly PWID (369).

Some countries, such as Georgia, have introduced a national program to reduce HCV prevalence by aiming to diagnose and treat all individuals with chronic HCV (370). However, there are certain settings that impact access to treatment, for example, in HIC many individuals at risk are PWID who might not access health care in the same way (371). The cost of DAAs is also too high for many countries with high HCV prevalence (371). The high cost of DAAs is one of the main limiting factors of increasing access to treatment, however steep price reductions have been achieved since 2015 (Figure 1.15) (228). This was mainly due to increasing competition from generic drug manufacturers (228). Globally 60% of individuals with HCV are living in countries that can produce affordable generic drugs (228). However, DAA prices are still unaffordable in many upper-middle and high-income countries, which is hindering equitable access to treatment (228).

Figure 1.15: Lowest price of sofosbuvir in low- and lower-middle-income countries, per 28 day supply, 2015-2017 (228)

While antivirals can cure HCV, they do not protect against reinfection (371). In the absence of a vaccine against HCV, those who have been cured are still at risk of reinfection (372). Recurrence of HCV can be due to a late relapse or reinfection, both of which reverse the benefits of achieving SVR (373). Data from human and chimpanzee studies of primary HCV infection suggest that previous HCV infection can provide some protection against persistent HCV reinfections (374). HCV infected individuals in Scotland were followed-up after achieving SVR, and the risk of reinfection was found to be low, however, reinfection is of particular concern among PWID and MSM (375,376). As the cost of DAA treatment is high, the risk of reinfection can cause some reluctance among physicians to treat PWID (375). A meta-analysis of studies analysing HCV reoccurrence 5-year post-treatment also found that SVR rates remained high (373). Co-infected individuals had a higher recurrence rate which was driven by reinfection rather than relapse (373). A recent study carried out across 8 centres in Western Europe retrospectively analysed HCV reinfections that occurred between 2002 and 2014 among 606 HIV positive MSM who cleared HCV (377). They reported an increase in reinfection rates after each subsequent reinfection among

HIV/HCV co-infected MSM (377). Therefore, as well as increasing access to HCV treatment, it is also important to target interventions at reducing high-risk behaviours to reduce HCV incidence (372).

Guidelines from the WHO, AASLD/IDSA, EASL and EACS all recommend prioritising the treatment of HCV in HIV/HCV co-infection individuals (188,236,358,359). Guidelines also recommend that HIV/HCV co-infected individuals are treated the same as HCV mono-infected individuals (188,236,358,359). DAAs have been shown to cure 91-100% of HIV/HCV co-infected individuals in clinical trials (347). However, drug-drug interactions exist between some DAAs and HIV antivirals such as efavirenz, nevirapine, lopinavir, ritonavir elvitegravir and cobicistat, therefore patients may need to switch their ARVs before starting HCV treatment (351,378). The interactions between DAAs and antiretrovirals occur due to the shared metabolic pathway via cytochrome P450, which can lead to drug concentrations increasing which causes toxicity or decreasing and causing virological rebound (379). Therefore, DAAs with strong inducers of the cytochrome P450 3A family and p-glycoprotein, such as PIs simeprevir and paritaprevir, are not recommended to be used in co-infected individuals (351,356). Potential drug interaction must be considered before starting HCV therapy to minimise risks (378). A cohort study found that sofosbuvir combined with an NS5A inhibitor to be the most suitable regimen to be co-administered with ART (379).

Chapter 2 Methods

2.1 Thesis aims

As described in Chapter 1, there are many challenges facing people living with HIV and HCV co-infection. As HIV and HCV are both blood-borne viruses with shared transmission routes, there are many individuals living with HIV and HCV co-infection (380). Following the introduction of effective cART, AIDS-related mortality has decreased, and as HIV positive individuals are living longer, issues surrounding HCV co-infection have become more prevalent (381). In the absence of ART, individuals co-infected with HIV are 3 times more likely than HCV mono-infected individuals to develop cirrhosis or liver decompensation (382). Therefore HCV co-infection has become a major public health concern globally and in Europe (227). The introduction of safe and highly effective DAAs in 2013 drastically improved the HCV treatment landscape and significantly helps to tackle the global burden of HCV (351). In 2016 the WHO adopted the Global Health Sector Strategy plan, committing to eliminating HCV by 2030 (227,231). This requires a 90% reduction in HCV incidence and a 65% reduction in HCV-related mortality compared to the 2015 baseline (227).

The aim of this thesis is to improve our understanding of the priority areas for action to achieve elimination 2030, by describing the epidemiologic characteristics of HIV/HCV co-infected individuals in Europe and identifying barriers to achieving optimal clinical outcomes. There are four results chapters included in this thesis (Chapters 3 to 6), each one providing useful information to help monitor progress towards the WHO goals and which also highlight areas that need work to achieve elimination by 2030. The aims and rationale of each analysis have been described in the specific chapters, however, below is a brief overview of the aims of each of the results chapters:

Chapter 3: Regional differences across Europe in advanced fibrosis and cirrhosis among HIV/HCV co-infected individuals, between 2010-2018

Liver-related deaths are the second most common non-AIDS related cause of death (after non-AIDS defining cancers) (383). Therefore, describing the burden of fibrosis is important to improve the management of individuals living with HIV/HCV co-infection. However, the burden of fibrosis has not been well described in Europe, with many studies having strict inclusion criteria or small sample size. The aim of this analysis was to explore the change in advanced fibrosis over time between 2010 and 2018, and also describe factors associated with having advanced fibrosis

Chapter 4: Establishing a cross-sectional and longitudinal hepatitis C continuum of care among HIV/HCV co-infected individuals in EuroSIDA

The CoC is a useful tool that is widely used to describe how PLWH transition through care. However, the CoC model can also be applied to other disease areas and is a very useful method to describe the movement of HCV positive individuals from diagnosis, to treatment, to cure (384). The literature on the HCV CoC lacked a standardised methodology, which created issues around comparability. Therefore, the aim of this chapter was to develop a cross-sectional and HCV CoC, to describe how HIV/HCV co-infected individuals transition through HCV care. While the cross-sectional CoC is a very useful tool, there are a few limitations with this method, mainly, only being able to see where individuals are at one point in time and not being able to formally explore changes over time. Therefore, another aim of this chapter was to develop a longitudinal method to explore the HCV CoC, based on the methodology developed by Jose et al. to express the HIV CoC longitudinally (385). Both the cross-sectional and longitudinal methodologies were applied to the EuroSIDA study at different time points to describe how people living with HIV/HCV co-infection transitioned through care before and after widespread access to DAA therapy, and how this varied for different regions in Europe

Chapter 5: Effectiveness and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected individuals: Results from a pan-European study

While there are many clinical trials highlighting the high efficacy and safety of new DAA treatments, results from real-world studies are limited. Real-world data is important as clinical trials tend to include a highly selective group of individuals who have better outcomes than the general population (386). This chapter aimed to explore the proportion of individuals who achieved SVR12 after being treated with an IFN-free DAA regimen and to determine the prevalence and reasons for premature discontinuation of DAA treatment. Treatment side effects and factors associated with achieving SVR12 were also explored. Finally, the change in laboratory values over time was described based on different factors.

Chapter 6: HCV reinfection among HIV/HCV co-infected individuals in Europe

In the era of new effective DAA treatment, curing HCV is possible in over 90% of HIV/HCV co-infected individuals (see Chapter 5). However, as no vaccine has been developed for HCV, reinfection is still possible after achieving SVR. Clearance of some viruses, such as hepatitis A, can provide lasting immunity against reinfection (387). However, spontaneously clearing HCV does not protect against reinfection (374). While there are some studies exploring reinfection after SVR, they were mainly carried out in the IFN era. The aim of this chapter was to describe the proportion of individuals who were reinfected after achieving SVR or spontaneously clearing HCV and explore factors associated with reinfection after achieving SVR.

2.2 The EuroSIDA study

The analysis carried out in this thesis is based on data from the EuroSIDA study (https://chip.dk/Studies/EuroSIDA), which is a large ongoing prospective observational cohort study that began enrolling HIV-1 positive patients in May 1994. In the summer of 2016 there was data on over 23071 HIV-positive individuals aged

16 or older enrolled into the study, which contributes to 174481 person-years of follow-up (PYFU) (388). There are around 100 participating centres in 35 European countries, Israel and Argentina. These countries are commonly categorised into 5 regions of Europe (Figure 2.1). The number of centres in each country and region can be seen in Table 2.1.

Figure 2.1: Map of countries* and regions† in EuroSIDA

Table 2.1: Countries and regions in EuroSIDA (n centres)

South (n=20)	Central-West (n=23)	North (n=21)	Central-East (n=16)	East (n=16)
Argentina (n=1)	Austria (n=2)	Denmark (n=6)	Bosnia-Herzegovina (n=1)	Belarus (n=3)
Greece (n=2)	Belgium (n=3)	Finland (n=1)	Croatia (n=1)	Estonia (n=2)
Israel (n=4)	France (n=4)	Iceland (n=1)	Czech Republic (n=2)	Georgia (n=1)
Italy (n=5)	Germany (n=7)	Ireland (n=1)	Hungary (n=1)	Latvia (n=1)*
Portugal (n=3)	Luxembourg (n=1)	Netherlands (n=1)	Poland (n=7)	Lithuania (n=2)
Spain (n=5)	Switzerland (n=6)	Norway (n=1)	Romania (n=2)	Russia (n=5)
		Sweden (n=3)	Serbia (n=1)	Ukraine (n=3)
		United Kingdom (n=7)	Slovakia (n=1)*	
			Slovenia (n=1)	

Central-East and Eastern Europe are sometimes combined when there is not enough data
*Not currently contributing data

The EuroSIDA study was established by Professor Jens D Lundgren in 1994. It was the successor of The AIDS in Europe Study, which aimed to determine factors associated with HIV-related mortality (389). They collected information on 6655 individuals with an AIDS diagnosis between 1979 and 1989 from 52 participating centres across 17 European countries (389). Improvements in HIV treatment (described in Chapter 1, Section 1.1.6) resulted in significantly improved survival among people living with HIV (PLWH), which led to the diversification of the cohort. While the main aims of the EuroSIDA study have remained the same, the study has grown and adapted to meet the changes in the HIV research field. Currently, the 4 main objectives of the study are (388):

1) Monitoring and safety of ART
2) Monitoring current or emerging late-onset adverse events
3) Monitoring temporal changes and regional differences in HIV care and management across Europe
4) Monitoring uptake and outcomes of HCV therapy, particularly DAAs

The EuroSIDA study contributed data to a number of other collaborative cohort studies, such as COHERE (Collaboration of Observational HIV Epidemiological Research in Europe) and D:A:D (Data collection on Adverse events of anti-HIV Drugs), both of which have now stopped data collection. EuroSIDA is also a founding partner of RESPOND (The International Cohort Consortium of Infectious Disease), which is a multi-cohort observational study (more details found here: https://chip.dk/Studies/RESPOND/About).

To date, EuroSIDA has published over 300 manuscripts (including those in collaboration with other cohorts) in peer-revived journals (h-index 52), details of which can be found at: https://chip.dk/Studies/EuroSIDA/. Finding from this study have also contributed to European HIV treatment guidelines.

2.2.1 Coordination

The study is coordinated by the Coordinating Centre based at the Centre of Excellence for Health, Immunity and Infections (CHIP) at Rigshospitalet, Copenhagen, Denmark. The statistical centre for EuroSIDA is based at the UCL Royal Free Hospital in London and has very close links with the Coordinating Centre in Copenhagen.

Each participating centre that contributes data has a principal investigator, who has a number of responsibilities, including obtaining and maintaining ethical approval, and enrolling patients, and obtaining informed consent forms from them. The EuroSIDA study is led by the steering committee, which is made up of principal investigators from participating centres across Europe. The members of the steering committee are elected every 5 years. There are currently 17 individuals on the steering committee, including the chair (Gilles Wandeler) and co-chair (Roger Paredes) who were elected by the steering committee. The committee communicates via teleconference approximately every 2 months and face-to-face at least once a year at a HIV conference (before the COVID-19 pandemic). During these meetings, they discuss current projects, new proposals, and the general running of the study. A full list of the EuroSIDA study group can be found in Appendix I.

The main responsibilities of the steering committee are to acquire funding and to approve research proposals. Research proposals (https://chip.dk/Studies/EuroSIDA/Submit-research-concept - Appendix II) can be submitted to EuroSIDA by a member of the study group or an external collaborator. All proposals go through a rigorous review process, which includes feasibility checks carried out by a member of the statistical centre. A minimum of 2 members of the steering committee is also required to independently review each proposal, which is then be discussed at the next steering committee meeting. Before the proposal is approved, changes or queries from the steering committee must be addressed. Also, depending on the project, funding may need to be provided by the individual

proposing the study (further project proposal details can be found here: https://chip.dk/Studies/EuroSIDA/Submit-research-concept).

2.2.2 Enrolment/recruitment

Recruitment at EuroSIDA is ongoing to ensure the study population is representative of the HIV population in Europe. Cohorts are enrolled at regular intervals, and to date, 10 patient cohorts have been recruited. An 11th cohort started enrolment at the end of 2019 and plans to include approximately 2000 HIV positive individuals, regardless of their HCV status. To ensure that participants with irregular follow-up are not excluded from the study, consecutive enrolment of unselected individuals is recommended. For each cohort, a predefined number of patients were enrolled from each site. Individuals enrolled in cohorts I-III were required to have a CD4 count of <500 cells/mm^3 in the 4 months prior to entry, however, this was not a criterion for the following cohorts. Participants from Central-Eastern Europe were first enrolled into the study in 1999 (cohort IV) from collaborating centres in the Czech Republic, Hungary and Poland, and participants from Eastern Europe were enrolled from cohort V. In an attempt to increase the limited amount of data from Eastern Europe, half of the individuals enrolled from cohort VI onwards were from Eastern Europe. This drive to include more data from Eastern Europe was to provide a clearer description of the increasing epidemic in East Europe and to ensure all regions of Europe were represented in EuroSIDA. Individuals in cohorts I to IX were enrolled irrespective of HCV status, however, HIV positive individuals enrolled in cohort X were also required to be anti-HCV positive (HCV-RNA positive or negative). Cohort X was enrolled from June 1st 2014 until December 31st 2016, and during this time, 4039 consecutive patients were enrolled into cohort X. The number of individuals enrolled in each cohort can be seen below in Table 2.2.

Table 2.2: Summary of individuals included in each cohort

Cohort	Number of people	Date of enrolment
I	3115	Spring 1994
II	1364	Winter 1995
III	2837	Spring 1997
IV	1225	Spring 1999
V	1223	Winter 2001
VI	2118	Winter 2003
VII	2458	Winter 2005
VIII	2254	Summer 2008
IX	2500	Spring 2012
X	4039	Summer 2014
XI	Still enrolling	Commencing winter 2019

2.2.3 Data collection

Data are collected prospectively at clinical sites, which are responsible for maintaining ethical approval and obtaining informed consent from all patients according to local regulations (as mentioned above). Since 2014 EuroSIDA has collected data using electronic forms through the Research Electronic Data Capture (REDCap) system. There are some centres that submit all their data, or just lab data, in an Access File in the HIV Cohorts Data Exchange Protocol (HICDEP) format (390). Prior to this data were collected on paper forms. The data is sent to the EuroSIDA coordinating centre at CHIP at 12-month intervals (data were previously sent every 6-months prior to 2017). Data collection forms are completed at enrolment, and then once a year to standardise data collection. EuroSIDA is a non-interventional study, which therefore collects data at routine clinic visits. Table 2.3 provides an outline of the data collected by EuroSIDA.

Table 2.3: Summary of data collected by EuroSIDA

Demographics	Date of birth
	Gender
	Race
	Cohort
	Centre ID
	Country of origin

	Region of Europe
	Mode of HIV infection
	Mode of HCV infection
Basic clinical information	Date of visit
	Height
	Weight
	Blood pressure
	Smoking status
	Alcohol abuse
	Injecting drug use
	Pregnancy
	Family history of MI
	Hospitalisation*
HIV	HIV-RNA
	CD4 count
	CD8 count
	HIV subtype
	Resistance testing*
HIV treatment	Start and stop dates
	Reason for discontinuation
	Adherence rating*
	Hypersensitivity reaction and liver toxicity to integrase inhibitor†
Hepatitis	Anti--HBs
	HBV surface antigen (HBsAg)
	HBV DNA
	HCV antibody
	HCV-RNA
	HCV genotype and subtype
HCV treatment	Start and stop dates
	Start and stop dosage*
	Reason for discontinuation
	Laboratory values during treatment*
	AEs associated with HCV treatment*
Laboratory values	Alanine aminotransferase
	Aspartate aminotransferase
	Alkaline phosphatase
	Bilirubin
	Glucose
	Haemoglobin
	INR
	Leukocytes*
	Platelet count
	S-creatinine
	S-lactate*
	S-amylase*
	Serum HDL cholesterol
	Serum total cholesterol

	Serum triglycerides
Other tests	Liver biopsy
	Fibroscan elastography
	Hyaluronic acid‡
	APRI (calculation)
	FIB-4 (calculation)
Cancers	Date and diagnosis of AIDS-defining cancer
	Date and diagnosis of non-AIDS defining cancer
AIDS-defining event	Date of AIDS onset
Liver-related events‖	Ascites
	Severe hepatic encephalopathy (grade III or IV§)
	Hepatorenal syndrome
	Oesophageal variceal bleeding
	Liver decompensation
	Hepatocellular carcinoma (HCC)
Other clinical events‖	Cardiovascular disease (CVD)
	Diabetes
	Pancreatitis
	Renal disease
	Lactic acidosis*
	Avascular necrosis*
	Bone fractures
	Lipodystrophy*
	Date and diagnosis of non-AIDS malignancies
Other treatments	Start and stop dates of medication to prevent/treat opportunistic infection
	Start and stop dates of medication related to CVD
Death	Death date
	Cause of Death (CoDe) form

*No longer collected
†Collected from D43 (2015) for a sub-study, no longer collected
‡Centrally tested individuals who were anti-HCV positive with data stored in the plasma sample repository
‖The EuroSIDA study uses standardised clinical event definitions, which can be found in the Manual of Operations (MOOP) for Clinical Events document on the EuroSIDA Study Documents webpage (https://chip.dk/Research/Studies/EuroSIDA/Study-documents)
§According to West Haven Criteria (391)

2.2.4 Quality Assurance

The coordinating centre has established an extensive quality assurance system that has been in place since the initiation of the EuroSIDA study. The coordinating centre regularly carries out data checks, verification of all new clinical events, and queries centrally. Previously, the coordinating centre would carry out on-site monitoring of the different centres, and all clinical events were checked against individual case notes by the coordinating centre. However, since 2017, data monitoring is only carried out centrally, and data checks are carried out on all patients. The monitoring

process is also occasionally used to collect additional information that is missing from the original data submission. If, through the quality assurance and monitoring process, a centre is found to continuously provide poor quality data (missing important values or multiple errors) or does not deliver the annual dataset, EuroSIDA reserves the right to halt the collaboration. These details can be found in the 'Criteria for participation in the EuroSIDA study' document (https://chip.dk/Studies/EuroSIDA/Study-documents).

Determining the cause of death among HIV positive individuals can be complicated if the quantity or quality of information is not sufficient, or if there are multiple potential causes. In 2004 a meeting was held in Copenhagen to discuss how best to determine the cause of death in HIV positive individuals. This meeting was attended by individuals from several large trial and cohort studies that collect cause of death data, including EuroSIDA. They created a unified methodology for classifying the cause of death among HIV positive individuals based on data such as demographics, treatment history, risk factors for death, and autopsy results which are collected on a 4 page Coding of Death in HIV (CoDe) form (https://chip.dk/Tools-Standards/CoDe) (392). Completed CoDe forms are reviewed centrally by clinicians at CHIP, however if the clinician is unsure of the cause of death, then the case is discussed internally at CHIP.

Data is sent annually to the statistical centre at UCL, the most recent of which (at the time of writing) was Dataset 46 which was received in 2019. The dataset is named according to the number of datasets that have been produced, for example, the previous dataset received in 2018 was named Dataset 45. Further data checks are carried out before any statistical analysis is performed and any problems with the data are formally queried with the coordination centre. The data arrives in approximately 30 separate tables in the HICDEP format (390), which have to be cleaned and merged to create datasets that can be used for analysis.

Table 2.4 highlights the datasets used in each chapter and the timeframe within which data was considered for analysis. Within each chapter different analyses were carried out which used different subpopulations. Therefore, detailed inclusion/exclusion criteria have been included in the methods section of each chapter. Also, a further table describing the number of individuals included in the different analyses has been included at the beginning of the results section of each chapter.

Table 2.4: Summary of dataset used for each chapter

Chapter	Title	Dataset	Date
Chapter 3	Regional differences across Europe in advanced fibrosis and cirrhosis among HIV/HCV co-infected individuals, between 2010-2018	46	2010-2018
Chapter 4	Establishing a cross-sectional and longitudinal hepatitis C continuum of care among HIV/HCV co-infected individuals in EuroSIDA	46	<1/1/2017
Chapter 5	Effectiveness and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected individuals: Results from a pan-European study	45	1/6/2014 - 1/3/2018
Chapter 6	HCV reinfection among HIV/HCV co-infected individuals in Europe	46	1/1/2019

2.2.5 Loss to follow-up

LTFU is an important issue to consider in observational cohort studies as it can lead to selection bias. Previously, it was assumed that individuals who are less healthy or with more chaotic lifestyles may not be attending FU appointments as frequently as healthier patients. However, since the introduction of cART, it may be the case that individuals who are healthier may not attend FU appointments as frequently as sicker individuals. Regardless, LTFU can introduce systematic differences in FU time and data provided which can introduce bias. Definitions and estimates of LTFU in the EuroSIDA study have previously been published (393). LTFU was defined as no CD4 count, HIV-RNA measurement or clinical visit for 12 months, using this definition they reported a LTFU rate of 3.72 per 100 PYFU (393). If an individual has no reported data for more than one year the clinic is queried by the coordinating centre. If there is still

no record of a clinic visit by 2 and 5 years, the clinic is queried again. Where possible, participants continue to be followed up if they transfer to another EuroSIDA clinic.

2.2.6 Plasma sample repository

The central plasma repository was set up in 1997 and receives plasma from most individuals enrolled in EuroSIDA every six months. There are currently over 160000 samples stored there. Each sample contains 3-5 ml of EDTA blood and is separated by centrifugation (e.g. 1.500 g, 15 min.). The blood is stored in 2 x 1 aliquots in 1.8 ml screw-top cryovials (e.g. Nunc 377267 or similar). The plasma samples should be stored at -70° Celsius or liquid nitrogen within 4-6 hours of venesection. If the site is not able to store the samples at -70° Celsius or liquid nitrogen is not available, then they are advised to use a -20° Celsius freezer. If samples are stored at temperatures above -50° Celsius or more than 6 hours have passed before the plasma has been frozen, then this is clearly indicated on the sample. The samples are also labelled with the EuroSIDA patient number and the date of collection, therefore the coordinating centre can extract samples from freezers and carry out analysis when necessary. Details on the collection and storage of plasma samples can be found here: https://chip.dk/Studies/EuroSIDA/Sample-shipment.

2.2.7 Hepatitis cohort

EuroSIDA started collecting data on hepatitis co-infection in 1997 (Cohort 3) to assess the natural history of hepatitis, and also to monitor uptake and effectiveness of HCV therapy. In 1998 EuroSIDA started collecting data on hepatic encephalopathy, in 2001 they started collecting data on hepatocellular carcinoma, and manifestations of decompensated liver disease have been collected since 2010. Since 1999, routine liver biochemistry has been collected. Liver biopsy and Fibroscan results have been collected since 2010, with sites required to provide data on previous tests and return the histological reports for internal review (394). In 2006, EuroSIDA centrally tested plasma samples stored in the sample repository of individuals with unknown

hepatitis B & C status. The samples were tested for anti-HCV antibodies, HCV-RNA, genotype and hepatitis B and D markers.

As previously mentioned, EuroSIDA enrolled over 4000 individuals who were also anti-HCV positive between January 2014 and December 2016. While EuroSIDA has collected HCV treatment start and stop date since 1997, in Cohort X, HCV treatment dosage, adherence, treatment-limiting adverse events, and the reason for discontinuing treatment was also collected for HIV/HCV co-infected individuals. This information was previously collected on separate HCV treatment forms (Appendix III) but is now collected on the general FU forms.

2.2.7.1 RESPOND Hepatitis Scientific Interest Groups

In 2016 the RESPOND Hepatitis co-infection Scientific Interest Group (previously EuroSIDA Hepatitis group) was set up to ensure leading clinicians and researchers across Europe could collaborate in shaping the hepatitis co-infection research agenda. The main goals are to describe the long-term effects of hepatic B and C treatment and factors associated with morbidity and mortality in co-infected individuals. The group meet every two months to discuss current projects and new project ideas and is currently led by Lars Peters and Jürgen Rockstroh.

2.2.8 Funding and ethics

At the time of writing (November 2019), EuroSIDA has received funding from ViiV Healthcare LLC, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Gilead Sciences and the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n˚ 260694. The participation of centres from Switzerland has been supported by The Swiss National Science Foundation (Grant 148522). The study is also supported by a grant [grant number

DNRF126] from the Danish National Research Foundation and by the International Cohort Consortium of Infectious Disease (RESPOND) (https://chip.dk/Studies/EuroSIDA/About). For a centre to be able to contribute data to the EuroSIDA study, they must obtain ethical approval from the appropriate authority. The coordinating centre at CHIP has a copy of each ethical approval form.

2.2.9 Summary of study participants

A summary of the individuals under FU in EuroSIDA on 1/1/2017 can be seen in Table 2.5. There were 12949 individuals under FU on 1/1/2017, 26.4% of whom were from Southern Europe, 24.5% from Central-Western Europe, 20.3% from Northern Europe, 14.4% Central-Eastern Europe, and 14.4% from Eastern Europe. The median FU time was 10 years (interquartile range [IQR]: 4-18), the median age was 51 years old (IQR: 43-57), and the median CD4 count was 618 cells/mm^3 (IQR: 442-829). The majority of individuals were male (72.6%) and of white ethnicity (85.9%). The main route of HIV transmission was men who have sex with men (MSM) (36.3%), followed by heterosexual (29.5%), and people who inject drugs (PWID) (27.0%). Specific baseline characteristics of individuals included in each analysis will be presented in the results chapters.

2.2.10 My role in EuroSIDA

As a member of the EuroSIDA statistical team at UCL, I take part in the coordinated effort to clean the data when we annually receive a new dataset. The cleaning varies for each table but commonly consists of removing improbable values and dates, ensuring values are in the same units, and cleaning out duplicate values. Standard checks are carried out and any issues are reported to the coordination centre in Copenhagen who explore the problem further.

After the data is cleaned, I carry out data management before any statistical analysis is performed. This involves merging all cleaned tables into a master dataset, selecting the study population based on the inclusion criteria, and ensuring that data is in the right format for the analysis (wide – one row per individual or long – multiple rows per individual). One of my main cleaning and data management responsibilities is to create a clean dataset with all the important HCV data, which is shared with colleagues who may also need HCV data for their work.

I am also a member of the RESPOND Hepatitis Scientific Interest Group and attend bi-monthly meetings with the group. At these meetings, new and current projects are discussed, and I provide an update of any ongoing HCV projects I am working on. I also attend the EuroSIDA steering committee meetings where I provide a status update on my work when necessary, and have also presented my project proposals for review by the wider steering committee for approval. I also occasionally attend face to face meetings at CHIP where I attend discussions about hepatitis projects.

Table 2.5: Characteristics of individuals under follow-up on 1/1/2017

		Overall	Region				
			South	Central - West	North	Central - East	East
Overall		12949 (100.0)	3416 (26.4)	3169 (24.5)	2634 (20.3)	1861 (14.4)	1869 (14.4)
Sex	**Male**	9401 (72.6)	2466 (72.2)	2423 (76.5)	2085 (79.2)	1373 (73.8)	1054 (56.4)
	Female	3548 (27.4)	950 (27.8)	746 (23.5)	549 (20.8)	488 (26.2)	815 (43.6)
Ethnicity	**White**	11118 (85.9)	3101 (90.8)	2406 (75.9)	1909 (72.5)	1846 (99.2)	1856 (99.3)
	Global majority	782 (6.0)	169 (4.9)	327 (10.3)	281 (10.7)	5 (0.3)	
	Unknown	1049 (8.1)	146 (4.3)	436 (13.8)	444 (16.9)	10 (0.5)	13 (0.7)
HIV risk group	**MSM***	4696 (36.3)	1070 (31.3)	1396 (44.1)	1433 (54.4)	718 (38.6)	79 (4.2)
	PWID†	3502 (27.0)	1113 (32.6)	552 (17.4)	382 (14.5)	536 (28.8)	919 (49.2)
	Heterosexual	3820 (29.5)	1016 (29.7)	850 (26.8)	676 (25.7)	460 (24.7)	818 (43.8)
	Other	931 (7.2)	217 (6.4)	371 (11.7)	143 (5.4)	147 (7.9)	53 (2.8)
HIV-RNA (cp/ml)	**≤500**	11219 (86.6)	2886 (84.5)	3047 (96.2)	2463 (93.5)	1697 (91.2)	1126 (60.2)
	>500	689 (5.3)	81 (2.4)	51 (1.6)	42 (1.6)	86 (4.6)	429 (23.0)
	Unknown	1041 (8.0)	449 (13.1)	71 (2.2)	129 (4.9)	78 (4.2)	314 (16.8)
Ever received cART	**No**	400 (3.1)	89 (2.6)	49 (1.5)	36 (1.4)	32 (1.7)	194 (10.4)
	Yes	12549 (96.9)	3327 (97.4)	3120 (98.5)	2598 (98.6)	1829 (98.3)	1675 (89.6)
AIDS event	**No**	9425 (72.8)	2506 (73.4)	2194 (69.2)	1925 (73.1)	1411 (75.8)	1389 (74.3)
	Yes	3524 (27.2)	910 (26.6)	975 (30.8)	709 (26.9)	450 (24.2)	480 (25.7)
Non-ADI‡	**No**	11152 (86.1)	2898 (84.8)	2545 (80.3)	2236 (84.9)	1700 (91.3)	1773 (94.9)
	Yes	1797 (13.9)	518 (15.2)	624 (19.7)	398 (15.1)	161 (8.7)	96 (5.1)
Anti-HCV positive§	**No**	6671 (51.5)	1692 (49.5)	1743 (55.0)	1723 (65.4)	1004 (53.9)	509 (27.2)
	Yes	6174 (47.7)	1685 (49.3)	1407 (44.4)	891 (33.8)	843 (45.3)	1348 (72.1)
	Unknown	104 (0.8)	39 (1.1)	19 (0.6)	20 (0.8)	14 (0.8)	12 (0.6)
Fibrosis stage‖	**F0/1**	4422 (71.6)	1249 (74.1)	1215 (86.4)	440 (49.4)	604 (71.6)	914 (67.8)
	F2	154 (2.5)	54 (3.2)	39 (2.8)	16 (1.8)	15 (1.8)	30 (2.2)
	F3	216 (3.5)	68 (4.0)	38 (2.7)	29 (3.3)	22 (2.6)	59 (4.4)

	F4	333 (5.4)	93 (5.5)	59 (4.2)	42 (4.7)	47 (5.6)	92 (6.8)
	Unknown	1049 (17.0)	221 (13.1)	56 (4.0)	364 (40.9)	155 (18.4)	253 (18.8)
HCV genotype‖	**G1**	2168 (35.1)	692 (41.1)	499 (35.5)	399 (44.8)	223 (26.5)	355 (26.3)
	G2	129 (2.1)	23 (1.4)	35 (2.5)	38 (4.3)	5 (0.6)	28 (2.1)
	G3	1064 (17.2)	304 (18.0)	186 (13.2)	144 (16.2)	167 (19.8)	263 (19.5)
	G4	621 (10.1)	240 (14.2)	181 (12.9)	68 (7.6)	132 (15.7)	
	Unknown	2192 (35.5)	426 (25.3)	506 (36.0)	242 (27.2)	316 (37.5)	702 (52.1)
Ever received HCV treatment‖	**No**	3149 (51.0)	652 (38.7)	512 (36.4)	428 (48.0)	557 (66.1)	1000 (74.2)
	Yes	3025 (49.0)	1033 (61.3)	895 (63.6)	463 (52.0)	286 (33.9)	348 (25.8)
HBV infection¶	**No**	11332 (87.5)	3062 (89.6)	2739 (86.4)	2282 (86.6)	1623 (87.2)	1626 (87.0)
	Yes	881 (6.8)	197 (5.8)	289 (9.1)	178 (6.8)	111 (6.0)	106 (5.7)
	Unknown	736 (5.7)	157 (4.6)	141 (4.4)	174 (6.6)	127 (6.8)	137 (7.3)
				Median (IQR)			
Age		51 (43-57)	52 (46-57)	54 (48-59)	54 (48-60)	45 (39-52)	39 (35-44)
CD4 count (cells/mm3)		618 (442-829)	657 (471-890)	644 (468-836)	625 (465-818)	622 (454-850)	488 (331-684)
CD4 nadir		167 (70-266)	182 (81-285)	150 (48-252)	160 (70-250)	170 (66-277)	178 (96-269)
PYFU		10 (4-18)	9 (2-18)	13 (5-20)	13 (5-20)	9 (5-13)	5 (2-9)

*MSM: men who have sex with men, †PWID: people who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, hepatocellular carcinoma, end-stage renal disease, pancreatitis

‖Anti-HCV positive: anti-HCV antibody positive test, HCV-RNA positive, HCV genotyped or received HCV treatment prior to 1/1/2017

§Calculated as a proportion of anti-HCV positive individuals

¶HBV infection: positive HBsAg surface antigen test or presence of detectable HBV DNA prior to 1/1/2017

n with CD4 count = 11617, n with CD4 nadir = 12870

2.3 Statistical methods

Different statistical methods have been used throughout this thesis. A brief description of the methods used have been provided below, however more detailed methods sections are included in each results chapter.

2.3.1 Univariable Statistics

Before carrying out statistical modelling, it is important to examine the data. Summary statistics are used to describe large amounts of data in a comprehensible way and can help identify any data errors. The total number of individuals (n) and the percentage (%) was used to describe categorical data. For continuous variables, the mean and standard deviation (SD) or the median and interquartile range (IQR) was presented depending on whether the data were normally distributed or skewed. The median is more robust than the mean with respect to outliers, therefore the values can be considerably different when the data is skewed. However, when the data is normally distributed the mean and median values are similar.

When examining the difference between different categorical variables the chi-squared test was used, however, if there are less than 5 individuals in any category, Fisher's exact was used instead. When comparing the means of two groups the unpaired (independent) or paired t-test was used depending on whether the two groups were independent or related, respectively. If the data are not normally distributed, then the nonparametric tests, Wilcoxon-Mann-Whitney or Wilcoxon-Signed rank-sum tests were used instead. Analysis of variance (ANOVA) was used to test for differences in more than two means (inference made about the mean based on the difference in variance). If the continuous variable did not fulfil the assumption of normality required to use ANOVA then the Kruskal-Wallis test was used instead, which is the generalised form of the Wilcoxon-Mann-Whitney test.

2.3.2 Multivariable statistics

Statistical methods to analyse the relationship between an outcome (dependent) variable of interest and different independent variables (explanatory variables, predictors, exposure) were used. Depending on the research question, outcome variable, and nature of the explanatory variables, different analysis techniques were used. This is specified in the following results chapters, however in this section details on multivariable techniques are described in more detail. The multivariable analysis techniques that have been used in the different chapters are outlined below in Table 2.6.

Table 2.6: Multivariable model used in each results chapter

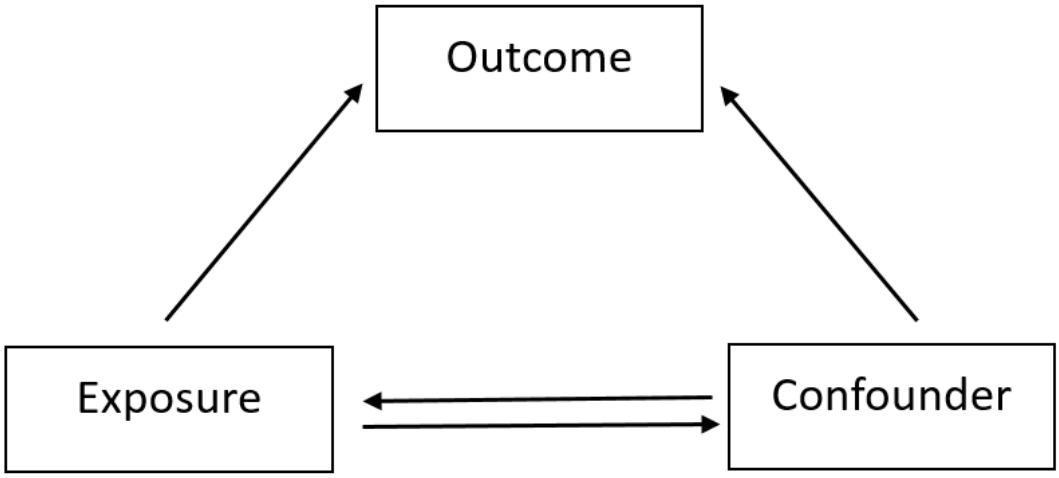
Chapter	Study endpoint(s)	Main Statistical Methods
Chapter 3	(1) Proportion with fibrosis ≥F3	Logistic regression with generalised estimating equations (GEEs)
Chapter 4	(1) Proportion HCV-RNA tested	Logistic regression
	(2) Proportion HCV-RNA negative – treated	Logistic regression with GEE
Chapter 5	(1) Proportion with known response to DAA	Logistic regression
	(2) Proportion achieved SVR	Logistic regression
	(3) Change in laboratory values over time	Random effects models
Chapter 6	(1) Proportion reinfected	Logistic regression

SAS 9.4 or higher will be used for all analyses (SAS Institute, Cary, North Carolina, USA)

2.3.2.1 Confounding

Confounders are variables that are associated with both the outcome and exposure variable (Figure 2.2). Confounders cannot lie on the causal pathway between the exposure and the outcome, otherwise the variable would be a mediator, not a confounder.

Figure 2.2: Illustration of a confounder impacting the association between exposure and outcome



Confounders impact the association between the exposure and outcome variable, as the presence of a confounder can increase or decrease the association between the exposure and outcome variable, or even reverse the observed effect. For example, if we found an association between gender (exposure) and Alzheimer's disease (outcome), but men were older than women in the study population. If we did not adjust for age (confounder) then we may conclude that men are more likely to develop Alzheimer's disease than women. Therefore, to assess the association between an outcome variable and exposure variables, the potential confounders must be accounted for.

Confounding can be avoided at the design stage of the study. Randomising a sufficiently large number of study participants can lead to natural balance in the groups. However, EuroSIDA is an observational study, which means it is not possible for individuals to be randomly assigned to an exposure group.

When confounding cannot be controlled for in the design stage, then statistical methods can be used. However, it is only possible to control for confounders in the analysis stage if the confounders are known and data on confounders have been

collected. Stratification is a technique that allows for the strength of an association to be measured separately for each well-defined group (stratum). Multivariable modelling also allows us to control for confounding and is especially useful when there is more than one potential confounder.

If a statistical model only includes one exposure variable, it is considered to be an unadjusted estimate as it does not control for the potential confounders. However, when potential confounders are included in a multivariable model, adjusted estimates are produced which control for potential confounding. As mentioned above, only measured confounders can be controlled for, and unfortunately it is not possible to rule out unmeasured confounding regardless of how well the cohort study is designed, which can lead to residual confounding. The extent to which the confounder can be adjusted for depends on how complete the data is and accurately it has been measured. If the confounder has been misclassified, it will underestimate the effect of the confounder and also lead to residual confounding.

2.3.2.1.1 Effect modification

Effect modification, interactions, or heterogeneity between strata, occur when the effect of the exposure on the outcome is modified by the presence of another exposure (the effect modifier). This happens when the relationship between an exposure and outcome is different across the strata of the effect modifier. For example, if a drug reduced the risk of Alzheimer's disease among women, but increased the risk of Alzheimer's disease among men. In this example, there would be an effect modification by gender or an interaction between the drug and gender. There does not need to be any association between the exposure and effect modifier for the interaction to occur. There are different ways to explore effect modifications, such as using regression analysis or the chi-squared test for heterogeneity. When using multivariable analysis, there are many different potential interactions, therefore it is important to determine any potential interactions that should be

included a priori based on clinical knowledge or scientific interest. It is not sensible to test for all interactions as multiple testing will increase the risk of a false positive result.

2.3.2.2 Logistic regression

Logistic regression models were used to find factors associated with a binary outcome variable, such as a success or failure, as opposed to a continuous outcome. For example, if we wanted to assess whether individuals have or don't have advanced fibrosis. A probability (π) represents the proportion of successes and can be any number between 0 and 1. When fitting a logistic regression model, the log odds are modelled instead of the odds. This is because the log odds can take any value between -∞ and ∞, whereas odds are restricted between 0 and 1. It is easier to model an unconstrained quantity as this avoids the chance of predicting impossible values (such as negative odds). The transformation used to carry out logistic regression is called the logit function (Equation 2.1), which is the most commonly used link function for binary data, and where the name logistic is derived.

Equation 2.1: Logit link function

$$logit(\pi) = \ln\left(\frac{\pi}{1-\pi}\right)$$

Equation 2.2: Logistic regression model

$$logit(\pi) = \ln\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n$$

An odds greater than 1 indicates an increased odds, whereas an odds lower than 1 indicates a reduced odds of the outcome occurring. If the confidence interval does not include 1, the finding is statistically significant. In the logistic regression model (Equation 2.2), β_{n} represents the independent effect of variable x_n on the log odds

ratio, while the exponential of β_{n} represents the effect of x_n on the odds ratio. The logistics regression model for a binary outcome is assumed to have a binomial distribution. Also, all observations are assumed to be independent, and individuals should have equal FU time.

2.3.2.2.1 Generalised estimating equations (GEEs)

As mentioned above, logistic regression assumes that observations are independent. Therefore, when there are clusters within the data (individuals from a certain subgroup are more similar than those not in the same subgroup), this assumption is no longer valid. Repeated measures from individuals also invalidate this assumption as data from the same individual is more similar than data from a different individual. In 1986 Liang and Zeger proposed an approach to analysis non-normal longitudinal data called generalised estimating equations (GEEs), (395). GEEs extend the regression model to account for correlation within the data, adjusting the parameters and standard errors accordingly. This method only requires making a 'working assumption' about the joint distribution of the outcomes. This means that the assumptions are not likely to be met, however, this will not invalidate the results drawn so long as the sample is sufficiently large. This is useful when the error structure of the model is not of inherent concern. Logistic regression with generalised GEEs was used to allow the inclusion of several measurements over time for each individual in Chapter 3 and Chapter 4.

2.3.2.3 Mixed effects models

Mixed effects models are also used to analyse longitudinal data and can account for repeated measures within individuals. Mixed effects models are different to using GEEs, as the parameter estimates drawn from mixed effects models are subject-specific, however those estimated in GEEs are population-averages. However, for normally distributed data, the estimates from random effects models and GEEs are identical (396). Mixed effects models include both random and fixed effects, where

fixed effects are consistent within each individual, such as sex, ethnicity, or treatment type. Including a random effect allows the explanatory variables to vary between individuals, but in a random intercept model, the individual regression lines have will still have the same slope as the overall regression line. However, in a random intercept and random slope model, the random intercept allows the overall level of the prevalence to vary between individuals after controlling for covariates, while the random slope allows the effect of the covariates to vary between individuals (397).

Below is the simple specification of the random intercept and random slope model (Equation 2.3), where i indicates the observation within individual j and X_{ij} is a vector of covariates. The variables in the first bracket are the fixed effects while the variables in the second bracket are the random effects. The random intercept for individual j is specified by u_{0j} while the individual specific random slope is specified by u_{1j}.

Equation 2.3:

$$Y_{ij} = \left(\beta_0 + \beta_1 X_{ij}\right) + \left(u_{0j} + u_{1j} X_{ij}\right) + e_{ij}$$

When we are describing data over time, it is likely that data collected closer together will be more closely correlated than data that is collected later on. Therefore, within-subject variance is likely to differ, which can be accounted for by specifying the covariance structure (Table 2.7).

Table 2.7: Description of within-subject covariance matrix (397)

Covariance structure	Definition
Independent	Repeated measures are uncorrelated
Unstructured	Correlations are unknown and unspecified
Compound symmetry (exchangeable) structure	Correlation between any 2 observations within a subject is the same
Autoregressive structure	Correlation is stronger between measurements that are closer together compared to measurements that are further apart. Assumes the distance between each observation is consistent

In clinical trials, data are generally collected on individuals at fixed time-points, which means the data is balanced and each individual has the same number of observations. However, in cohort studies the data is more likely to be unbalanced, as data is collected at varying time-points. When the data is unbalanced the overall averages at each time-point would not represent the true average as individuals are contributing data to different time-points. Therefore, for the results to be unbiased, we have to assume the data is missing at random (MAR – see Section 2.3.3 Missing data).

2.3.2.4 Modelling approach

Variables considered for each analysis are described in the analysis chapters (3-6). As mentioned above different modelling techniques were used depending on the research question. When carrying out longitudinal analysis, baseline or time-updated variables were included where suitable. Variables such as CD4 count and HIV-RNA that were collected frequently and likely to change depending on disease progression were time-updated. However, variables such as HIV risk group, gender, and ethnicity are fixed over time and not time-updated. Univariable analysis was carried out first, and any variables statistically significant at the 10% level ($p<0.1$) were included in the multivariable model along with any additional variables that were decided to be of importance a priori.

2.3.3 Missing data

Missing data can introduce bias into analysis if not appropriately considered. When the number of missing values among the explanatory variable is low, complete case analysis (where individuals with missing data are excluded) can be used without much impact on the size of the study population. This method is unbiased when the data are missing completely at random (MCAR), which is when there is no systematic reason for data to be missing. However data are rarely MCAR, also if there are large amounts of missing data it can be wasteful of important information (398).

To deal with missing values when carrying out statistical modelling, missing values categories, also known as indicator variables, were used. For example, CD4 count was categorised as ≤500 cells/mm^3, >500 cells/mm^3, and unknown (indicator variable). This method reduced the risk of selection bias and helps to maintain statistical power as this allows us to include as much data in the model as possible. However, in some circumstances this method can also lead to bias (399). While there are other more advanced methods for dealing with missing data, such as imputation, these methods also have limitations and require data to be MAR (where the reason for missing data is can be explained by collected data) which may not always be the case (400). There are potential limitations with all methods of dealing with missing data, therefore it is important to ensure the chosen method is clearly stated as well as the limitations (401).

Chapter 3 Regional differences across Europe in advanced fibrosis and cirrhosis among HIV/HCV co-infected individuals, between 2010-2018

3.1 Introduction

3.1.1 Liver fibrosis among HIV/HCV co-infected individuals

Co-infection with HIV has been shown to adversely affect the natural history of the HCV infection in many ways (described in Chapter 1, Section 1.2.5). With regards to the liver, HIV co-infected individuals with advanced immunodeficiency (CD4 count <200 cells/mm^3) or individuals with AIDS are more likely to develop cirrhosis or liver decompensation than those HCV mono-infected (382), and have been shown to have an increased acceleration to cirrhosis or liver disease (248,402). However, the increased acceleration can be slowed with HIV treatment to control HIV viraemia, as those with undetectable HIV-RNA have slower progression to cirrhosis (402). Other factors such as age at diagnosis and duration of infection have been found to increase the progression of fibrosis among HIV/HCV co-infected individuals (248).

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study described liver-related deaths as the second most common non-AIDS related cause of death after non-AIDS defining cancers between 1999-2011 among HIV positive individuals (383). They found the occurrence of liver-related deaths had decreased over time, and that over 95% of liver-related deaths occurred in individuals co-infected with hepatitis B or C. Therefore, it is important to target interventions to reduce liver-related mortality at those co-infected with hepatitis. While living with untreated HCV can lead to liver cirrhosis or HCC in some individuals, achieving sustained virological response (SVR) has been found to significantly reduce the risk of HCV related mortality (403,404). The newer, highly effective and tolerable directly acting antivirals (DAAs) can cure the majority of patients with HIV/HCV co-infection (405,406). The World Health Organisation (WHO) developed targets to achieve the elimination of viral hepatitis by 2030, which includes providing HCV treatment to 80%

of eligible individuals, which will reduce the burden of liver-related mortality. However, due to the high cost of DAAs, some countries in Europe initially targeted DAAs at those most in need of treatment (fibrosis ≥F2/F3) as they are at a higher risk of developing decompensated cirrhosis and HCC (366). Also, the length of HCV treatment regimens and the addition of ribavirin can vary depending on the presence of cirrhosis (367). Therefore, it is important to have reliable epidemiological data on the burden of fibrosis for the planning of HCV treatment management programmes (367).

3.1.2 Burden of advanced liver fibrosis or cirrhosis among individuals with chronic HCV

The World Health Organisation estimated that 10%-30% of individuals with chronic HCV infection have a fibrosis stage of F3 or F4 (236). However, the burden of advanced fibrosis or cirrhosis can vary significantly depending on the geographical region or risk group. Table 3.1 shows a summary of studies describing the burden of advanced fibrosis or cirrhosis. A study carried out in the USA between 2010 and 2013 analysed data from a large commercial laboratory and included 186794 individuals who were ever HCV-RNA positive (mono-infected) (407). They found that overall, 20% of individuals had advanced fibrosis. Of those born between 1945-1965 (n=123716) the proportion of advanced fibrosis was slightly higher, at 24% (407).

De Ledinghen et al. explored the prevalence of fibrosis among patients at a hospital in France and Spain and included 656 HCV mono-infected individuals and 287 HIV co-infected individuals between 2004 and 2006 (408). They found the proportion of advanced fibrosis was significantly higher among those co-infected with HIV (39%) compared to individuals mono-infected with HCV (18%) (408). In multivariable analysis age >45 years old, BMI >25 kg/m^2 and HIV infection were found to be associated with advanced liver fibrosis (408). A more recent study that was published

in 2017 found the proportion of advanced fibrosis to be 19% among 334 HIV co-infected individuals in Italy (409).

Some studies have been carried out among certain sub-populations of individuals with chronic HCV. For example, Bailey et al. explored the burden of advanced fibrosis or cirrhosis among HIV/HCV co-infected women in Ukraine using the APRI score or FIB-4 score (410). They found that 12% of the 171 co-infected women included had fibrosis ≥F3. They also explored factors associated with an increased risk of advanced fibrosis and found that IDU history and advanced HIV disease to be significant predictors (410). Also, a study carried in African Americans with HCV mono-infection or HIV/HCV co-infection described the prevalence of advanced fibrosis to be 28% (411). A multicentre study carried out in Europe included 914 HIV/HCV co-infected individuals and estimated the proportion of advanced fibrosis to be 35% (412). However, they only assessed liver fibrosis in those with elevated alanine aminotransferase (ALT) levels, which indicates abnormal liver function therefore this study could be overestimating the burden of fibrosis (412).

Béguelin et al, carried out an analysis on HCV treatment and liver fibrosis in the Swiss HIV Cohort Study and described the proportion of advanced fibrosis at March 2014 to be 33% among 623 HCV-RNA positive individuals (413). By December 2015 this had reduced to 15% among 438 individuals with chronic HCV, indicating a decrease in advanced fibrosis over time, which they attribute to improvements in HCV treatment (413).

Table 3.1: Summary of studies describing the burden of advanced fibrosis or cirrhosis among HCV mono-infected or HIV/HCV co-infected individuals

Reference	Country/Subpopulation*	HIV co-infected	Year	Liver fibrosis markers	Number of individuals†	Fibrosis ≥F3 n (%)
Bailey H et al. (410)	Ukraine/Childbearing women	Yes	2007-2012	APRI	171	21 (12)
Béguelin C et al. (413)	Switzerland	Yes	Sep 2011 - Mar 2014	Liver biopsy/Fibroscan	623	204 (33)
			Apr 2014 - Dec 2015	Liver biopsy/Fibroscan	438	67 (15)
de Ledinghen V et al. (408)	Spain/France	No	Jan 2004 - April 2006	Fibroscan	656	115 (18)
		Yes	Jan 2004 - April 2006	Fibroscan	287	112 (39)
Klevens R et al. (407)	USA	No	Jan 2010 - Dec 2013	APRI/FIB-4	186794	36850 (20)
Martin-Carbonero L et al. (412)	Multicentre (Europe)	Yes	1992 - 2002	Liver biopsy	914	320 (35)
Puoti M et al. (409)	Italy	Yes	-	FIB-4	185	35 (19)
Silver D et al. (411)	USA/African American individuals	No	Aug 2010 - Mar 2011	Liver biopsy	334	95 (28)

* If not specified, then the study did not include a specific subpopulation of HCV mono-infected or HIV/HCV co-infected individuals

† Only included those ever HCV-RNA positive

3.1.3 Late presentation

According to the 2017 Global Hepatitis Report, 80% of individuals living with HCV are undiagnosed (227). As individuals with HCV can remain asymptomatic for decades, there are many individuals who already have advanced liver disease when they are diagnosed (225). In fact, in the absence of widespread testing, many individuals are diagnosed based on the development of late stage liver disease (225). Early treatment can improve outcomes for individuals with chronic HCV, and also reduce the risk of onwards transmission. Late diagnosis and treatment of HCV is detrimental to individual and population health, and hinders the global effort to reach the goal of HCV elimination by 2030 (227).

A consensus definition for late presentation of HIV was published in 2007, where a late presenter was someone who presented for care with a CD4 count <350 cells/µL or with an AIDS-defining event (414). Identifying late presenters and targeting interventions to reduce late diagnosis of HIV is essential to ensure successful outcomes, reduce the risk of onward transmission, and reduce the economic burden (415,416). In 2017, a European working group developed a consensus definition for late presentation of chronic viral hepatitis B and C (225). They state that patients who have advanced liver fibrosis at diagnosis can be considered 'late presenters', where earlier diagnosis and initiation of treatment could have resulted in significant benefit to the individual (225). Their definition is useful to measure the proportion of chronic HCV cases that are not identified in a timely manner and the impact this may have (225). A single-centre study carried out in Denmark on late presentation used this consensus definition (among mainly HCV mono-infected individuals) and found 32.1% of 427 individuals were late presenters (417).

3.1.4 Aims

There were 3 main aims for this chapter:

1) To describe the change in the burden of advanced fibrosis or cirrhosis and liver-related events in Europe over time
2) To describe the regional differences in the prevalence of fibrosis ≥F3 and liver-related events over time
3) To investigate factors associated with developing fibrosis ≥F3, and how this changes over time across different regions

3.1.5 What this analysis adds

As mentioned, HCV is one of the leading causes of liver-related morbidity and mortality, therefore staging of fibrosis is crucial for management and prognosis of individuals with HCV (316). However, the burden of fibrosis in Europe is not well described; while there are a few studies describing the burden of advanced fibrosis in Europe (Table 3.1), the small sample sizes and restrictions on the study populations (e.g. studies only in women, among individuals of Black ethnicity, or individuals with elevated ALT) affects the generalisability of these studies. As HIV has been found to increase the speed of liver fibrosis progression (408), it is important to explore the burden of fibrosis specifically among the HIV co-infected population. The extent to which the burden of advanced fibrosis has changed over time in different European regions is also not well described. Therefore, understanding how the burden of advanced fibrosis has changed over time is crucial to help inform healthcare providers in making treatment decisions. While it has been shown that treating HCV early is cost-effective (418), there are still some countries in (mainly Eastern) Europe that have restrictions set by payers, which is a major barrier to improving treatment uptake (419). Therefore, identifying individuals with advanced fibrosis and cirrhosis that should be prioritised for HCV treatment is important to help inform decision-makers and healthcare professionals where to target screening and treatment.

3.2 Methods

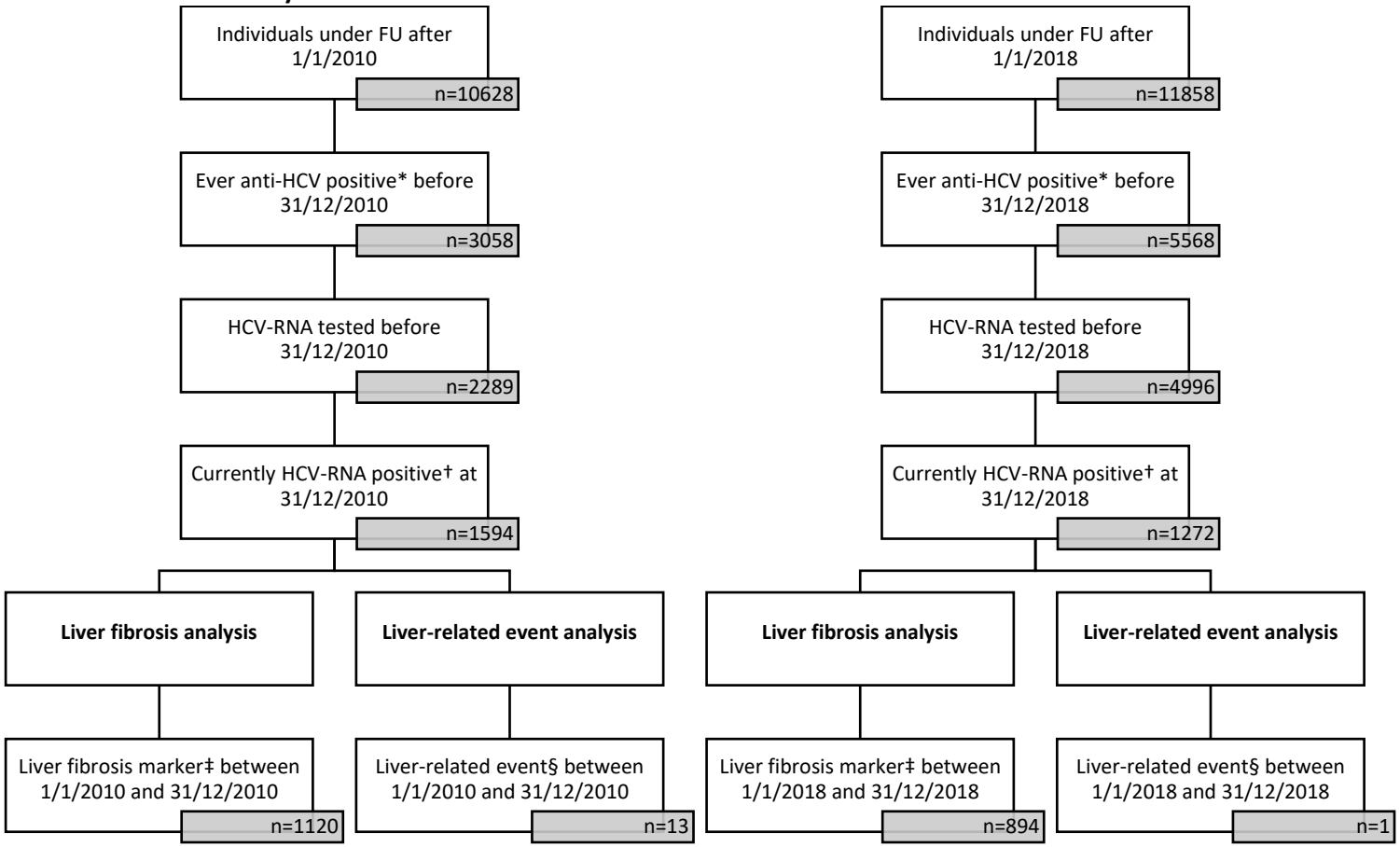
This analysis was carried out using data from the EuroSIDA study's (defined in Chapter 2) D46 dataset, which included 22825 HIV positive individuals.

3.2.1 Inclusion criteria

This analysis explored the burden of advanced fibrosis each year between 2010 and 2018. For each of the 9 years, I explored how many individuals had prospective follow-up (FU) at 31st December. Individuals were considered to be under FU until death, or up to one year from their latest clinic visit, CD4 count, HIV-RNA, anti-HCV, HCV-RNA, HCV genotype measurement HCV treatment. I then determined how many were ever anti-HCV positive, and how many were currently HCV-RNA positive at 31st December (both defined in the footnote of Figure 3.1). Currently, HCV-RNA positive individuals who had a liver fibrosis marker measurement during that year were included in the advanced fibrosis analysis, and used as the denominator to determine the proportion of individuals with fibrosis ≥F3 (defined in Section 3.2.2) for that year. The proportion of individuals with a liver-related event (defined in Section 3.2.3) was also explored as a proportion of those currently HCV-RNA positive at 31st Dec.

For example, in 2010 there were 10628 individuals who were under FU between 1st January and 31st December (Figure 3.1). Of those under FU, 3058 individuals were ever anti-HCV positive before 31/12/2010, and 1594 were currently HCV-RNA positive at 31/12/2010. There were 1120 individuals who had a liver fibrosis marker between 1/1/2010 and 31/12/2010, and were included in the 2010 advanced fibrosis analysis. The denominator for the fibrosis analysis was the 1120 individuals with a fibrosis marker. Individuals who were currently HCV-RNA positive at 31/12/2010 (n=1594) were used as the denominator to determine the proportion of individuals who had a liver-related event within the calendar year. Figure 3.1 also describes the number of individuals included in the 2018 analysis

Figure 3.1: Flowchart for inclusion in analysis in 2010 and 2018



* Anti-HCV positive test, HCV-RNA positive, HCV genotyped or received HCV treatment before 31st Dec

† Most recent HCV-RNA test before 31st Dec was positive, HCV genotyped but not treated before 31st Dec, started treatment for the first time after 31st Dec or the first HCV-RNA test result after 31st Dec is positive and never treated

‡ Defined below in Section 3.2.2

§ Defined below in Section 3.2.3

3.2.2 Definition of fibrosis ≥F3

Liver fibrosis stage was determined using the most recent of the most reliable liver fibrosis marker available between 1st Jan and 31st December for each year. The most reliable liver fibrosis marker was considered to be a liver biopsy, followed by Fibroscan, APRI score, and then plasma hyaluronic acid level, as defined in previous EuroSIDA publications (368). Therefore, if an individual had 3 liver fibrosis marker results in 2010: an APRI score on 1/1/2010, a liver biopsy on 1/1/2010, and a liver biopsy on 1/6/2010, then the liver biopsy on 1/6/2010 would be used, as a liver biopsy is considered more reliable than and APRI score and the most recent of the liver biopsies is on the 1/6/2010. The cut-offs used in this analysis to define fibrosis METAVIR ≥F3 are based on the consensus definition by Mauss et al., and can be seen below in Table 3.2 (225).

Table 3.2: Fibrosis ≥F3 cut-offs

Liver fibrosis biomarker	Result
Liver biopsy	≥F3 (296)
FibroScan	≥9kPa (225)
APRI	score >1.5 (225)
Hyaluronic acid	>160ng/mL (420)

3.2.3 Definition of liver events

The liver events considered in this analysis were: ascites, hepatic encephalopathy, hepatorenal syndrome, oesophageal variceal bleeding, liver decompensation, and HCC. Only liver events among individuals who were currently HCV-RNA positive on 31st December for each calendar year were included.

3.2.4 Variables included in this analysis

The definitions of the different variables included in this analysis have been described below in Table 3.3

Table 3.3: Definition of variables included in analysis

Variable	Levels	Definitions and comments	Time updated*
Age (years)	Continuous (per 1 year older) and categorised as ≤40, 40-50, 50-60 and >60 years old		Yes (once yearly)
Sex	Male, female		
Region	South (including Argentina and Israel), Central - West, North, Central - East, Eastern Europe	Defined in Chapter 2 Section 2.2	
Ethnicity	White, Global Majority, unknown		
HIV risk group	MSM, PWID, heterosexual, and other	'Other' includes those with unknown risk group	
CD4 count (cells/mm^3)	Continuous and categorised as ≤500, >500 (cells/mm^3), and unknown	Most recent measurement prior to 31st Dec (within one year), if not available then measurement up to 6 months after 31st Dec included	Yes (once yearly)
CD4 nadir (cells/mm^3)	Continuous and categorised as ≤50, 50-200, and >200 (cells/mm^3), and unknown	Lowest CD4 count prior to 31st Dec, if not available then measurement up to 6 months of after 31st Dec included	Yes (once yearly)
HIV-RNA (cp/ml)	≤500, >500, unknown	Most recent measurement prior to 31st Dec (within one year), if not available then measurement up to 6 months of after 31st Dec included.	Yes (once yearly)
AIDS-defining event	Yes, no	Defined using CDC's 1993 clinical definition (421)	Yes (once yearly)
Non-ADI	No, liver-related, other	Non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, end-stage renal disease, and pancreatitis, as in previous publications (422)	Yes (once yearly)
Year of FU	≤2014, 2015-2016, 2017-2018		
HCV genotype	G1, G2, G3, G4, unknown		
On cART	Yes, no	Individual on cART (≥3 drugs) treatment on 31st Dec	Yes (once yearly)
Prior HCV treatment	Yes, no, and IFN only, DAA+IFN DAA only, no	Based on most recent treatment regimen prior to 31st Dec	Yes (once yearly)
HBV infection	Yes, no, unknown	HBV DNA, hepatitis B surface antigen (HBsAg)	Yes (once yearly)
HCV-RNA (IU/ml)	<500000, ≥500000, positive (unknown value),		

*Time updated variables included in logistic regression analysis with generalised estimating equations (GEEs)

3.2.5 Statistical analysis

3.2.5.1 Baseline characteristics

We described the characteristics of all individuals who were currently HCV-RNA positive at 31st December and included in the 2010 analysis and the 2018 analysis. Characteristics were defined based on the most recent measurement prior to 31st December. Definitions of characteristics have been provided in Table 3.3. Categorical data were described with numbers and percentages while numerical characteristics were described with medians and interquartile ranges. Differences in characteristics were explored using the chi-squared test (or Fisher's exact test if the number of individuals in each group/cell was <5) for categorical variables and the Kruskal-Wallis tests for continuous variables.

As mentioned above, the number of individuals who had a liver fibrosis marker within each calendar year (among those who were currently HCV-RNA positive at 31st December) was explored, then the proportion with fibrosis ≥F3 was calculated. The change in the proportion of individuals with fibrosis ≥F3 between 2010 and 2018 was then described. Differences between regions at each year were compared using the chi-squared test. The proportion of currently HCV-RNA positive individuals with a liver-related event (defined in Section 3.2.3) at each calendar year was also described, and compared between regions using Fisher's exact test due to the small number of events.

3.2.5.2 Factors associated with fibrosis ≥F3

Logistic regression was used to determine the adjusted odds ratio of having fibrosis ≥F3, including data from each calendar year. For this analysis, characteristics were defined based on the most recent measurement prior to the liver fibrosis marker included instead of 31st December. Generalised estimating equations were used to allow for the inclusion of data from individuals included at multiple years. Variables described in Table 3.3 that were significant ($p<0.1$) in the univariable analysis were

included in the multivariable model (unless there was evidence of collinearity). Table 3.3 also highlights which variables included in the model were time-updated (once yearly). The impact of time on the burden of liver fibrosis in each region was of particular interest, and therefore the interaction between region and time was included a priori in the adjusted model.

SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, North Carolina, USA).

3.3 Results

Table 3.4 below shows the number of individuals included in each analysis.

Table 3.4: Description of individuals included in each analysis

Section	Analysis	n included
3.1.1 Study population 2010	Description of individuals eligible Comparison of those included vs excluded	1594 1120 vs 474
3.1.2 Baseline characteristics 2010	Comparison between individuals with fibrosis <F3 vs ≥F3	875 vs 245
3.1.3 Study population 2018	Description of individuals eligible Comparison of those included vs excluded	1272 894 vs 378
3.1.4 Baseline characteristics 2018	Comparison between individuals with fibrosis <F3 vs ≥F3	759 vs 135
3.1.5 Proportion of advanced fibrosis, over time	Change in proportion over time	Year 2010-2018
3.1.6 Proportion of liver events, over time	Change in proportion over time	Year 2010-2018
3.1.7 Factors associated with advanced fibrosis	Odds of advanced fibrosis	3744

3.3.1 Study population for 2010 analysis

There were 1594 individuals who were currently HCV-RNA positive at 31st December 2010, 1120 (70.3%) of whom had a liver fibrosis marker during the calendar year and were included in this analysis, and 474 that did not and were excluded (Table 3.5). After adjustment, individuals from Northern Europe had a lower odds of being included in this analysis compared to individuals from Southern Europe [adjusted odds ratio (aOR)=0.38, 95% CI=0.25-0.57]. Individuals who were on cART had a higher odds of being included [aOR=1.97, 95% CI=1.37-2.81], as did individuals who previously received HCV treatment [aOR=1.48, 95% CI=1.07-2.06]. The majority of the liver fibrosis results were based on an APRI score (n=925, 85.6%), followed by a Fibroscan test (n=149, 13.3%), liver biopsy (n=45, 4.0%), and hyaluronic acid result (n=1, 0.1%). Of those with a fibrosis marker, 245 (21.9%, 95% confidence interval (CI)=19.5-24.3) individuals had fibrosis ≥F3.

3.3.2 Baseline characteristics of individuals included in the 2010 analysis

Baseline characteristics by fibrosis stage can be seen below in Table 3.5. The majority of individuals with a fibrosis marker were from Southern Europe (36.5%), followed by Central-West (20.4%), East (18.4), Central-East (15.5%), and Northern Europe (9.2%). The majority of individuals were male (68.5%) and of white ethnicity (91.3%). The median age was 46 years old (interquartile range [IQR]: 39-50), and the most common route of HIV transmission was injection drug use (IDU) (65.4%), followed by heterosexual (14.3%), men who have sex with men (MSM) (10.8%), and other routes (9.5%). The median CD4 count was 491 cells/mm^3 (IQR: 320-680), and 92% of individuals were on HIV treatment on 31st December 2010. There were 129 individuals who had at least 1 non-AIDS defining illness (non-ADI), 53 (41.1%) of whom ever had a liver-related event and 76 (58.9%) of whom had other non-AIDS defining malignancies (NADM), cardiovascular disease (CVD), end-stage renal disease (ESRD), or pancreatitis. Overall there were 153 non-ADI events as some individuals had multiple non-ADIs, which has been described further in Figure 3.2, the most common non-ADI was ESLD (n=50) followed by NADM (n=42), CVD (n=32), pancreatitis (n=16), HCC (n=7), and ESRD (n=6). The majority of individuals included had HCV genotype measurement (80.8%). Among the 905 individuals who were genotyped, genotype 1 was the most common (55.0%), followed by genotype 3 (26.1%), genotype 4 (16.6%), and genotype 2 (2.3%). There were 846 (71.7%) individuals who had never previously received HCV treatment and 317 (28.3%) individuals who had, all of whom received an interferon (IFN) based regimen.

There were significant differences in the proportion of individuals with advanced fibrosis or cirrhosis based on certain characteristics ($p<0.05$). The proportion of individuals who had fibrosis ≥F3 was significantly higher in Northern (31.1%) and Southern (28.1%) Europe compared to Central-West (19.3%), Central-East (19.0%), and Eastern Europe (10.2%). The median age was higher (48 years old, IQR: 38-50) among those with advanced fibrosis compared to those with fibrosis <F3 (45 years old, IQR: 43-51), and the median CD4 count was lower among those with fibrosis ≥F3

(410 cells/mm^3, IQR: 272-620) compared to those with fibrosis <F3 (512 cells/mm^3, IQR: 338-697). Individuals with a liver-related non-ADI had a higher proportion of fibrosis ≥F3 (45.3%) compared to individuals with other non-ADIs (21.1%), or no non-ADI (20.7%). Individuals with genotype 3 (30.1%) and genotype 2 (28.6%) also had a higher proportion of advanced fibrosis compared to those with genotype 1 (21.7%), or genotype 4 (12.7%). The proportion of fibrosis ≥F3 was higher among those who had previously received HCV treatment (27.8%) compared to those that did not receive HCV treatment (19.6%).

Table 3.5: Baseline characteristics of individuals included in 2010 analysis

		Currently HCV-RNA positive	Available fibrosis marker	Fibrosis <F3	Fibrosis ≥F3	p-value
		n (%)				
Overall		1594 (100.0)	1120 (70.3)	875 (78.1)	245 (21.9)	
Sex	**Male**	1093 (68.6)	767 (68.5)	587 (76.5)	180 (23.5)	0.0573
	Female	501 (31.4)	353 (31.5)	288 (81.6)	65 (18.4)	
Ethnicity	**White**	1461 (91.7)	1022 (91.3)	799 (78.2)	223 (21.8)	
	GM*	38 (2.4)	30 (2.7)	27 (90.0)	3 (10.0)	0.1383
	Unknown	95 (6.0)	68 (6.1)	49 (72.1)	19 (27.9)	
Region of Europe	**South**	530 (33.2)	409 (36.5)	294 (71.9)	115 (28.1)	
	Central-West	290 (18.2)	228 (20.4)	184 (80.7)	44 (19.3)	
	North	183 (11.5)	103 (9.2)	71 (68.9)	32 (31.1)	<.0001
	Central-East	264 (16.6)	174 (15.5)	141 (81.0)	33 (19.0)	
	East	327 (20.5)	206 (18.4)	185 (89.8)	21 (10.2)	
HIV risk group	**MSM†**	175 (11.0)	121 (10.8)	95 (78.5)	26 (21.5)	
	PWID‡	1084 (68.0)	733 (65.4)	563 (76.8)	170 (23.2)	0.2934
	Heterosexual	208 (13.0)	160 (14.3)	134 (83.8)	26 (16.3)	
	Other	127 (8.0)	106 (9.5)	83 (78.3)	23 (21.7)	
HIV-RNA (cp/ml)	**≤500**	1162 (72.9)	954 (85.2)	741 (77.7)	213 (22.3)	
	>500	171 (10.7)	126 (11.3)	105 (83.3)	21 (16.7)	0.2400
	Unknown	261 (16.4)	40 (3.6)	29 (72.5)	11 (27.5)	
AIDS event	**No**	1106 (69.4)	760 (67.9)	602 (79.2)	158 (20.8)	0.2017
	Yes	488 (30.6)	360 (32.1)	273 (75.8)	87 (24.2)	
Non-ADI	**No**	1416 (88.8)	991 (88.5)	786 (79.3)	205 (20.7)	
	Liver related	73 (4.6)	53 (4.7)	29 (54.7)	24 (45.3)	0.0001
	Other§	105 (6.6)	76 (6.8)	60 (78.9)	16 (21.1)	
HCV genotype	**G1**	691 (43.4)	498 (44.5)	390 (78.3)	108 (21.7)	
	G2	30 (1.9)	21 (1.9)	15 (71.4)	6 (28.6)	
	G3	343 (21.5)	236 (21.1)	165 (69.9)	71 (30.1)	0.0011
	G4	205 (12.9)	150 (13.4)	131 (87.3)	19 (12.7)	
	Unknown	325 (20.4)	215 (19.2)	174 (80.9)	41 (19.1)	
On cART	**No**	303 (19.0)	141 (12.6)	113 (80.1)	28 (19.9)	0.5355
	Yes	1291 (81.0)	979 (87.4)	762 (77.8)	217 (22.2)	
Prior HCV treatment	**No**	1196 (75.0)	803 (71.7)	646 (80.4)	157 (19.6)	0.0028
	Yes	398 (25.0)	317 (28.3)	229 (72.2)	88 (27.8)	
HBV infection	**No**	1388 (87.1)	990 (88.4)	770 (77.8)	220 (22.2)	
	Yes	104 (6.5)	71 (6.3)	56 (78.9)	15 (21.1)	0.6279
	Unknown	102 (6.4)	59 (5.3)	49 (83.1)	10 (16.9)	
HCV-RNA (IU/ml)	**<500000**	482 (30.2)	334 (29.8)	253 (75.7)	81 (24.3)	
	≥500000	750 (47.1)	537 (47.9)	422 (78.6)	115 (21.4)	0.392
	Positive|	362 (22.7)	249 (22.2)	200 (80.3)	49 (19.7)	
		Median (IQR)				
Age (years)		46 (37-50)	46 (39-50)	45 (38-50)	48 (43-51)	<.0001
CD4 count (cells/mm³)		484 (315-676)	491 (320-680)	512 (338-697)	410 (272-620)	<.0001
CD4 nadir (cells/mm³)		144 (63-230)	140 (65-223)	144 (67-226)	128 (60-206)	0.0760

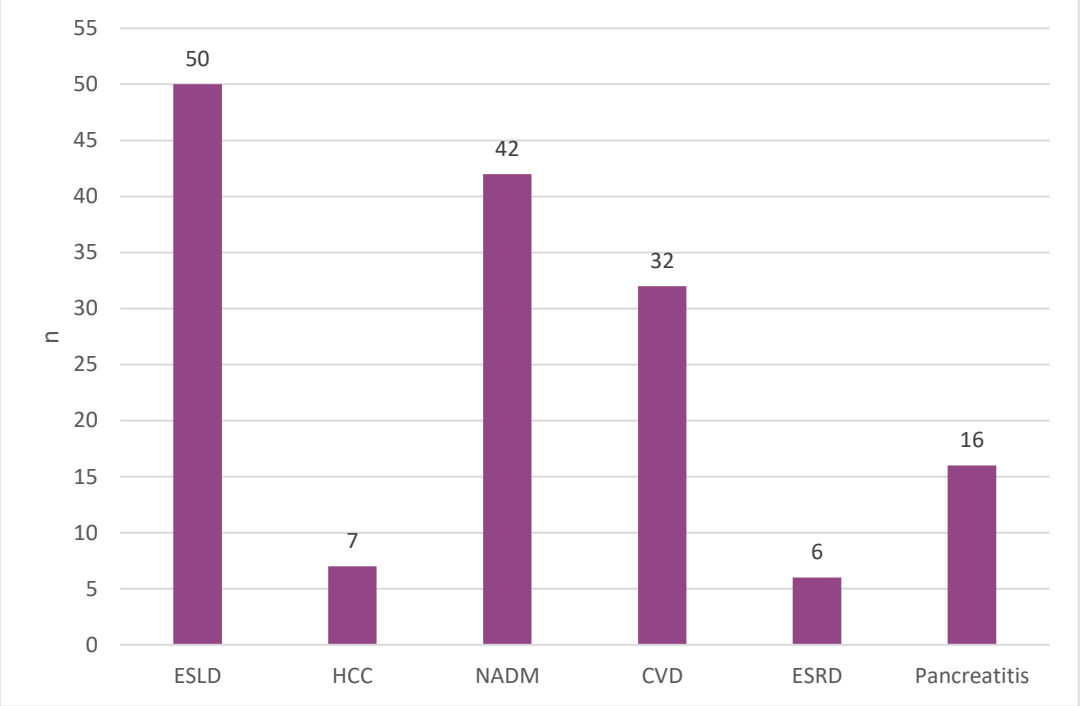
*Global majority, MSM: †Men who have sex with men, ‡PWID: People who inject drugs

§Other non-ADI: non-AIDS defining malignancy (excluding HCC), cardiovascular disease, end-stage renal disease, or pancreatitis

|HCV-RNA positive, but unknown value

n with CD4 count = 1370, n with CD4 nadir = 1594

Figure 3.2: Number of individuals with non-ADI



ESLD: end-stage liver disease, HCC: Hepatocellular carcinoma, NADM: non-AIDS defining malignancy, CVD: cardiovascular disease, ESRD: end-stage renal disease

3.3.3 Study population for 2018 analysis

There were 1272 individuals who were currently HCV-RNA positive at 31st December 2018, 894 (70.3%) had a liver fibrosis marker. After adjustment, individuals included in this analysis had a higher odds of being on cART [aOR=2.11, 95% CI=1.25-3.56] and had a lower odds of being from Central-Western Europe [aOR=0.36, 95% CI=0.21-0.64]. The most common liver fibrosis marker used was APRI score (80.1%), followed by fibroscan (19.0%), and liver biopsy (0.9%). Among those with a fibrosis marker, 15.1% (95%=12.8-17.5) had advanced fibrosis, which is 6.8% less than the proportion with advanced fibrosis in 2010.

3.3.4 Baseline characteristics of individuals included in the 2018 analysis

Among all individuals with a fibrosis marker (n=894), the median age was 47 years old (IQR: 40-54), which is similar to the median age in 2010 (46 years old, IQR: 39-50) (Table 3.6). Also, there was no difference in the median age between those with

fibrosis <F3 and with fibrosis ≥F3 in 2018. The median CD4 count was 564 cells/mm^3 (IQR: 383-775), which is 73 cells/mm^3 higher than the median CD4 count in 2010. There were 312 (34.9%) individuals who previously received HCV treatment, of whom 45.8% received an IFN-based regimen, 1.9% received IFN + DAA, and 52.2% received an IFN-free DAA regimen. Individuals treated with DAA only regimens had a lower proportion of advanced fibrosis (6.7%) than those treated with IFN-based regimens (14.0%). More individuals had access to HCV treatment by 2018 (34.9% vs 28.3%), and the proportion of advanced fibrosis was lower among those treated compared to 2010 (11.2% vs 27.8%)

Individuals with an HIV-RNA ≤500 (cp/ml) had a lower proportion of advanced fibrosis (14.1%) compared to those with HIV-RNA >500 (27.1%), however there was no significant difference among the individuals included in the 2010 analysis. The proportion of advanced fibrosis was highest among those with genotype 3 (22.6%), which was also the case in 2010 (30.1%), however it was 7.5% lower.

Table 3.6: Baseline characteristics of individuals included in 2018 analysis

		Currently HCV-RNA positive	Available fibrosis marker	Fibrosis <F3	Fibrosis ≥F3	P-value
		n (%)				
Overall		1272 (100.0)	894 (70.3)	759 (84.9)	135 (15.1)	
Sex	**Male**	864 (67.9)	600 (67.1)	503 (83.8)	97 (16.2)	0.2035
	Female	408 (32.1)	294 (32.9)	256 (87.1)	38 (12.9)	
Ethnicity	**White**	1172 (92.1)	827 (92.5)	700 (84.6)	127 (15.4)	
	GM*	34 (2.7)	25 (2.8)	23 (92.0)	2 (8.0)	0.7581
	Unknown	66 (5.2)	42 (4.7)	36 (85.7)	6 (14.3)	
Region of Europe	**South**	232 (18.2)	167 (18.7)	146 (87.4)	21 (12.6)	
	Central-West	197 (15.5)	158 (17.7)	146 (92.4)	12 (7.6)	
	North	174 (13.7)	90 (10.1)	72 (80.0)	18 (20.0)	0.0019
	Central-East	302 (23.7)	199 (22.3)	173 (86.9)	26 (13.1)	
	East	367 (28.9)	280 (31.3)	222 (79.3)	58 (20.7)	
HIV risk group	**MSM†**	185 (14.5)	135 (15.1)	121 (89.6)	14 (10.4)	
	PWID‡	771 (60.6)	536 (60.0)	443 (82.6)	93 (17.4)	0.0686
	Heterosexual	222 (17.5)	159 (17.8)	136 (85.5)	23 (14.5)	
	Other	94 (7.4)	64 (7.2)	59 (92.2)	5 (7.8)	
HIV-RNA (cp/ml)	**≤500**	800 (62.9)	725 (81.1)	623 (85.9)	102 (14.1)	
	>500	83 (6.5)	70 (7.8)	51 (72.9)	19 (27.1)	0.0136
	Unknown	389 (30.6)	99 (11.1)	85 (85.9)	14 (14.1)	
AIDS event	**No**	957 (75.2)	676 (75.6)	574 (84.9)	102 (15.1)	0.986
	Yes	315 (24.8)	218 (24.4)	185 (84.9)	33 (15.1)	
Non-ADI	**No**	1141 (89.7)	799 (89.4)	684 (85.6)	115 (14.4)	
	Liver related	27 (2.1)	21 (2.3)	14 (66.7)	7 (33.3)	0.0472
	Other§	104 (8.2)	74 (8.3)	61 (82.4)	13 (17.6)	
HCV genotype	**G1**	515 (40.5)	372 (41.6)	320 (86.0)	52 (14.0)	
	G2	32 (2.5)	23 (2.6)	23 (100.0)		
	G3	262 (20.6)	177 (19.8)	137 (77.4)	40 (22.6)	0.0007
	G4	151 (11.9)	95 (10.6)	89 (93.7)	6 (6.3)	
	Unknown	312 (24.5)	227 (25.4)	190 (83.7)	37 (16.3)	
On cART	**No**	118 (9.3)	68 (7.6)	63 (92.6)	5 (7.4)	0.0634
	Yes	1154 (90.7)	826 (92.4)	696 (84.3)	130 (15.7)	
Prior HCV treatment|	**No**	851 (66.9)	582 (65.1)	482 (82.8)	100 (17.2)	
	IFN	203 (16.0)	143 (16.0)	123 (86.0)	20 (14.0)	<.0001
	IFN+DAA	9 (0.7)	6 (0.7)	2 (33.3)	4 (66.7)	
	DAA only	209 (16.4)	163 (18.2)	152 (93.3)	11 (6.7)	
HBV infection	**No**	1124 (88.4)	807 (90.3)	691 (85.6)	116 (14.4)	
	Yes	65 (5.1)	48 (5.4)	36 (75.0)	12 (25.0)	0.1196
	Unknown	83 (6.5)	39 (4.4)	32 (82.1)	7 (17.9)	
HCV-RNA (IU/ml)	**<500000**	399 (31.4)	281 (31.4)	243 (86.5)	38 (13.5)	
	≥500000	649 (51.0)	465 (52.0)	395 (84.9)	70 (15.1)	0.4303
	Positive¶	224 (17.6)	148 (16.6)	121 (81.8)	27 (18.2)	
			Median (IQR)			
Age (years)		47 (40-55)	47 (40-54)	47 (40-55)	47 (39-55)	0.5255
CD4 count (cells/mm³)		558 (380-763)	564 (383-775)	571 (399-787)	525 (340-667)	0.0010
CD4 nadir (cells/mm³)		166 (79-265)	165 (80-260)	167 (80-262)	170 (71-276)	0.3093

*Global majority, MSM: †Men who have sex with men, ‡PWID: People who inject drugs

§Other non-ADI: non-AIDS defining malignancy (excluding HCC), cardiovascular disease, end-stage renal disease, or pancreatitis

|Based on most recent treatment prior to 31st December

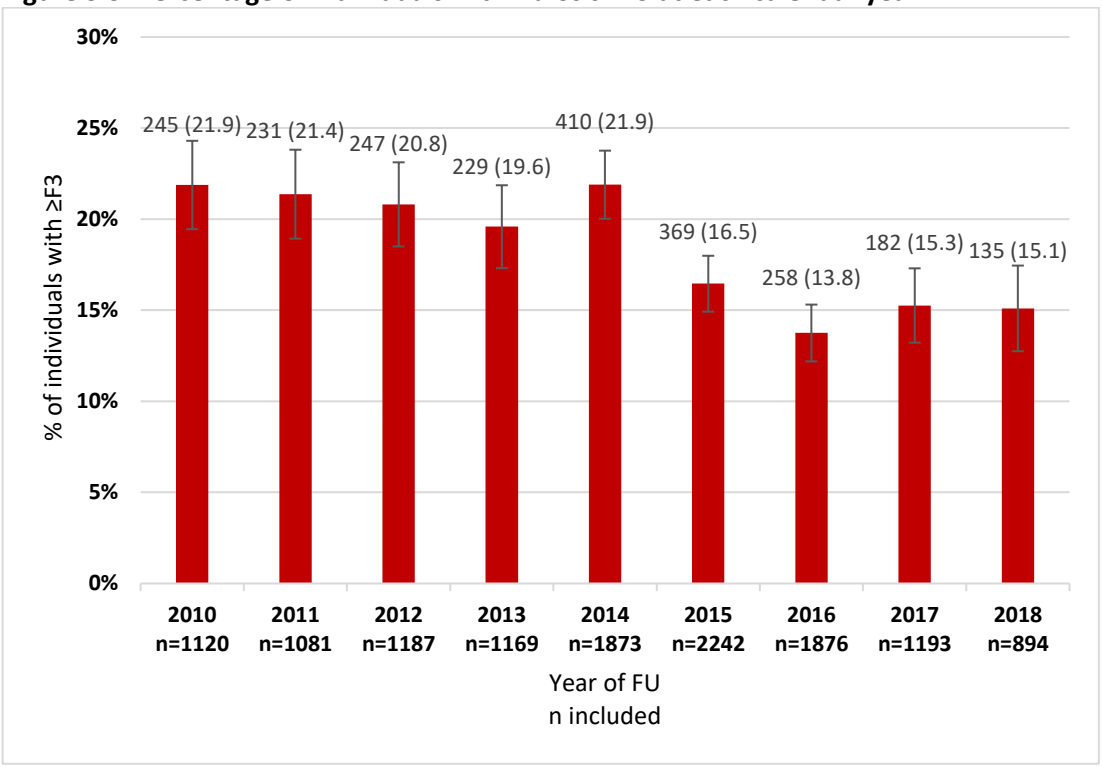
¶HCV-RNA positive, but unknown value

n with CD4 count = 920, n with CD4 nadir = 1268

3.3.5 The burden of advanced fibrosis over time

Figure 3.3 shows the proportion of individuals who had fibrosis stage F3 or F4 at each calendar year (from 1st January to 31st December). There were 1120, 1081, 1187, 1169, 1873, 2242, 1876, 1193, and 894 individuals under FU who were ever HCV-RNA positive with a liver fibrosis marker in 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, and 2018, respectively. The proportion of these individuals with fibrosis ≥F3 decreased by 6.8% over time, from 21.9% (95% CI=19.5-24.3) in 2010 to 15.1% (95% CI=12.8-17.5) in 2018. While there was a steady decline in the prevalence of advanced fibrosis over time, there was a 2.3% increase in advanced fibrosis from 19.6% (95% CI=17.3-21.9) in 2013 to 21.9% (95% CI=20.0-23.8) in 2014. By 2015 the proportion of individuals with advanced fibrosis dropped again by 5.4% to 16.5% (95% CI=14.9-18.0) and gradually decreased until 2018, with slight fluctuation between 2016 and 2017 (1.5% increase).

Figure 3.3: Percentage of individuals with fibrosis ≥F3 at each calendar year



3.3.5.1 Change in the burden of advanced fibrosis over time, by region

Figure 3.4 shows the change in the proportion of individuals with fibrosis ≥F3 over time for each region, and the number of individuals with advanced fibrosis at each region and year can be seen in Table 3.7. The burden of advanced fibrosis decreased the most in Southern Europe, from 28.1% in 2010 to 12.6% in 2018 (15.5% decrease). There was an 11.7% decrease in the proportion of individuals with fibrosis ≥F3 in Central-Western Europe between 2010 and 2018, an 11.1% decrease in Northern Europe, and a 5.9% decrease in Central-East. While there was an overall decrease in the proportion of individuals with fibrosis ≥F3 in South, Central-west, North and Central-Eastern Europe between 2010 and 2018, the burden of advanced liver fibrosis varied between 2010 and 2014, only consistently decreasing each year from 2014. The proportion of individuals with fibrosis ≥F3 in Eastern Europe increased over time, from 10.2% in 2010 to 20.7% in 2018, which is a 100% increase over 8 years. However, the prevalence of fibrosis ≥F3 increased most between 2013 and 2014, from 12.0% to 18.1%. While the proportion of individuals with advanced fibrosis was lowest in Eastern Europe between 2010 and 2014, this was no longer the case from 2015 as the burden of fibrosis ≥F3 increased in Eastern Europe, while decreasing in all other regions.

There were significant differences in the proportion of individuals with advanced fibrosis between regions ($p<0.05$) for all years, except 2015 ($p=0.2191$). In 2010 the burden of fibrosis ≥F3 was highest in Northern (31.1%) and Southern Europe (28.1%), and lowest in Eastern Europe (10.2%). However by 2018 the proportion of individuals with advanced fibrosis was highest in Eastern (20.7%) and Northern Europe (20.0%), and lowest in Central-West (7.6%).

Figure 3.4: Regional difference in advanced fibrosis and cirrhosis over time

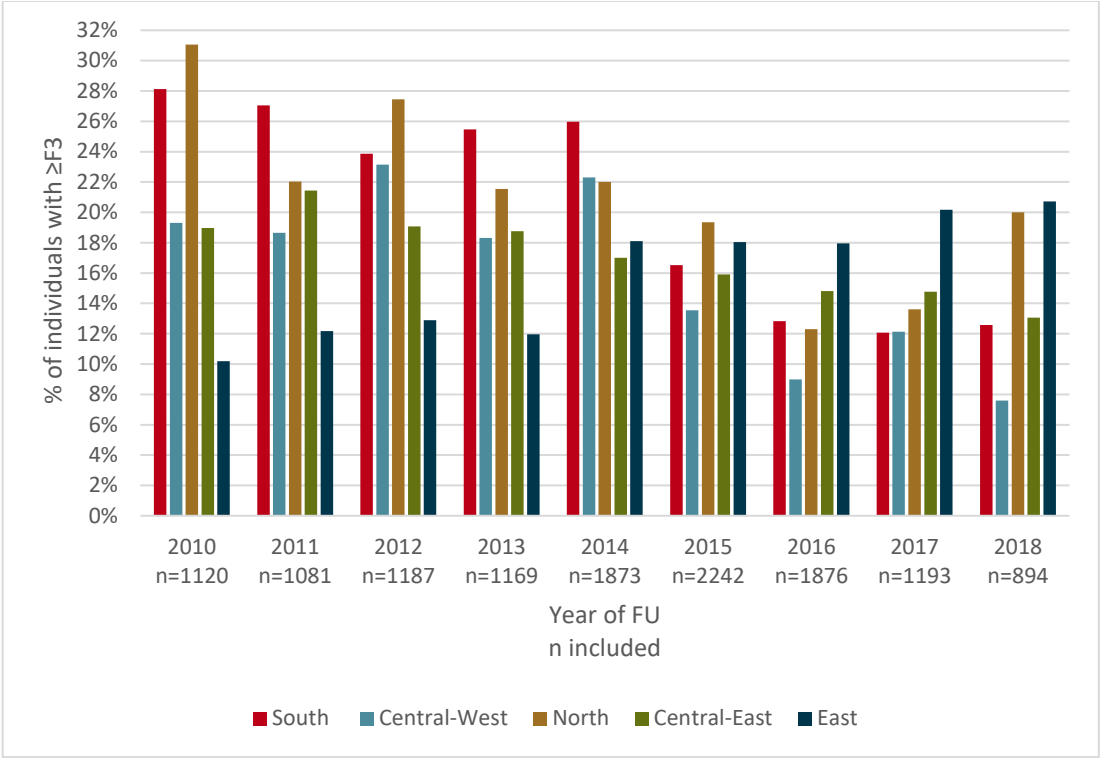


Table 3.7: Advanced fibrosis over time, by region

	n (%)								
Year	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
Overall	245 (21.9)	231 (21.4)	247 (20.8)	229 (19.6)	410 (21.9)	369 (16.5)	258 (13.8)	182 (15.3)	135 (15.1)
South	115 (28.1)	106 (27.0)	95 (23.9)	95 (25.5)	159 (26.0)	100 (16.5)	60 (12.8)	28 (12.1)	21 (12.6)
Central-West	44 (19.3)	39 (18.7)	50 (23.1)	39 (18.3)	97 (22.3)	66 (13.6)	30 (9.0)	24 (12.1)	12 (7.6)
North	32 (31.1)	24 (22.0)	28 (27.5)	25 (21.6)	44 (22.0)	59 (19.3)	30 (12.3)	17 (13.6)	18 (20.0)
Central-East	33 (19.0)	39 (21.4)	41 (19.1)	39 (18.8)	51 (17.0)	63 (15.9)	52 (14.8)	43 (14.8)	26 (13.1)
East	21 (10.2)	23 (12.2)	33 (12.9)	31 (12.0)	59 (18.1)	81 (18.0)	86 (18.0)	70 (20.2)	58 (20.7)

3.3.5.2 Factors associated with odds of fibrosis ≥F3

There were 3744 individuals who had at least 1 fibrosis marker between 2010 and 2019. Not every individual had a fibrosis measurement at each calendar year, therefore the data was unbalanced. There were a total of 12635 observations and the median number of measurements included per individual was 3 (IQR=2-5), however this ranged from 1 to 9. Across all 12635 observations from the 3744 individuals, the proportion of fibrosis ≥F3 was 18.3% (2306/12635, 95% CI=17.6-18.9). Among the 3744 individuals included, 1249 (33.4%, 95% CI=31.9-34.9) had advanced fibrosis at some point between 2010 and 2018, and 2541 (67.9%, 95% CI=66.4-69.4) individuals never received HCV treatment between 2010 and 2018. Among the 3744 individuals included in this analysis, 28.4%, 21.3%, 13.9%, 15.5%, and 20.9% were from South, Central-West, North, Central-East, and Eastern Europe, respectively. The majority of 3744 individuals were male (71.5%), of white ethnicity (89.6%), and PWID (59.8%). The most common genotype was 1 (45.6%) followed by genotype 3 (19.6%), genotype 4 (13.5%), and genotype 2 (2.5%) (18.8% had an unknown genotype).

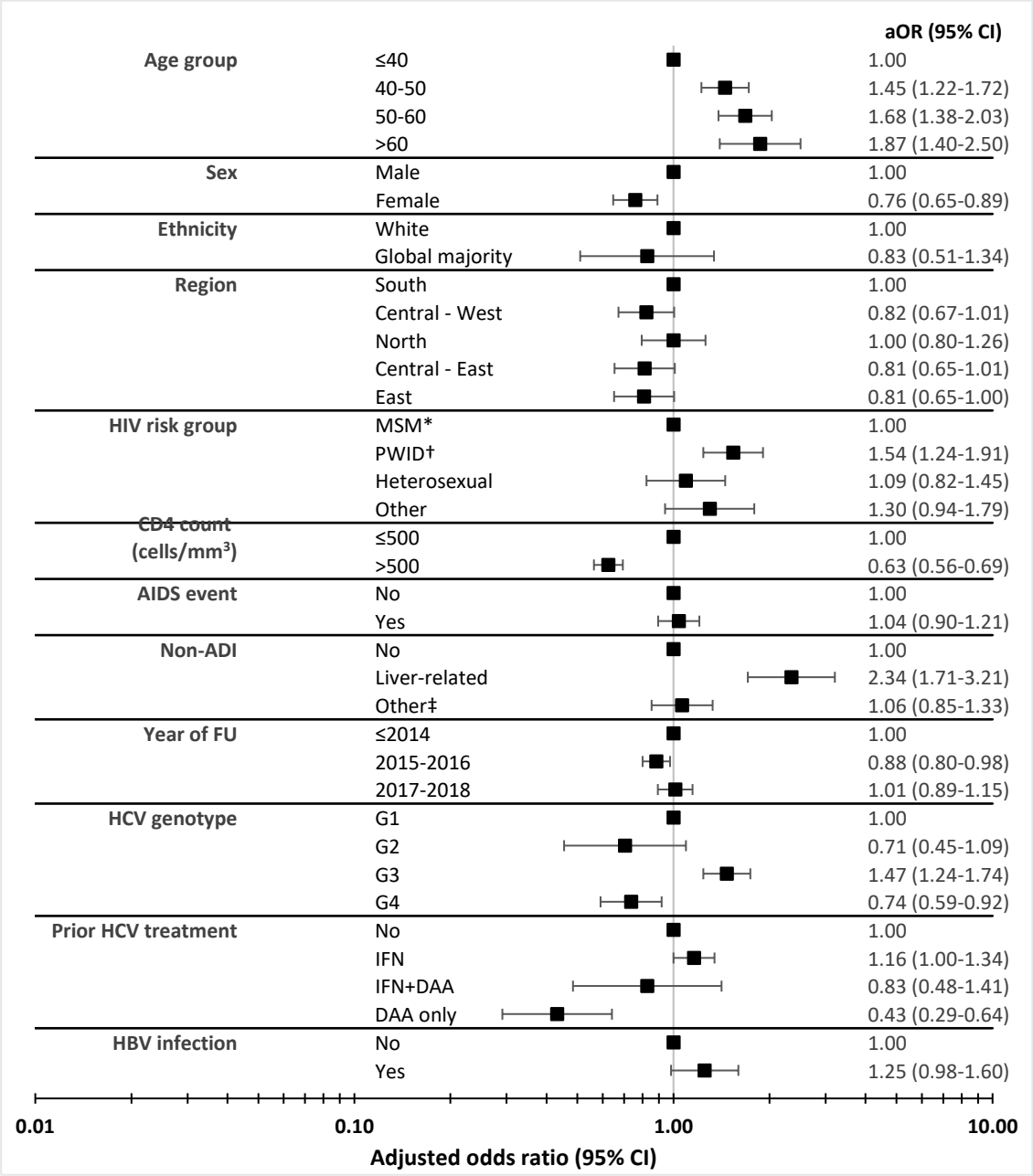
In univariable analysis, females were found to have a lower odds of having fibrosis ≥F3 compared to males [odds ratio (OR)=0.74, 95% CI=0.64-0.86], as were individuals from Central-West, Central-East and Eastern Europe (compared to Southern Europe) [OR=0.73, 95% CI=0.60-0.88, OR=0.67, 95% CI=0.54-0.83, and OR=0.69, 95% CI=0.57-0.82, respectively], those with CD4 count >500 cells/mm^3 [OR=0.63, 95% CI=0.57-0.69], and individuals from the global majority [OR=0.65, 95% CI=0.41-1.04]. Calendar year of fibrosis measurement also impacted the odds of having fibrosis ≥F3 as individuals in 2015-2016 had a lower odds compared to those in 2014 or earlier [OR=0.86, 95% CI=0.78-0.94]. Individuals with genotype 4 had a lower odds while those with genotype 3 had a higher odds (compared to genotype 1) [OR=0.73, 95% CI=0.59-0.91 and OR=1.49, 95% CI=1.26-1.76, respectively]. Finally previously being treated with a DAA only regimen was also associated with a lower odds of fibrosis ≥F3 compared to those not treated

[OR=0.47, 95% CI=0.32-0.70] while being treated with an IFN only regimen led to an increased odds of advanced fibrosis [OR=1.19, 95% CI=1.03-1.37]. Individuals 40-50, 50-60 and >60 years old were found to have a higher odds of fibrosis ≥F3 compared to those 40 years old or younger [OR=1.48, 95% CI=1.27-1.72, OR=1.69, 95% CI=1.44-1.98, and OR=1.73, 95% CI=1.34-2.24 respectively]. PWID and other HIV risk groups also had a higher odds of advanced fibrosis compared to MSM [OR=1.67, 95% CI=1.37-2.04 and OR=1.42, 95% CI=1.05-1.93], as did individuals with a previous AIDS event [OR=1.17, 95% CI=1.01-1.36] or liver-related non-ADI [OR=2.62, 95% CI=1.92-3.59]. HBV co-infected individuals also had a higher odds of advanced fibrosis [OR=1.27, 95% CI=0.99-1.62]

After adjusting for fixed time and time-updated variables, individuals aged 40-50, 50-60, or >60 years were all found to have a higher odds of advanced fibrosis compared to those ≤40 years [aOR=1.45, 95% CI=1.22-1.72, aOR=1.68, 95% CI=1.38-2.03, and aOR=1.87, 95% CI=1.40-2.50] (Figure 3.5). PWID also had an increased odds of fibrosis ≥F3 (compared to MSM) [aOR=1.54, 95% CI=1.24-1.91], as did those with a liver-related non-ADI [aOR=2.34, 95% CI=1.71-3.21]. Individuals with genotype 3 had a higher odds of advanced fibrosis [aOR=1.47, 95% CI=1.24-1.74], while individuals with genotype 4 had a lower odds [aOR=0.74, 95% CI=0.59-0.92]. Individuals who had previously received IFN based treatment (most recent treatment before the fibrosis marker for those who received multiple treatments) had a higher odds of advanced fibrosis [aOR=1.16, 95% CI=1.00-1.34] and those who received DAA only regimen had a lower odds of advanced fibrosis [aOR=0.43, 95% CI=0.29-0.64]. Females had a lower odds of fibrosis ≥F3 [aOR=0.76, 95% CI=0.65-0.89], as did individuals from Eastern Europe (compared to individuals from Southern Europe) [aOR=0.81, 95% CI=0.65-1.00, respectively], and individuals with a CD4 count >500 cells/mm^3 [aOR=0.63, 95% CI=0.56-0.69]. Over time the odds of advanced fibrosis also reduced, as those under FU and with a fibrosis measurement in 2015-2016 had a lower odds of fibrosis ≥F3 (compared to those included

≤2014) [aOR=0.88, 95% CI=0.80-0.98]. After adjustment ethnicity, prior AIDS event, and HBV infection were no longer significantly associated with the odds of fibrosis ≥F3.

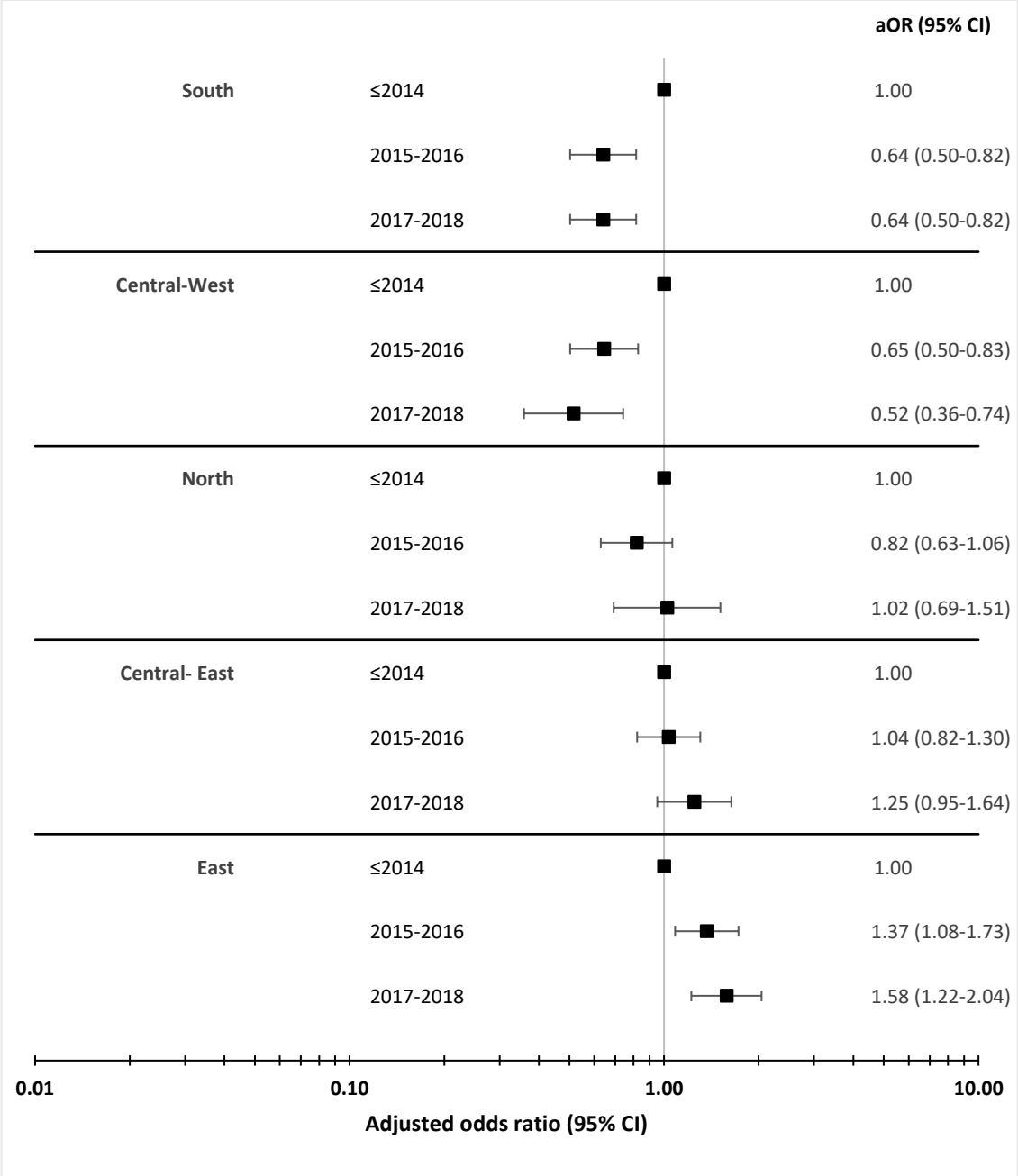
Figure 3.5: Adjusted odds of having fibrosis ≥F3



Model also adjusted for unknown ethnicity, CD4 count, genotype, and HBV infection
*MSM: Men who have sex with men, †PWID: people who inject drugs
‡Other non-ADI: non-AIDS defining malignancy (excluding HCC), cardiovascular disease, end-stage renal disease, or pancreatitis

We also tested for an interaction between region and year in the multivariable model and the interaction effect was found to be significant (p=0.0001), which shows that the change in the level of advanced fibrosis over time differed based on the region of Europe. The multivariable model in Figure 3.5 was then carried out within each region to explore how the effect of time on the odds of having advanced fibrosis varied by region. Due to data sparseness in the stratified analysis, ethnicity was taken out of the model, and prior HCV treatment was recategorised as 'yes' or 'no'. Figure 3.6 shows the results of the 5 multivariable models. In Southern Europe, the odds of advanced fibrosis decreased over time as the odds were lower in 2015-2016 and 2017-2018 (compared to ≤2014) [aOR=0.64, 95% CI=0.50-0.82 and aOR=0.64, 95% CI=0.50-0.82]. The odds of advanced fibrosis also decreased over time in Central-Western Europe [aOR=0.65, 95% CI=0.50-0.83 and aOR=0.52, 95% CI=0.36-0.74]. There was also evidence to suggest the odds of having advanced fibrosis increased over time in Eastern Europe [aOR=1.37, 95% CI=1.08-1.73, aOR=1.58, 95% CI=1.22-2.04, respectively]. There was no significant evidence to suggest there was any difference over time in Northern and Central-Eastern Europe.

Figure 3.6: Adjusted odds ratio of having fibrosis ≥F3, by region



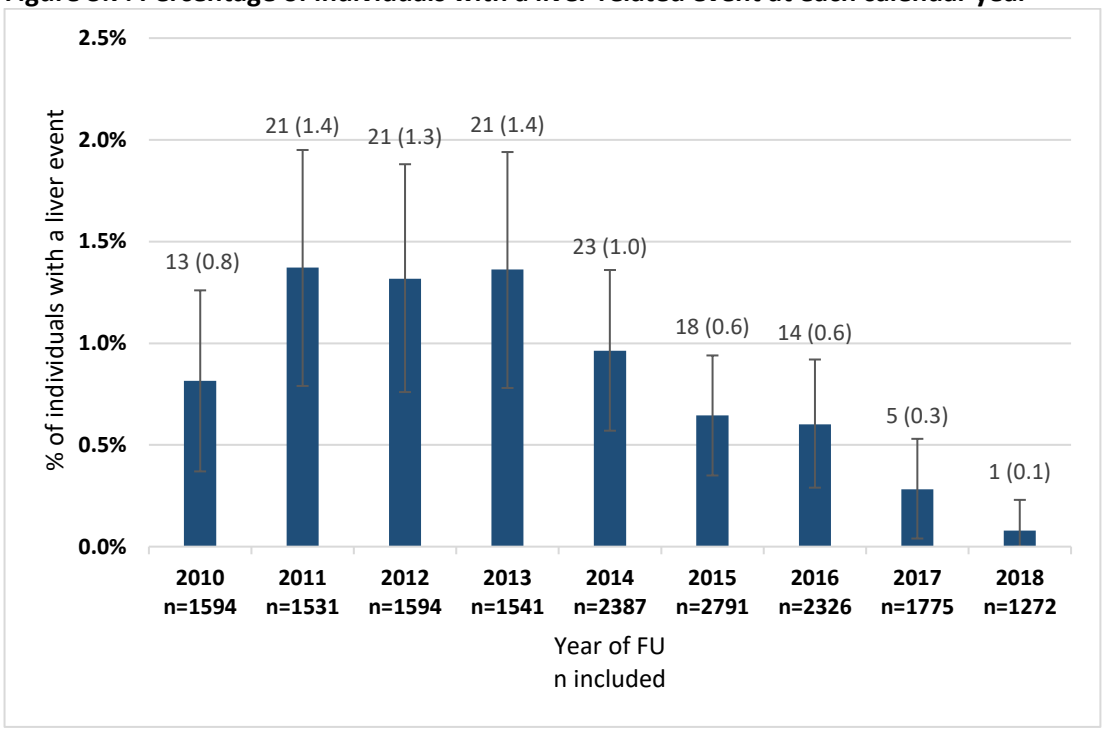
Results from 5 multivariable models which also adjusted for age, sex, HIV risk group, CD4 count, AIDS event, non-ADI, year of FU, HCV genotype, prior HCV treatment, and HCV infection

Ethnicity was not included and prior HCV treatment was categorised as 'yes' or 'no' due to data sparseness

3.3.6 The proportion of liver-related events over time

The proportion of individuals with a liver-related event between 1st January and 31st December, among those who were under FU and currently HCV-RNA positive at 31st December can be seen in Figure 3.7. The number of currently HCV-RNA positive individuals on 31st December at each year can be seen in the x-axis of Figure 3.7. There was an overall downward trend in the proportion of liver events over time, with a 0.7% decrease from 0.8% (95% CI=0.4-1.3) in 2010 to 0.1% (95% CI=0.0-0.2) in 2018. There was some small (0.6%) fluctuation in the proportion of liver events over time between 2011 and 2013. However, the proportion of liver events halved between 2016 and 2017, dropping from 0.6% (95% CI=0.3-0.9) to 0.3% (95% CI=0.0-0.5). The highest proportion of events occurred in 2011 and 2013 (1.4%, 95% CI=0.8-2.0 and 0.8-1.9, respectively), and the lowest proportion of events occurred in 2018 (0.1%, 95% CI=0.0-0.2). The number of events was very low across all years, with a maximum of 21 events in 2011, 2012, and 2013 and a minimum of 1 event in 2018.

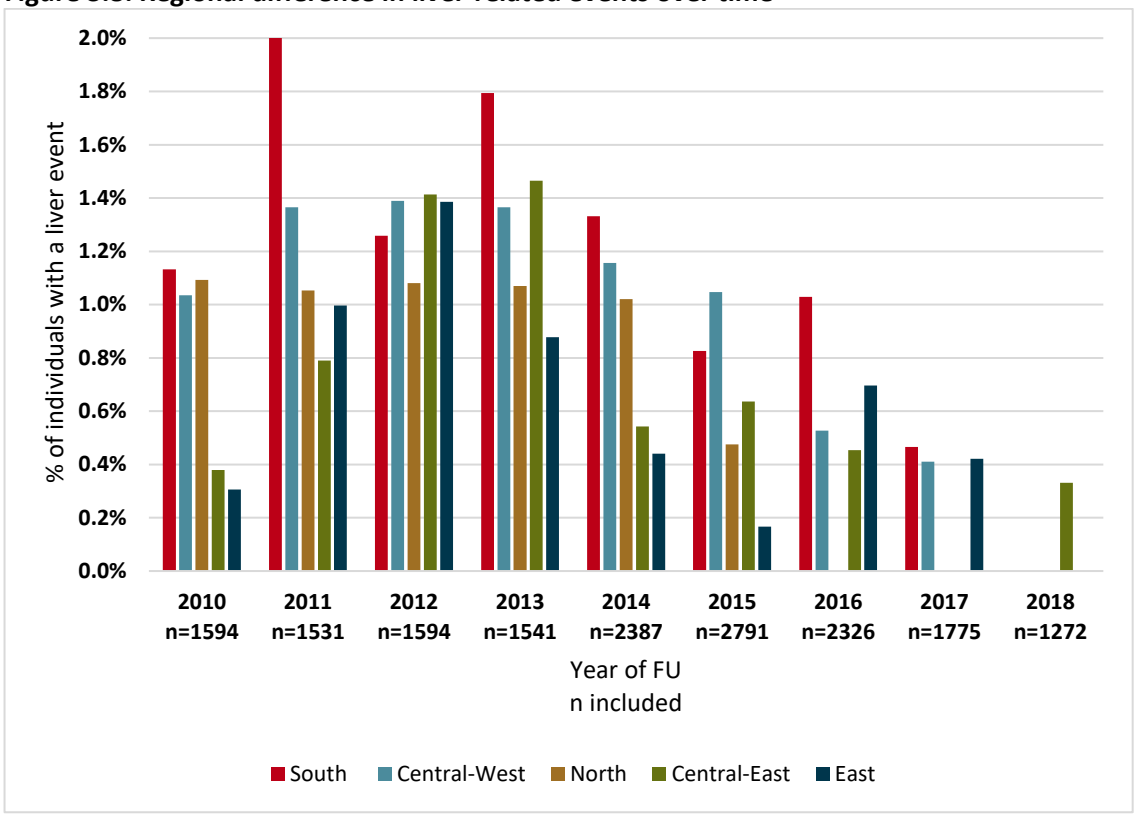
Figure 3.7: Percentage of individuals with a liver-related event at each calendar year



3.3.6.1 Change in the proportion of liver events over time, by region

Figure 3.8 shows the proportion of HCV-RNA positive individuals with a liver-related event at each calendar year for each region. The proportion of liver-related events decreased the most between 2010 and 2018 in South, North, and Central-Western Europe (1.1%, 1.1% and 1.0% difference, respectively). There were no significant differences in the proportion of liver-related events between regions at any calendar year ($p>0.1$). This may be due to the smaller number of liver-related events. Therefore, while Figure 3.8 appears to show regional differences across most time-points, the low number of liver-related events limited the power to explore regional differences.

Figure 3.8: Regional difference in liver-related events over time



3.4 Discussion

Among all HIV/HCV co-infected individuals included in this analysis between 2010 and 2018 (n=3744), the prevalence of fibrosis ≥F3 was 33.4% (n=1249, 95% CI=31.9-34.9). Age, gender, CD4 count, HCV genotype, non-ADI, and HCV treatment were all found to be associated with advanced fibrosis in multivariable analysis. After adjustment there were significant differences between regions, likely attributable to the duration of HCV infection and differences in clinic resources. There were also significant changes in the burden of fibrosis over time, however the changes over time differed between regions as the burden of fibrosis has increased over time in Eastern Europe and decreased in Southern and Central-Western Europe. There was also a considerable proportion of HCV-RNA positive individuals included in this analysis that never received HCV treatment (67.9%). These findings highlight the importance of better screening programs and improved access to HCV treatment.

3.4.1 Burden of fibrosis

The overall prevalence of advanced fibrosis or cirrhosis among individuals under FU between 1/1/2010 and 1/1/2019 and HCV-RNA positive was 33.4%. This finding is similar to the proportion of advanced fibrosis reported by studies in HIV/HCV co-infected individuals. De Ledinghen et al. found that 39% of co-infected individuals included between 2004 and 2006 (n=112) had advanced fibrosis (408). Also, Béguelin et al. reported that 33% of individuals included between 2011 and 2014 in the Swiss HIV Cohort Study had advanced fibrosis (413). This finding is higher than the proportion of advanced fibrosis among HCV mono-infected individuals reported by Klevens et al. (20%) and de Ledinghen et al. (18%) (407,408). Silver et al. reported a higher proportion of advanced fibrosis compared to other studies in HCV mono-infected individuals (28%). However, the analysis by Sliver et at. was carried out among African Americans during a

time when interferon-based treatment regimens were used, which were less effective among Black individuals compared to white individuals (411).

I found that the percentage of HCV-RNA positive individuals with advanced fibrosis decreased over time, from 21.9% in 2010 to 15.1% in 2018. There was some fluctuation between 2010 and 2014, however, the more substantial decreases occurred after 2014 as there was a 5.4% decrease between 2014 and 2015. The year 2014 was around the time that uptake of the new highly effective DAA treatment increased in Europe (368). Therefore the decrease in advanced fibrosis may be due to the increased uptake of safe and effective HCV treatment, as treating chronic HCV has been found to prevent further degeneration of the liver. Within each calendar year, there were significant differences between regions ($p<0.05$, except in 2015 ($p=0.2191$)), therefore the difference in the proportion of advanced fibrosis over time was also explored within each region. Overall, there was a downward trend in South, Central-West, North and Central-Eastern Europe. However, the proportion of fibrosis ≥F3 increased over time in Eastern Europe. Béguelin et al. also described a decrease in the burden of advanced fibrosis over time among individuals enrolled in the Swiss HIV Cohort Study (33% in March 2014 and 15% in December 2015) (413). They also found the majority of those treated between April 2014 and December 2015 (n=180) had advanced fibrosis (76.1%) due to treatment priorities (413). Treatment with DAAs was only reimbursed by Swiss health insurance for people with fibrosis ≥F3 until August 2015, when the threshold was reduced to Metavir F2 (413).

There was also a downward trend in the proportion of liver-related events between 2010 and 2018, from 0.8% to 0.1%. However, the number of liver-related events within each year was very low, ranging from 1 event in 2018 to 21 events in 2011, 2012, and 2013, therefore there was very limited power to explore regional differences in liver-related events.

3.4.2 Factors associated with fibrosis ≥F3

Factors associated with having fibrosis ≥F3 between 2010 and 2018 were explored using logistic regression with generalised estimating equations to account for repeated measures from individuals included in multiple years of FU. During univariable analysis, most regions (except Northern Europe) had a significantly lower odds of advanced fibrosis compared to Southern Europe. Older individuals, PWID (compared to MSM), individuals with genotype 3 (compared to genotype 1), and individuals who had previously received an IFN-based regimen (compared to no HCV treatment) had a higher odds of having advanced fibrosis. However, females, individuals from Eastern Europe (compared to Southern Europe), CD4 count >500 cell/mm^3, genotype 4, and individuals who previously received an IFN-free DAA regimen had a lower odds of having fibrosis ≥F3. After adjusting for other characteristics associated with advanced fibrosis such as age, gender, and CD4 count, the regional differences were still significant. Also after adjustment, the odds of advanced fibrosis was lower in 2015-2016 compared to 2010-2014.

The potential interaction between region and time was considered to be clinically important a priori and was therefore assessed, and the change in advanced fibrosis over time was found to vary significantly between regions. The effect of time within each region was explored in separate multivariable models for each region. The odds of having advanced fibrosis decreased over time in Southern and Central-Western Europe, increased over time in Eastern Europe, and there was no significant change over time in Northern or Central-Eastern Europe. As mentioned before, according to Peters et al. the uptake of effective DAA therapy increased in 2015, however they also found regional differences in treatment uptake (368). They described individuals from Central-East and Eastern as having a lower rate of DAA treatment uptake, and individuals from Central-Western Europe having a higher rate of DAA treatment uptake (compared to individuals from Southern Europe) (368). Therefore this finding is not surprising, as successful DAA

treatment is associated with a reduction in advanced fibrosis (413), and individuals from Eastern Europe had less access to DAAs. Also, Eastern Europe had the highest proportion of PWID (72%), which Peters et al. also described as having a reduced rate of DAA uptake (368).

While the Swiss HIV Cohort Study described the temporal change in the burden of fibrosis, it was limited to analysis of individuals within Switzerland (413). There are no published studies describing the regional differences in the change in the burden of advanced fibrosis over time in Europe, which limits comparisons with the regional difference over time found in this analysis.

Bailey et al. described the burden of advanced fibrosis among women between 2007 and 2012 and found 12.3% had fibrosis ≥F3 (410). While women had a lower odds of advanced fibrosis than men (aOR=0.76, 95% CI=0.65-0.89), the proportion of advanced fibrosis among women (18.4% vs 23.5% in men, p=0.0573) in the 2010 analysis was still around 6% higher than the study carried out in Ukraine. However, the median age of the participants of the Ukrainian study was 27.7 years old compared to 45.8 years old in this analysis. As described in the results, older individuals had a higher odds of fibrosis ≥F3, therefore this difference may be due to the differences in the study population age.

After adjustment individuals aged over 40 years were found to have a higher odds of advanced fibrosis, with those aged over 60 having the most increased odds. This finding is consistent with HCV mono-infected (303) and HIV co-infected studies (412) that have also found an association between older age and advanced fibrosis. This analysis also showed that poorly controlled CD4 count increased the odds of advanced fibrosis which is also consistent with other studies (410). Some studies have indicated that HIV

treatment reduces fibrosis progression (423,424), however I did not find any association between HIV treatment and advanced fibrosis.

3.4.3 Strengths and limitations

This analysis had several limitations, firstly, the EuroSIDA Study did not have reliable data on the date of HCV diagnosis, and therefore, I was not able to describe late presentation, or the impact of the infection duration on fibrosis in this analysis. This creates bias in regard to who is being included in this analysis. The EuroSIDA Study also did not have reliable data on alcohol usage, which is associated with fibrosis progression (303,412). Also, the proportion of patients with a liver-related event was small, which meant the analysis was not sufficiently powered to explore regional differences. Silver et al. found a higher rate of fibrosis among individuals of Black ethnicity, however their analysis was carried out in the IFN treatment era, and IFN based regimens were not as effective at treating chronic HCV in Black individuals (411). In the univariable analysis, individuals from the global majority had a borderline lower odds of advanced fibrosis compared to individuals of white ethnicity, however after adjustment the finding was no longer significant. This finding may be because the study was not sufficiently powered as only 2.6% of the study population were from the global majority. It would have been useful to explore the change in the prevalence of fibrosis in Black individuals since the introduction of DAAs so as to determine whether treatment type is the reason for the higher prevalence of fibrosis ≥F3 among Black individuals, or whether there are other systematic barriers to care that need to be considered. Also, I found that only 45.3% of individuals included in 2010 with a liver-related event had advanced fibrosis. However, as it is unlikely that a liver-related even would occur in someone with fibrosis <F3, therefore this finding may be due to the poor sensitivity of the APRI score in predicting cirrhosis, which is also a limitation of this study. Finally, clinics that participate in the EuroSIDA study are usually university affiliated and located in urban areas, therefore the care provided may not be representative of the standard of care in the country or region.

This analysis only included individuals who were HCV-RNA positive, however in some settings HCV-RNA testing is only carried out if HCV treatment can be offered. If this is the case, then there may be some individuals who are HCV-RNA positive and should be included in this analysis but are not included due to lack of testing and treatment resourses which may also affect the representativeness of these findings.

A major strength of this study is the large size as well as the inclusion of data from across Europe. Data is collected systematically and is centrally reviewed, which allows for comparisons between regions. Also, the longitudinal nature of this study allowed us to explore temporal changes within regions in the prevalence of advanced fibrosis, which has not been carried out in many other real-world studies. Over 59% of the study population were PWID, who are generally excluded from studies and not well reported on. This analysis also included 582 individuals (36% of study) from Central-East and Eastern Europe where the burden of advanced fibrosis is not well described.

3.5 Dissemination of results

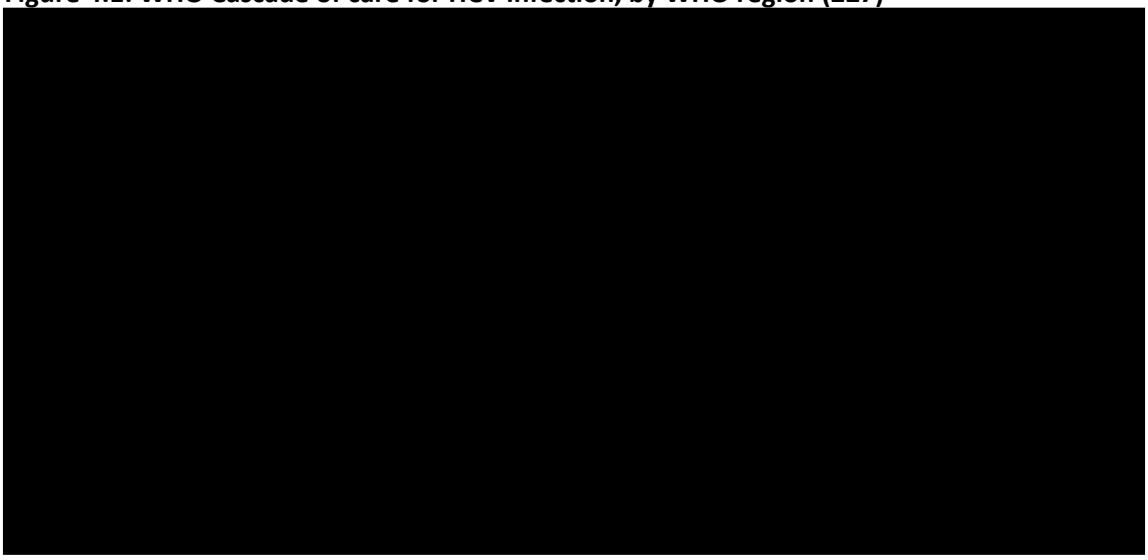
An early version of the results from this chapter was presented as a poster at the HepHIV conference in 2017, which can be seen in Appendix IV. The results presented at HepHIV were based on an older version of the dataset, however the results in this chapter have been further developed and updated to include more data.

Chapter 4 Establishing a cross-sectional and longitudinal hepatitis C continuum of care among HIV/HCV co-infected individuals in EuroSIDA

A continuum of care (CoC) is a framework that describes the successive steps in healthcare required for individuals to go through to achieve optimal health outcomes (384). The HIV continuum has become an integral public health tool for evaluating the outcome of HIV programmes, from diagnosis, to linkage to care, initiation of antiretroviral therapy and virological suppression. (425,426). The care continuum is not limited to HIV however and can be constructed for other conditions, such as HCV (384,427).

The World Health Organisation (WHO) published a Global Hepatitis Report in 2017, which estimated the global chronic HCV CoC in 2015 (Figure 4.1) (227). They reported the prevalence of HCV to be 71 million globally, of who only 14 million were diagnosed (20%), 1.1 million (2%) initiated treatment, and 843000 (1%) achieved SVR (227). In 2017, the WHO set a goal of eliminating viral hepatitis as a public health threat by 2030 (227). Achieving this goal would require a reduction in new infections by 90% and a reduction in mortality due to viral hepatitis by 65% compared with the 2015 estimates (227). Reaching this ambitious goal of elimination by 2030 requires a huge effort to increase testing, linkage to care and access to effective anti-viral therapy (227). Therefore a HCV CoC is an essential framework to predict, monitor and evaluate progress in achieving these targets and allows cross-country or population comparisons. A CoC can also be used to identify leaks, or breaks, in HCV care that need to be addressed in order to ensure individuals' transition through all stages and achieve SVR.

Figure 4.1: WHO Cascade of care for HCV infection, by WHO region (227)



This chapter has been split into two parts, Section 4.1 and Section 4.2. Section 4.1 is the main part of this chapter, which describes the cross-sectional approach to describing the HCV CoC among HIV/HCV co-infected individuals. Section 4.2 is an extension to the CoC chapter, where a novel technique to describe the longitudinal CoC is explored.

4.1 Cross-sectional HCV CoC

4.1.1 Introduction

4.1.1.1 HCV CoC

Several different HCV care continuums have been proposed for HCV mono-infected individuals, however the majority of these studies were carried out in the interferon (IFN) era (Table 4.1). Yehia et al. carried out a systematic review and meta-analysis of all studies carried out in the USA between 2003 and 2013 (428). They estimated that 3.5 million individuals in the USA were chronically infected with HCV, 50% of whom were diagnosed and 9% of whom achieved cure (428). Of those diagnosed, they estimated that only 37% were prescribed treatment and 22% achieved SVR (428). Hajarizadeh et al. estimated the HCV CoC in Australia in 2014 during the IFN treatment era (427). They

reported that of the 230470 individuals estimated to be living with chronic HCV, 75% were diagnosed, only 20% initiated treatment, and 11% were cured (427). While they estimated a high diagnosis rate, the rate of treatment initiation was still very low (427).

Zukerman et al. explored the HCV CoC in the USA during the DAA era (2015-2016). They found much higher rates of treatment initiation (60%) and SVR (53%) than the HCV CoC studies carried out in the IFN-era, however linking individuals to appropriate care providers was shown to be a challenging barrier to achieving SVR (429).

Table 4.1: Summary of HCV mono-infected CoC studies

Reference	Country	Stages	Year	Treatments	Number of individuals†	SVR, n (%)
Anderson E et al. (430)	**USA**	Part 1: Detection Undiagnosed HCV infection Tested and HCV-ab positive Viral load performed Chronically infected Part 2: Treatment **Chronically Infected*** Follow-up arranged Follow-up attended Treatment initiated SVR	May 2014 - Oct 2014	IFN-free DAA regimen	301	19 (6)
Hajarizadeh B et al. (427)	**Australia**	Living with chronic HCV infection* Diagnosed living with chronic HCV infection Ever received HCV treatment HCV cured	2014	IFN-based (± DAA)	230470	24750 (11)
Hawks L et al. (431)	**USA**	Total patients AB + VL checked **Chronic HCV*** Referred Specialist evaluation Tx started Tx completed SVR	Jul 09 - Sep 14	IFN-based	84	3 (4)
Iversen J et al. (432)	**Australia**	PWID in Australia Screened for HCV antibody HCV antibody positive Confirmatory HCV RNA or genotype test **HCV RNA positive or cured with treatment*** Confirmatory HCV RNA or genotype test HCV specialist assessment HCV antiviral treatment Cured	2015	IFN-based	43201	1391 (3)
Janjua N et al. (433)	**Canada**	Estimated prevalence Antibody diagnosed	>Dec 2012	IFN-based	30814	5197 (17)

		HCV RNA tested (only included those positive)*				
		Genotyped				
		Treatment initiated				
		Cured				
Machado S et al. (434)	**Brazil**	Blood donors anti-HCV+	1994 2012	IFN-based	631	133 (20)
		Aware*				
		Referred for consultation				
		Attended by specialist				
		Referred for therapy				
		Initiated treatment				
		SVR				
		Lost follow-up				
Maier M et al. (435)	**USA**	**Chronic HCV (estimated)***	> Dec 2013	IFN-based (± DAA)	233898	15983 (7)
		Diagnosed with chronic HCV				
		Linked to HCV care				
		Treated with HCV antivirals				
		Achieved SVR				
Noska A et al. (436)	**USA**	**Estimated No. of veterans with HCV infection***	2015	IFN-free DAA regimen	32449‡	5041 (16)
		Diagnosed with chronic HCV				
		Linked to HCV care			188156§	42878 (23)
		Received HCV antiviral therapy				
		Achieved SVR				
Simmons R et al. (437)	**UK**	Diagnosed anti-HCV positive	2005-2014	IFN-based (± DAA)	29557	3130 (11)
		RNA following anti-HCV result				
		RNA positive*				
		Ever treated				
		SVR				
Wade A et al. (438)	**Australia**	Referred to community hepatitis service	Apr 2011 - Aug 2014	IFN-based (± DAA)	279	33 (12)
		Attended community hepatitis				
		Diagnosed with chronic hepatitis C*				
		Had a valid fibroscan				
		Attended specialist appointment				
		Commenced treatment				
		Eligible for SVR assessment				
		Obtained SVR				

Yehia B et al. (428)	**USA**	**Chronic HCV-infected (estimated)*** Diagnosed and aware Access to outpatient care HCV RNA confirmed Underwent liver biopsy Prescribed HCV treatment Achieved SVR	Jan 2003 - Jul 2013	IFN-based	3500000	326859 (9)
Zuckerman A et al. (429)	**USA**	**Referred*** Evaluated Prescribed Approved Initiated Completed Achieved SVR	Oct 2015 - Sep 2016	IFN-free DAA regimen	187	100 (53)

* Stage used to determine SVR
† See column “Stages” for stage used for denominator, identified with “*”
‡ Homeless veterans
§ Non-homeless veterans

4.1.1.2 HCV CoC among HIV co-infected individuals

HIV/HCV co-infected individuals are considered a group with high priority for HCV therapy due to the increased speed of progression to liver disease compared to those with HCV mono-infection (382). However, they were previously considered to be a difficult to treat population due to reduced efficacy of treatment and drug interactions (227). However, the introduction of new effective and well tolerated direct-acting antivirals (DAAs) can lead to SVR in more than 90% of individuals co-infected with HIV (439) (see Chapter 5). Unfortunately, the benefits of the new and improved HCV treatment regimens will not be realised unless barriers to care and retention can be addressed. The CoC model is a very useful way to explore the impact of DAAs on transition through care, and to highlight where there are still gaps to ensure individuals are achieving SVR. While none of the steps in the HCV continuum of care are unique to HIV/HCV co-infected individuals, the optimal design of a continuum of care might be different for co-infected individuals already linked to specialist HIV care. However, proposed continuums for co-infected individuals use diverse methodology, therefore more work was required to develop a standardised continuum of care for HCV infected people living with HIV.

There are not many HCV CoCs studies in individuals also living with HIV (Table 4.2). Cachay et al. investigated the HCV CoC among HIV positive individuals under care at a university hospital in the USA. Between 2008 and 2012, 96% of the 4725 HIV positive individuals in care were screened for HCV. While they reported very high HCV screening rates among the HIV positive individuals, only 16% of the 562 HCV-RNA positive individuals initiated treatment, and only 7% achieved cure. Tsui et al. explored the HCV continuum among HIV positive PWID (440). They included individuals from the Linking Infectious and Narcology Care (LINC) and Russia Alcohol Research Collaboration on HIV/AIDS (Russia ARCH) studies, however follow-up was limited, and treatment outcome was only available for individuals in the ARCH study. Of the 201 individuals included in

the ARCH study only 10 were treated, 5 of whom achieved SVR (2%). Saris et al. described the HCV CoC among co-infected individuals receiving care at two HIV clinics in Amsterdam during the DAA era (441). They included 255 individuals with chronic HCV, 233 (91%) received DAA treatment, and 186 (73%) achieved SVR12 (441).

From the three studies described above, it seems the proportion of individuals retained in the CoC has improved in the DAA-era compared to the IFN-era (73% SVR in DAA-era vs 7% and 2% SVR in IFN-era). The link between access to DAAs and increased retention in care leading to viral suppression was explored by Roberson et al. (442). They produced their HCV CoC among HIV positive individuals at two time-points, comparing the results in the IFN-era (2008-2013) and DAA-era (2014-2015) to explore how the CoC changed over time (442). During the IFN-era, only 5% of HCV-RNA positive individuals received treatment, and only 2% achieved cure. However, during the DAA era, they found that 36% of individuals started HCV treatment and 31% achieved cure, highlighting that not only did treatment efficacy improve in the DAA era, but also the rate of treatment initiation.

Table 4.2: Summary of HCV CoC studies in HIV positive individuals

Reference	Country	Stages	Year	Treatments	Number of individuals†	SVR, n (%)
Cachay E et al. (443)	**USA**	Total number of patients followed at clinic Total number of patients who were screened for hepatitis C infection Total number of patients who had a reactive HCV serum antibody **Active HCV infection by detectable HCV RNA*** Referred for HCV treatment Attended at least 1 clinic visit for HCV treatment evaluation Final decision made regarding HCV therapy initiation Initiate HCV treatment HCV cure	2008 - 2012	IFN-based (± DAA)	562	41 (7)
Roberson J et al. (442)	**USA**	**HCV diagnosis*** Engagement in medical care HCV treatment SVR	2008 - 2013	IFN-based (± DAA)	408	4 (1)
			2014 - 2015	IFN-free DAA regimen	300	93 (31)
Saris J et al. (441)	**Holland**	**Chronic HCV*** Planned for DAA Started with DAA Virological outcome (only included those who achieved SVR12)	2014	IFN-free DAA regimen	255	186 (73)
Tsui J et al. (440)	**Russia**	HCV tested **HCV diagnosed*** HCV treatment status Was SVR achieved?	Jul 2012 - Jul 2015	IFN-based (± DAA)	201†	5 (2)

* Stage used to determine SVR

† See column "Stages" for stage used for denominator, identified with "*"

‡ Only included individuals from the ARCH study as there was insufficient FU to calculate SVR in the LINC study

4.1.1.3 Aims

There were 4 main aims of this analysis:

1) To establish a methodology for analysing the cross-sectional HCV continuum of care
2) To apply this methodology to the EuroSIDA study to identify key points of clinical HCV management across Europe, with a focus on regional differences in 2015 and 2017 (IFN-era and DAA era).
3) To informally compare differences in the cross-sectional CoC between 1/1/2015 and 1/1/2017
4) To describe factors associated with being HCV-RNA tested once already anti-HCV positive as a key point in HCV management.

4.1.1.4 What this analysis adds

As can be seen in Table 4.2, there are very few studies describing the HCV continuum of care among HIV positive individuals. While the introduction of DAAs has improved the treatment landscape for all, including HIV co-infected individuals, the literature shows that individuals are still lost at every stage of the CoC. This analysis aims to initially assess the HCV CoC at 1/1/2015, before widespread access to DAA therapy (368). As described above, there were significant differences in the CoC in the IFN-and DAA-era. Therefore, the CoC methodology used was then repeated at 1/1/2017 after the uptake of DAAs increased in Europe, and was compared with the 1/1/2015 CoC. This will allow us to explore how the introduction of DAA therapy impacted the progression of individuals through the continuum. While a similar analysis has been carried out by Roberson et al., they only included data from one medical centre in Washington, USA (442). The HCV pandemic is heterogeneous across and within regions, carrying out this analysis in the

EuroSIDA study will allow us to include data from all over Europe, and explore regional differences. Table 4.2 shows that only one CoC study has been carried out in Eastern Europe which had limited data (440), therefore this analysis will allow us to explore the CoC in regions not previously well described. Also, HCV diagnosis is a crucial step in the HCV CoC to ensure movement into other stages of the CoC such as treatment and cure, however there are still many barriers to successful testing (227). There are many anti-HCV positive individuals who do not receive a confirmatory HCV-RNA test, which is necessary to determine whether treatment is needed (444). Therefore, I explored which anti-HCV positive individuals were not HCV-RNA tested and unaware of the current HCV status, to better understand where to target interventions.

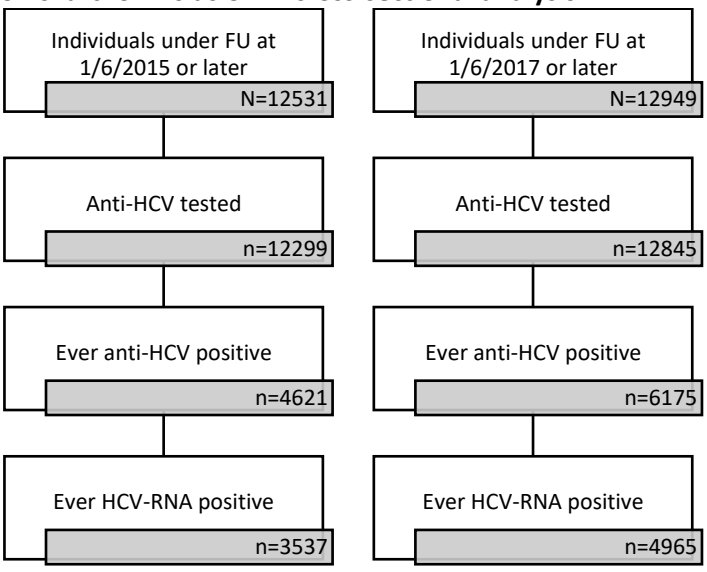
4.1.2 Methods

This analysis was based on data from the EuroSIDA D46 dataset. Cohort details and information on the collection of HCV data have been described in Chapter 2, Section2.2.

4.1.2.1 Inclusion criteria

There were 22825 individuals included in the D46 dataset, 12531 of whom were under follow-up (FU) up at 1/1/2015. I included all anti-HCV positive individuals who were under FU at the index date, defined as 1/1/2015 (last visit 1/1/2014 or later). Using this index date allows us to set the scene and understand the CoC prior to widespread access to DAA therapy in Europe (368). This analysis was then repeated at a later index date 1/1/2017 to explore the impact of DAAs on the CoC. There were 12949 individuals under FU at 1/1/2017 (last visit 1/1/2016 or later) who were included in this analysis. Figure 4.2 shows the number of individuals included in both the 2015 and 2017 cross-sectional CoC.

Figure 4.2: Flowchart for inclusion in cross-sectional analysis



4.1.2.2 Definition of cross-sectional Continuum of Care stages

The stages and definitions of the cross-sectional continuum of care are defined in Table 4.3. Individuals who satisfied the inclusion criteria of being under follow-up and anti-HCV positive before 1/1/2015 were included in this analysis (stage 1). The number of anti-HCV positive individuals who were HCV-RNA tested before the index date (stage 2) and currently HCV-RNA positive (stage 3) was then determined. The Stage 3 row of Table 4.3 below describes how individuals with missing HCV-RNA test data were assessed to explore whether they were HCV-RNA positive. Those ever HCV-RNA positive prior to the index date were included in stage 4, the proportion of whom initiated treatment before the index date (stage 5), completed treatment before the index date (stage 6), had a follow-up HCV-RNA test after completing treatment (stage 7), and achieved cure (stage 8) was also determined. SVR could only be assessed for those with a follow-up HCV-RNA test which was defined as an HCV-RNA negative result measured more than 12 or 24 weeks (for IFN-free or IFN based regimens respectively) after stopping treatment. Depending on the denominator, the term 'cure' or 'SVR' was used. The term 'cure' was used to indicate the number of individuals with a negative HCV-RNA test at more than 12 or 24 weeks post-treatment, among all individuals ever HCV-RNA positive. However, 'SVR' was used to describe the same number, among those that have completed HCV treatment and had a follow-up HCV-RNA test for SVR assessment.

Table 4.3: Cross-sectional HCV continuum of care definitions

Stage	Definition
Stage 1: Anti-HCV positive	Anti-HCV positive test, HCV-RNA positive, HCV genotyped or received HCV treatment before index date
Stage 2: Ever HCV-RNA tested	HCV-RNA tested, HCV genotyped or received HCV treatment before index date
Stage 3: Currently HCV-RNA positive	Most recent HCV-RNA test before index date was positive, HCV genotyped but not treated before index date, started treatment for the first time after index date, or the first HCV-RNA test result after index date is positive and never treated
Stage 4: Ever HCV-RNA positive	HCV-RNA positive test, received HCV treatment or HCV genotyped before index date
Stage 5: Ever received treatment	Started HCV treatment on or before index date
Stage 6: Treatment completed	Completed HCV treatment on or before index date
Stage 7: FU HCV-RNA available	HCV-RNA test more than 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively). HCV-RNA test data included for the duration of FU to allow for assessment of SVR
Stage 8: Cured/SVR*	HCV-RNA negative test at least 12 or 24 weeks post-treatment (for IFN-free and IFN-based therapy, respectively)

*If denominator is 'Ever HCV-RNA positive' then described as cure, if denominator is 'FU HCV-RNA available' then described as SVR

4.1.2.3 Variables included in this analysis

The baseline variables used in the different analyses have been described below in Table 4.4.

Table 4.4: Definitions of baseline variables included analysis

Variable	Levels	Definitions and comments
Age (years)	Continuous (per 1 year older) and categorised as ≤50 and >50 years old	
Sex	Male, female	
Region	South, Central - West, North, Central - East, Eastern Europe	Defined in Chapter 2 Section 2.2
Ethnicity	White, Global Majority, unknown	
HIV risk group	MSM, PWID, heterosexual, and other	'Other' includes those with unknown risk group
CD4 count (cells/mm^3)	Continuous and categorised as ≤500, >500 (cells/mm^3), and unknown	Most recent measurement prior to index date/baseline (within one year), if not available then measurement up to 6 months after index date/baseline included
CD4 nadir (cells/mm^3)	Continuous and categorised as ≤50, 50-200, and >200 (cells/mm^3), and unknown	Lowest CD4 count prior to index date/baseline, if not available then measurement up to 6 months after index date/baseline included
HIV-RNA (cp/ml)	≤500, >500, unknown	Most recent measurement prior to index date/baseline (within one year), if not available then

		measurement up to 6 months after index date/baseline included
AIDS-defining event	Yes, no	Defined using CDC's 1993 definition (421)
nADI	Yes, no	Non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, end-stage renal disease, pancreatitis (422)
Fibrosis	F0/1, F2, F3, F4, unknown and <F3, ≥F3*	Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels measured 1 year prior to baseline
HCV genotype	G1, G2, G3, G4, unknown, and G1, other/unknown	
On cART	Yes, no	Individual on cART (≥3 drugs) treatment at baseline
Prior HCV treatment	Yes, no	Individual received any HCV treatment prior to regimen included in analysis
Year of enrolment	<2016, ≥2016	Date individual was enrolled in EuroSIDA study
HBV infection	Yes, no, unknown	Defined using HBsAg surface antigen test or HBV DNA

*Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

4.1.2.4 Statistical analysis

4.1.2.4.1 Baseline characteristics

Baseline characteristics of individuals included in the 2015 cross-sectional analysis were described, and were based on the most recent measurement prior to the index data (1/1/2015). If an individual did not have a CD4 count or HIV-RNA value within 12 months prior to baseline, then a value up to 6 months after baseline was included instead. Fibrosis stage was defined using a consensus definition (225) and was determined based on the most reliable fibrosis marker measured within one year prior to the index date/baseline. The most reliable fibrosis marker was considered to be a biopsy result, followed by a Fibroscan result, an APRI score then finally a plasma hyaluronic acid level. Information on how fibrosis data is collected and defined in EuroSIDA has been described in Chapter 2, Section 2.2.7 (245). Categorical characteristics were described with numbers and percentages and numerical variables were described with medians and interquartile ranges. Regional differences in baseline characteristics were compared using chi-squared and Kruskal-Wallis tests for categorical and continuous variables, respectively.

4.1.2.4.2 Continuum of Care

The percentage of individuals at each stage of the CoC was described at both the 2015 and 2017 index date. The overall change in the percentage of people at each stage between the 2 index dates was then described. The change between the 2015 and 2017 CoC within each region was also described.

4.1.2.4.3 Factors associated with HCV-RNA testing

We wanted to explore which individuals in the cross-sectional CoC had a follow-up HCV-RNA test after being diagnosed as anti-HCV positive. Therefore, logistic regression was used to identify predictors of being HCV-RNA tested (Ever HCV-RNA tested (Stage 2) compared to those who were not tested). Variables found to be significant in univariable analysis ($p<0.1$) were included in the multivariable model. As regional difference in the continuum was one of the main research questions, it was included in the multivariable model a priori.

SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, North Carolina, USA).

4.1.3 Results

Different individuals were included in each analysis, this has been summarised below in Table 4.5

Table 4.5: Description of individuals included in each analysis

Section	Analysis	n included
4.1.3.1 Baseline characteristics of individuals included in 2015 CoC analysis	Description of individuals eligible	4621
4.1.3.2 Continuum of care: index date 1/1/2015	Description of CoC at 1/1/2015	4621
	Comparison of regional difference	4621
4.1.3.3 Predictors of HCV-RNA testing	Odds of being HCV-RNA tested (vs not tested)	3614 vs 1007
4.1.3.4 Continuum of care: index date 1/1/2017	Description of CoC at 1/1/2017	6175
	Comparison of regional difference	6175
	Comparison with 2015 CoC	4621 vs 6175

4.1.3.1 Baseline characteristic of individual included in analysis

Among 12531 HIV positive individuals under follow-up in EuroSIDA at the index date (1/1/2015), 12299 (98.6%) had been tested for anti-HCV. Of those anti-HCV tested, 4621 (37.6%) were anti-HCV positive (Stage 1) and included in these analyses. Of the 4621 anti-HCV positive individuals, 1311 (28.4%) were from Southern Europe, 1018 (22.0%) from Central-West, 552 (11.9%) from Northern, 665 (14.4%) from Central-East, and 1075 (23.3%) from Eastern Europe. Overall and regional characteristics of individuals who were anti-HCV positive and included in the analysis are shown in Table 4.6. There were significant differences ($p<0.001$) between regions for all characteristics in Table 4.6. The overall study population was mostly male (68.8%), ranging from 60.3% in Eastern Europe to 73.7% in Northern Europe. The median age was 47 years old (interquartile range [IQR]: 39-53), with a median age of 52 (IQR: 47-56) in Central-West and a younger median age of 37 (IQR: 33-41) in Eastern Europe. The most common route of HIV transmission route was injection drug use (IDU) in all regions (58.1% overall), however the highest proportion was in Eastern Europe (70.1%). Over 90% of individuals in from South,

Central-West, and Northern Europe had an HIV viral load <500 cp/ml, however only 85.9% and 50.9% of individuals were virally suppressed in Central-East and Eastern Europe (respectively). The median CD4 cell count was highest in Central-Western Europe (614 cells/mm^3 IQR: 427-816) and lowest in Eastern Europe (432 cells/mm^3 IQR: 290-600).

4.1.3.1.1 HCV genotype and fibrosis measurement

Of the 4621 individuals who were anti-HCV positive before 1/1/2015, 3567 (77.2%) had a liver fibrosis marker a maximum of 1 year before the index date (Figure 4.3). The majority of liver marker results were based on an APRI score (81.0%) followed by FibroScan (17.7%), and liver biopsy (1.3%). Central-Western Europe had the highest proportion of individuals with a fibrosis marker (86.6%) while Northern Europe had the lowest (56.3%). Of those with a fibrosis marker, 16.4% had advanced fibrosis or cirrhosis (METAVIR ≥F3). The burden of ≥F3 fibrosis ranged from 14.3% in Central-Eastern Europe to 20.6% in Northern Europe. Overall, 61.6% of those included in this analysis had been genotyped. Over 65% of individuals were genotyped from each region, except Eastern Europe where only 36.8% of individuals were genotyped. Genotype 1 was the most common genotype overall (53.6%) and in all regions, however 60.8% of individuals from Central-Eastern Europe had genotype 2-4.

Table 4.6: Characteristics of anti-HCV positive individuals included in 2015 cross-sectional analysis, overall and by region

		Overall	South	Central - West	North	Central - East	East
		n (%)					
Overall		**4621 (100.0)**	**1311 (28.4)**	**1018 (22.0)**	**552 (11.9)**	**665 (14.4)**	**1075 (23.3)**
Sex	**Male**	3180 (68.8)	934 (71.2)	737 (72.4)	407 (73.7)	454 (68.3)	648 (60.3)
	Female	1441 (31.2)	377 (28.8)	281 (27.6)	145 (26.3)	211 (31.7)	427 (39.7)
Ethnicity	**White**	4215 (91.2)	1227 (93.6)	859 (84.4)	400 (72.5)	656 (98.6)	1073 (99.8)
	Global majority	99 (2.1)	17 (1.3)	53 (5.2)	28 (5.1)	1 (0.2)	#VALUE!
	Unknown	307 (6.6)	67 (5.1)	106 (10.4)	124 (22.5)	8 (1.2)	2 (0.2)
HIV risk group	**MSM***	729 (15.8)	192 (14.6)	246 (24.2)	178 (32.2)	93 (14.0)	20 (1.9)
	PWID†	2684 (58.1)	792 (60.4)	441 (43.3)	258 (46.7)	439 (66.0)	754 (70.1)
	Heterosexual	825 (17.9)	222 (16.9)	167 (16.4)	75 (13.6)	82 (12.3)	279 (26.0)
	Other	383 (8.3)	105 (8.0)	164 (16.1)	41 (7.4)	51 (7.7)	22 (2.0)
HIV-RNA (cp/ml)	**≤500**	3740 (80.9)	1192 (90.9)	911 (89.5)	519 (94.0)	571 (85.9)	547 (50.9)
	>500	443 (9.6)	33 (2.5)	35 (3.4)	20 (3.6)	56 (8.4)	299 (27.8)
	Unknown	438 (9.5)	86 (6.6)	72 (7.1)	13 (2.4)	38 (5.7)	229 (21.3)
AIDS event	**No**	3311 (71.7)	940 (71.7)	683 (67.1)	429 (77.7)	514 (77.3)	745 (69.3)
	Yes	1310 (28.3)	371 (28.3)	335 (32.9)	123 (22.3)	151 (22.7)	330 (30.7)
Non-ADI‡	**No**	4082 (88.3)	1114 (85.0)	834 (81.9)	475 (86.1)	628 (94.4)	1031 (95.9)
	Yes	539 (11.7)	197 (15.0)	184 (18.1)	77 (13.9)	37 (5.6)	44 (4.1)
Fibrosis§	**F0/1**	2878 (62.3)	835 (63.7)	721 (70.8)	230 (41.7)	469 (70.5)	623 (58.0)
	F2	103 (2.2)	42 (3.2)	32 (3.1)	17 (3.1)	9 (1.4)	3 (0.3)
	F3	206 (4.5)	62 (4.7)	49 (4.8)	20 (3.6)	31 (4.7)	44 (4.1)
	F4	380 (8.2)	133 (10.1)	80 (7.9)	44 (8.0)	49 (7.4)	74 (6.9)
	Unknown	1054 (22.8)	239 (18.2)	136 (13.4)	241 (43.7)	107 (16.1)	331 (30.8)
HCV genotype	**G1**	1524 (33.0)	529 (40.4)	388 (38.1)	229 (41.5)	171 (25.7)	207 (19.3)
	G2	84 (1.8)	15 (1.1)	27 (2.7)	28 (5.1)	4 (0.6)	10 (0.9)
	G3	821 (17.8)	235 (17.9)	162 (15.9)	97 (17.6)	148 (22.3)	179 (16.7)
	G4	416 (9.0)	167 (12.7)	106 (10.4)	30 (5.4)	113 (17.0)	#VALUE!
	Unknown	1776 (38.4)	365 (27.8)	335 (32.9)	168 (30.4)	229 (34.4)	679 (63.2)
On cART	**No**	703 (15.2)	191 (14.6)	117 (11.5)	44 (8.0)	68 (10.2)	283 (26.3)
	Yes	3918 (84.8)	1120 (85.4)	901 (88.5)	508 (92.0)	597 (89.8)	792 (73.7)
Prior HCV treatment	**No**	2979 (64.5)	701 (53.5)	593 (58.3)	357 (64.7)	463 (69.6)	865 (80.5)

	Yes	1642 (35.5)	610 (46.5)	425 (41.7)	195 (35.3)	202 (30.4)	210 (19.5)
HBV infection	**No**	3887 (84.1)	1121 (85.5)	881 (86.5)	430 (77.9)	552 (83.0)	903 (84.0)
	Yes	320 (6.9)	77 (5.9)	85 (8.3)	41 (7.4)	56 (8.4)	61 (5.7)
	Unknown	414 (9.0)	113 (8.6)	52 (5.1)	81 (14.7)	57 (8.6)	111 (10.3)
				Median (IQR)			
Age (years)		47 (39-53)	50 (46-54)	52 (47-56)	51 (46-56)	41 (35-47)	37 (33-41)
CD4 count (cells/mm^3)		544 (376-760)	600 (416-815)	614 (427-816)	560 (402-788)	525 (369-723)	432 (290-600)
CD4 nadir (cells/mm^3)		158 (74-253)	163 (72-258)	146 (60-233)	156 (70-247)	156 (66-255)	171 (93-270)

Evidence of regional differences for all variables (p<0.0001)

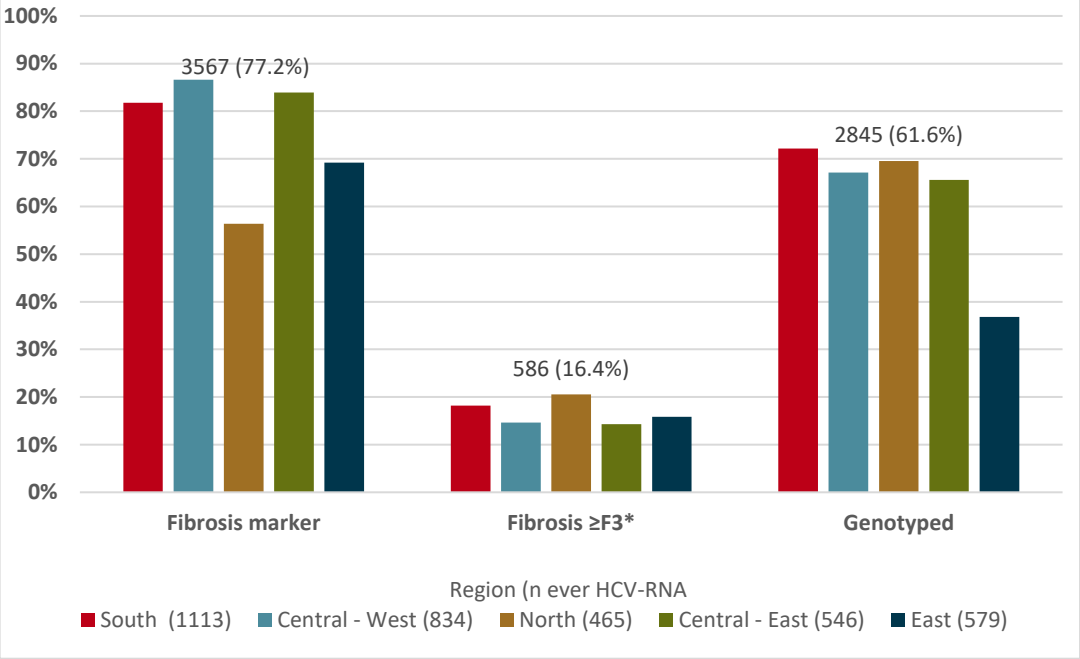
*MSM: Men who have sex with men, †PWID: People who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

§Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels

n with CD4 count =4300, n with CD4 nadir =4603

Figure 4.3: Liver fibrosis and HCV genotype, by region



*Calculated as a percentage of individuals with a fibrosis marker

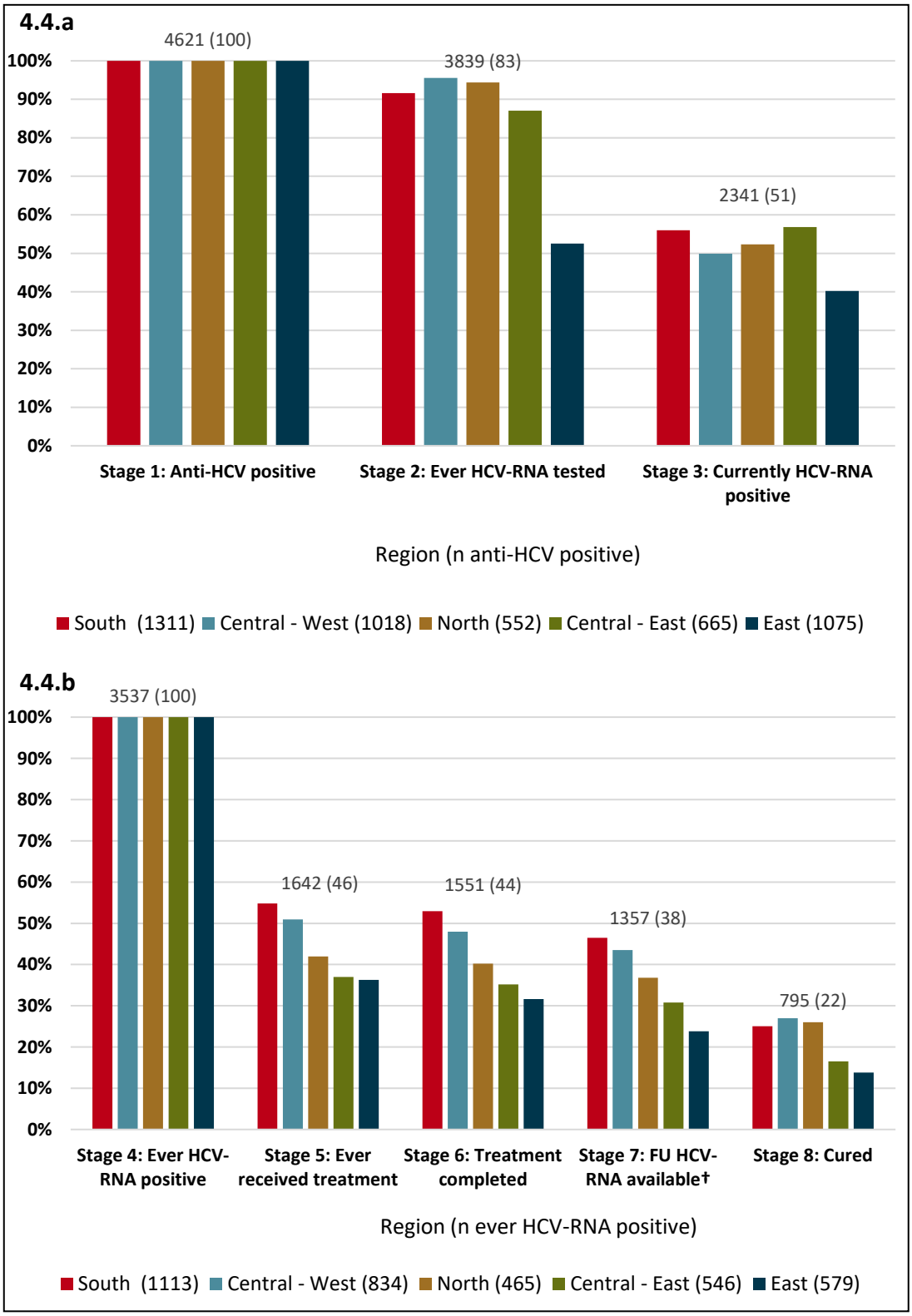
4.1.3.2 Continuum of care: index date 1/1/2015

Of the 4621 anti-HCV positive individuals who were included in this analysis, 3839 (83.1%) were HCV-RNA tested and 2341 (50.7%) were HCV-RNA positive at the index date 1/1/2015 (Figure 4.4.a). There were 3537 individuals with confirmed current or past positive HCV-RNA prior to 1/1/2015, among which 1642 (46.4%) had started HCV treatment, 1551 (43.9%) had completed HCV treatment, and 1357 (38.4%) had an HCV-RNA test result after completing treatment (allowing for SVR assessment) (Figure 4.4.b). Although 43.9% of all HCV-RNA positive individuals had completed HCV treatment, only 795 (22.5%) of the entire HCV-RNA positive population had confirmed HCV cure. However, 194/1551 (12.5%) of all who had completed treatment had missing follow-up HCV-RNA for SVR assessment. The proportion of individuals with SVR, of those that could have SVR assessed, was 58.6% (795 individuals). Of all the individuals who started HCV treatment, 62.6% received IFN+RBV, 6.7% IFN+DAA regimens, and 30.7% received IFN-free DAA regimens. The majority of individuals eligible for SVR assessment received an IFN-based regimen (84.7%) and had genotype 1 or 4 (65.7%), which is harder to treat with IFN-based regimens.

4.1.3.2.1 Regional differences in the continuum of care

There were significant differences between regions at each stage of the continuum ($p<0.0001$). The proportion of anti-HCV positive individuals who were HCV-RNA tested was >85% in South, Central-West, Northern, and Central-Eastern Europe, and much lower in Eastern Europe (52.6%). The proportion of individuals who had not started treatment after a positive HCV-RNA test result was consistently high across all regions. The proportion of ever HCV-RNA positive individuals who completed treatment ranged from 52.9% (589/1113) in Southern Europe to 31.6% (183/579) in Eastern Europe, while the proportion of individuals that completed treatment with a follow-up HCV-RNA test 12 or 24 weeks after completing treatment ranged from 75.4% (138/183) in Eastern Europe to 91.4% (171/187) in Northern Europe. There were also large regional differences in the proportion of ever HCV-RNA positive individuals with a confirmed cure, ranging from 13.8% in East and 16.5% in Central-Eastern Europe, to >25% in North, Central-West, and Southern Europe. Among individuals with a FU HCV-RNA test, Northern Europe also had the highest proportion of individuals who had received a DAA (IFN-free) treatment (15.8%). No individuals in Central-East or Eastern Europe received IFN-free regimens.

Figure 4.4: Cross-sectional HCV continuum of care at 1/1/2015, by region



The figure shows the diagnostic (Figure 4.4.a) and treatment (Figure 4.4.b) stages of the continuum of HCV care among HIV/HCV co-infected individuals in different geographical regions of Europe. Overall values for each stage of the continuum are shown above each stage, with percentages in parenthesis. Chi-squared test provides evidence of regional difference at all stages (p<0.0001)

†Individuals who had a FU HCV-RNA test at least 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively

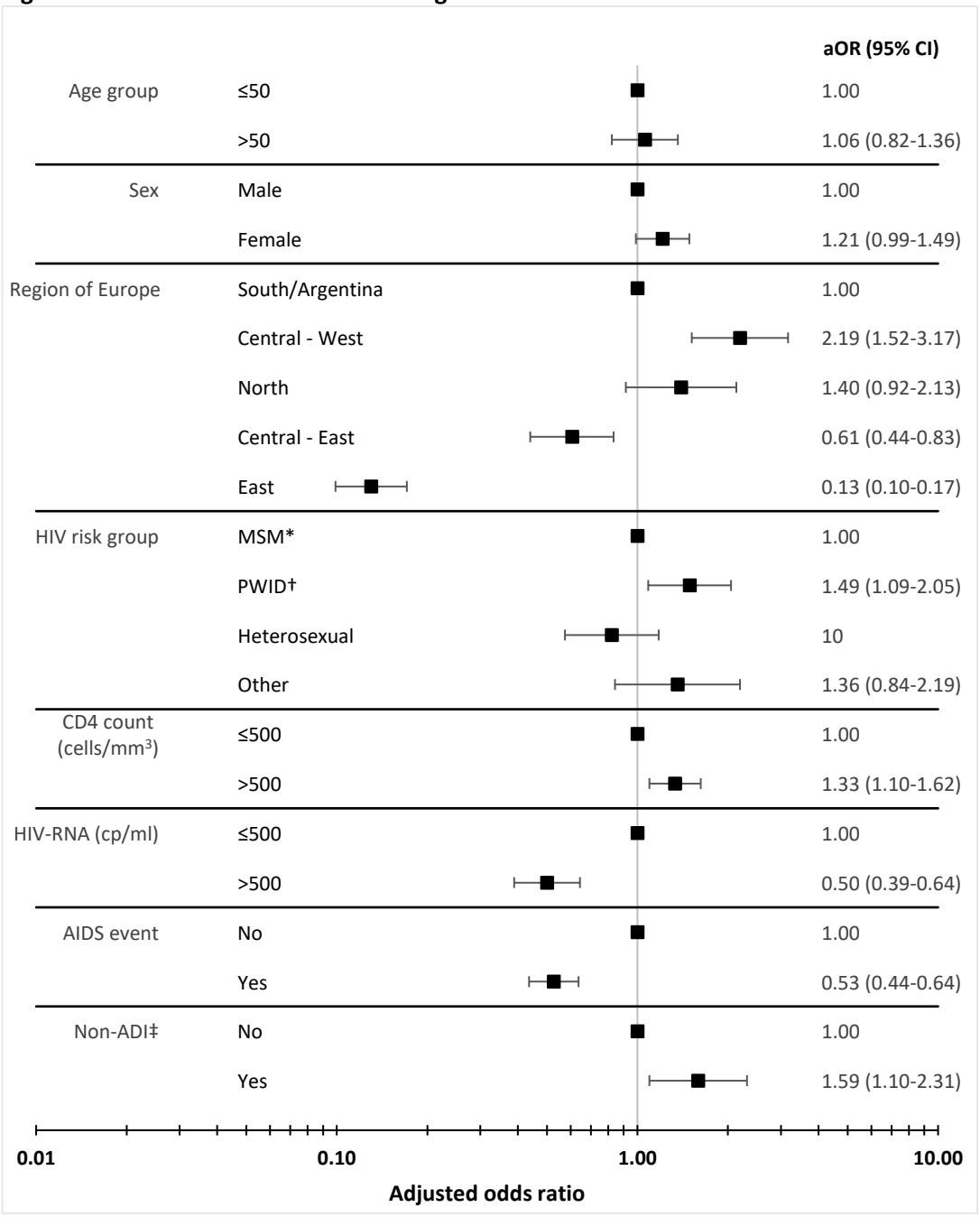
4.1.3.3 Predictors of being HCV-RNA tested

The odds of ever being HCV-RNA tested was assessed among all individuals included (4162 anti-HCV positive individuals). In univariable analysis being over 50 years old [odds ratio (OR)=3.51, 95% confidence interval (CI) 2.89-4.27], from Central-West or Northern Europe (compared to Southern Europe) [OR=1.98, 95% CI=1.39-2.83 and OR=1.54, 95% CI=1.02-2.32, respectively], having contracted HIV through PWID or heterosexual transmission (compared to MSM) [OR=2.09, 95% CI=1.59-2.73 and OR=3.46, 95% CI=2.58-4.65], having a CD4 count >500 cells/mm^3 [OR=2.13, 95% CI=1.80-2.53], a non-ADI [OR=2.77, 95% CI=1.99-3.86], and current cART usage [OR=1.83, 95% CI=1.51-2.21] were found to increase the odds of being HCV-RNA tested. Conversely being female [OR=0.86, 95% CI=0.73-1.01], from Central-East, or Eastern Europe [OR=0.62, 95% CI=0.46-0.83 and OR=0.10, 95% CI=0.08-0.13, respectively], having a HIV viral load >500 cp/ml [OR=0.17, 95% CI=0.14-0.21], and having an AIDS event [OR=0.61, 95% CI=0.52-0.72] were found to decrease the odds of being HCV-RNA tested. CD4 nadir, liver fibrosis, HCV genotype, and HBV co-infection were not found to impact the odds of being HCV-RNA tested. There were not enough individuals from the Global Majority to explore the impact of ethnicity on HCV-RNA testing.

Variables found to be associated with being HCV-RNA tested in the univariable analysis were included in the multivariable model (Figure 4.5). After adjustment, living in Central-West [adjusted odds ratio (aOR)=2.19, 95% CI=1.52-3.17], having contracted HIV through PWID transmission [aOR=1.49, 95% CI=1.09-2.05], having a CD4 count >500 cells/mm^3 [aOR=1.33, 95% CI=1.10-1.62], and having a non-ADI [aOR=1.59, 95% CI=1.10-2.31] were found to increase the odds of being HCV-RNA tested. Factors found to reduce the odds of being HCV-RNA tested included living in Central-East and Eastern Europe [aOR=0.61, 95% CI=0.44-0.83 and aOR=0.13, 95% CI=0.10-0.17 respectively], undetectable HIV viral load [aOR=0.50, 95% CI=0.39-0.64], and having a prior AIDS event [aOR=0.53, 95% CI=0.44-0.64]. After adjustment age, and sex were not found to have an association with being HCV-RNA tested. While

cART usage was significant in the univariable analysis, it was excluded from the multivariable model due to collinearity with HIV-RNA.

Figure 4.5: Factors associated with being HCV-RNA tested



Logistic regression model was also adjusted for unknown CD4 count and unknown HIV-RNA
*MSM: Men who have sex with men, †PWID: People who inject drugs
‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

4.1.3.4 Continuum of care: index data 1/1/2017

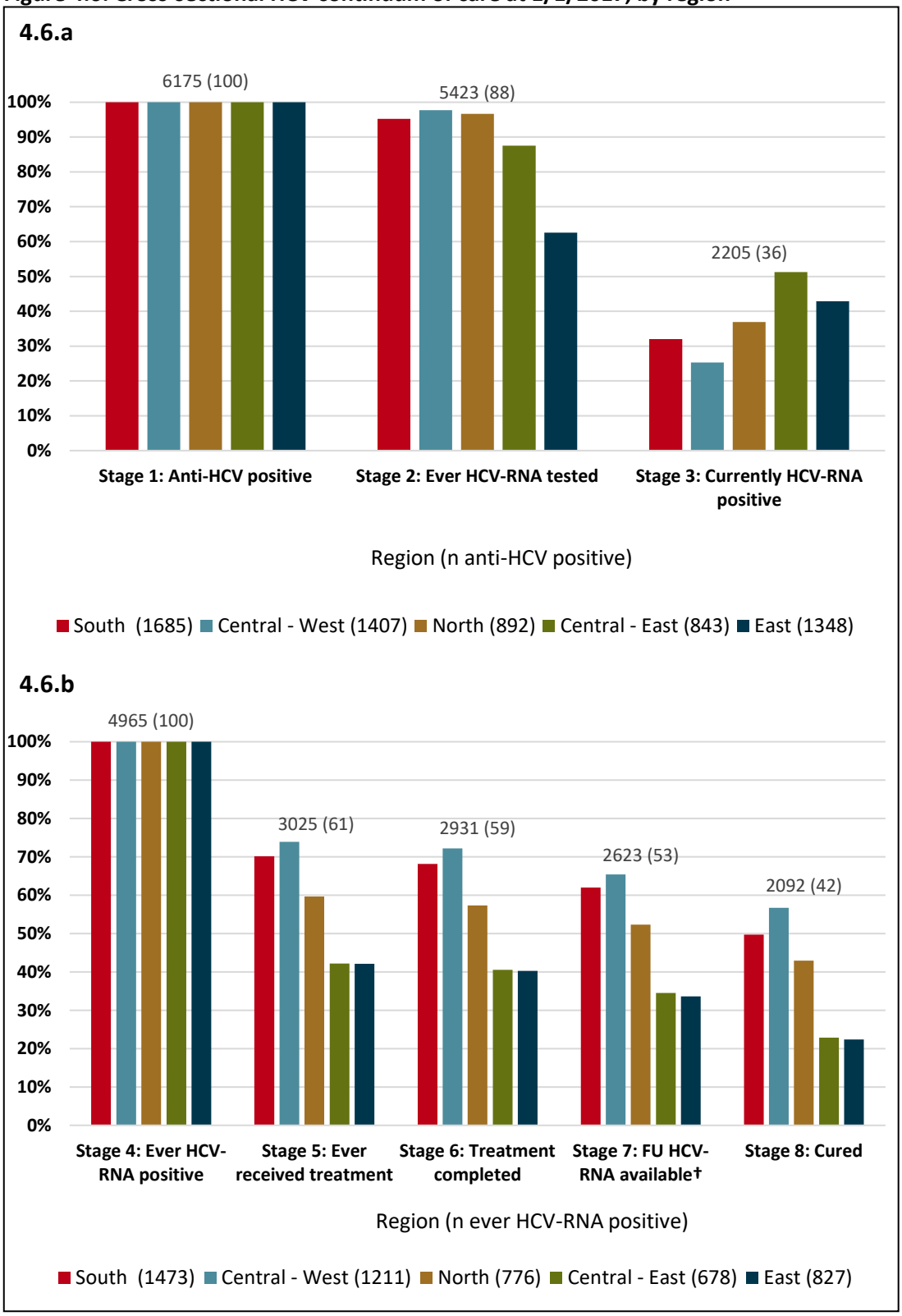
The CoC analysis was repeated at the index date of 1/1/2017 and included 6175 individuals who were under FU and anti-HCV positive at 1/1/2017. Of those anti-HCV positive, 5423 (87.8%) were ever HCV-RNA tested and 2205 (35.7%) were currently HCV-RNA positive (Figure 4.6.a). There were 4965 individuals who were ever HCV-RNA positive, of whom 3025 (60.9%) ever received treatment, 2931 (59.0%) completed treatment, 2623 (52.8%) had a FU HCV-RNA test available, and 2092 (42.1%) were cured (Figure 4.6.b). Of those with a FU HCV-RNA test available, 79.8% (2092/2623) of individuals had achieved SVR. Most individuals with a FU HCV-RNA test were treated with IFN (n=1395, 53.2%), followed by DAAs (n=1053, 40.1%), and IFN + DAA regimens (n=175, 6.7%). There were 5126 (83.0%) anti-HCV positive individuals who had a liver fibrosis marker, 10.7% of whom had fibrosis stage F3 or F4. Of those HCV-RNA positive, 80.0% of individuals were HCV genotyped.

4.1.3.4.1 Regional differences in the continuum of care

Figure 4.6 shows the regional differences at each stage of the CoC at index date 1/1/2017. Similarly to the 1/1/2015, there was evidence of regional differences at each stage of the continuum ($p<0.0001$). The proportion of individuals tested for HCV-RNA in South, Central-West and Northern Europe was >90%, however was only 80.3% in Central-East and 56.0% in Eastern Europe. The proportion of individuals who were currently HCV-RNA positive was highest in Central-Eastern Europe (49.9%) and lowest in Central-Western Europe (25.3%). Treatment was initiated in 74.0% of individuals in Central-Western Europe and only 42.6% in Eastern Europe. The proportion of individuals who did not complete treatment was around 2% across all regions. Among individuals who did complete HCV treatment, around 82% of individuals in Central-East and Eastern Europe had a FU HCV-RNA result available, compared to over 88% in Southern, Central-West, and Northern Europe. The proportion of individuals cured was lowest in East (22.4%) and Central-Eastern Europe (22.9%), and highest in Central-West (56.7%). SVR rates were also lowest in East and Central-East (67.3% and 68.2%), and highest in Central-West (89.0%).

However, the proportion of individuals with a FU HCV-RNA test who were treated with IFN-free DAAs was highest in North (48.5%), Central-West (46.7%), and Southern Europe (44.0%) and lower in Central-East (20.1%) and Eastern Europe (13.3%).

Figure 4.6: Cross-sectional HCV continuum of care at 1/1/2017, by region



The figure shows the diagnostic (Figure 4.6.a) and treatment (Figure 4.6.b) stages of the continuum of HCV care among HIV/HCV co-infected individuals in different geographical regions of Europe. Overall values for each stage of the continuum are shown above each stage, with percentages in parenthesis. Chi-squared test provides evidence of regional difference at all stages (p<0.0001)

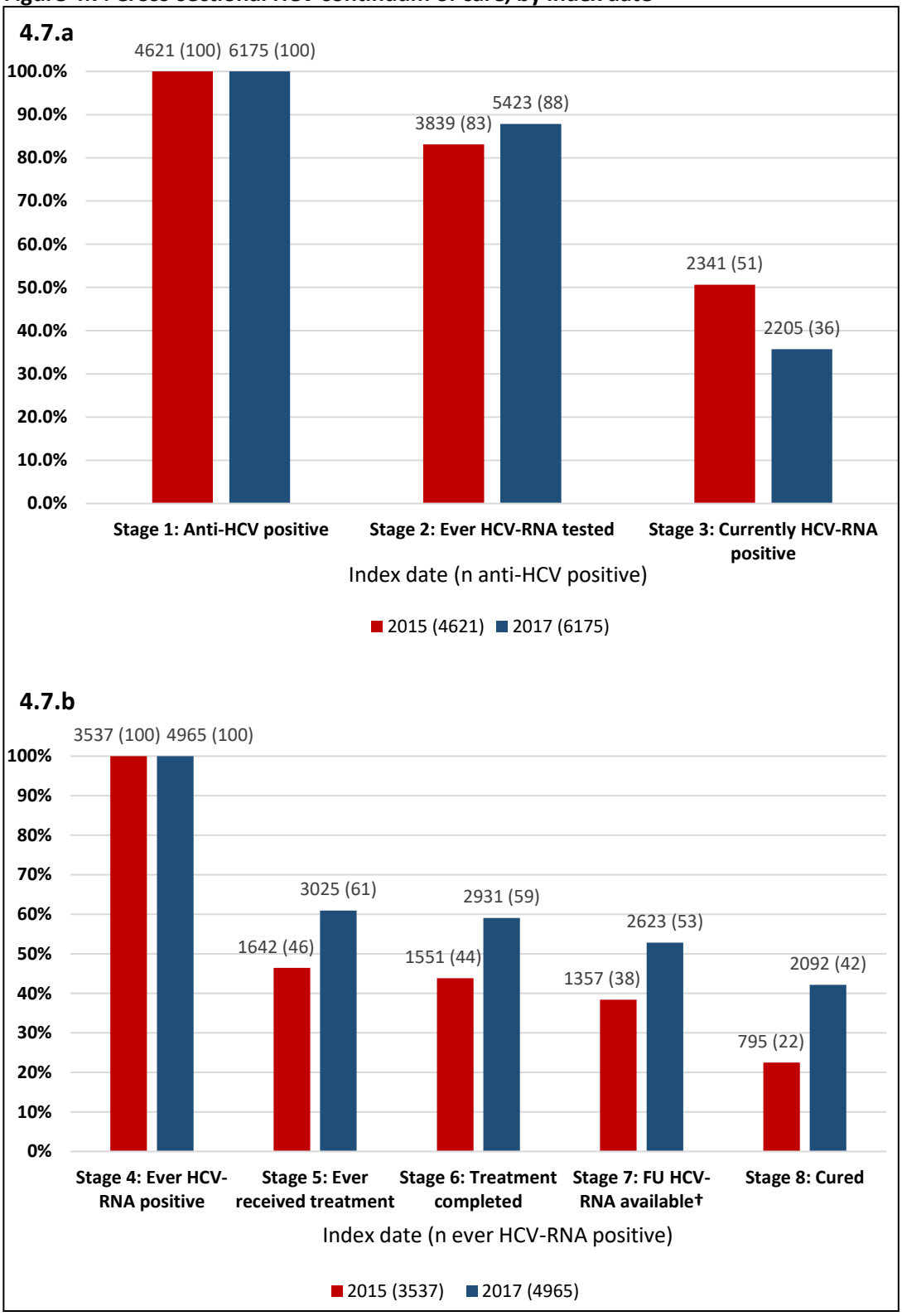
†Individuals who had a FU HCV-RNA test at least 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively

4.1.3.4.2 Comparison with 2015 CoC

Figure 4.7 shows the 2015 CoC compared with the 2017 CoC, where the denominator is calculated based on the total number of individuals included at each index date. Overall. the proportion of individuals transitioning to the next stage improved in 2017. In 2015, 83.1% of individuals of those anti-HCV positive were HCV-RNA tested, however this increased to 87.8% in 2017. The prevalence of being HCV-RNA positive at the index date decreased by 15.0% over 2 years (from 50.7% in 2015 to 35.7% in 2017). The percentage of ever HCV-RNA positive individuals who started treatment and completed treatment increased from 46.4% in 2015 to 60.9% in 2017 and 43.9% in 2015 to 59.0% in 2017, respectively. The largest improvement in the CoC was the percentage of individuals who were cured, which went from 22.5% to 42.1% between 2015 and 2017. The rate of SVR was also higher in 2017 (79.8%) compared to 2015 (58.6%). This improvement in the SVR rate corresponds to the increase in the proportion of individuals with a FU HCV-RNA test that received an IFN-free DAA regimen (6.6% vs 40.1%).

The proportion of anti-HCV positive individuals with a liver fibrosis mark within a year of the index date was higher at index date 1/1/2017 compared to 1/1/2015 (83.0% vs 77.2%), however, the proportion of those with fibrosis stage ≥F3 was higher in 2015 (16.4%) compared to 2017 (10.7%). The proportion of HCV-RNA positive individuals who were genotyped was similar at both index dates (81.4% at 1/1/2015 and 80.6% at 1/1/2017).

Figure 4.7: Cross-sectional HCV continuum of care, by index date



The figure shows the diagnostic (Figure 4.7.a) and treatment (Figure 4.7.b) stages of the continuum of HCV care among HIV/HCV co-infected individuals at different index dates. n included in each stage of the continuum is shown above each bar, with percentages in parenthesis.

†Individuals who had a FU HCV-RNA test at least 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively.

4.1.3.4.3 Comparison with 2015 CoC, by region

Table 4.8 shows the comparison between the 2015 and 2017 CoC for each region. This table shows that there were improvements over time across all regions. The largest improvement in HCV-RNA testing was in Eastern Europe, as they increased from 52.6% tested to 62.5% tested. However, the proportion in Eastern Europe is still low compared to other regions, where at least 87% of individuals were HCV-RNA tested in both 2015 and 2017. There was an absolute decrease of 24.6% and 23.9% in and Central-West and Southern Europe (respectively) in the percentage of individuals currently HCV-RNA positive, however this increased slightly in Eastern Europe (2.7%). There was a 22.9%, 17.7% and 15.3% absolute increase in the proportion of ever HCV-RNA positive individuals who received HCV treatment in Central-West, North, and Southern Europe. However, the percentage of ever HCV-RNA positive individuals who started treatment in Central-East and Eastern Europe only increased by around from around 37% in 2015 to 42% in 2017. There was a 29.8% increase in the proportion of individuals who were cured in Central-West (2015: 27.0%, 2017: 56.7%), however this was not as high in Central-East and Eastern Europe where there was only a 6.3% and 8.4% increase, respectively.

Table 4.7: Cross-sectional HCV continuum of care, by index date and region

Region	Year	Stage 1: Anti-HCV positive	Stage 2: Ever HCV-RNA tested	Stage 3: Currently HCV-RNA positive	Stage 4: Ever HCV-RNA positive	Stage 5: Ever received treatment	Stage 6: Treatment completed	Stage 7: FU HCV-RNA available†	Stage 8: Cured
					n (%)				
Overall	2015	4621 (100.0)	3839 (83.1)	2341 (50.7)	3537 (100.0)	1642 (46.4)	1551 (43.9)	1357 (38.4)	795 (22.5)
	2017	6175 (100.0)	5423 (87.8)	2205 (35.7)	4965 (100.0)	3025 (60.9)	2931 (59.0)	2623 (52.8)	2092 (42.1)
South	2015	1311 (100.0)	1201 (91.6)	734 (56.0)	1113 (100.0)	610 (54.8)	589 (52.9)	517 (46.5)	279 (25.1)
	2017	1685 (100.0)	1605 (95.3)	540 (32.0)	1473 (100.0)	1033 (70.1)	1004 (68.2)	913 (62.0)	732 (49.7)
Central - West	2015	1018 (100.0)	973 (95.6)	508 (49.9)	834 (100.0)	425 (51.0)	400 (48.0)	363 (43.5)	225 (27.0)
	2017	1407 (100.0)	1375 (97.7)	356 (25.3)	1211 (100.0)	895 (73.9)	874 (72.2)	792 (65.4)	687 (56.7)
North	2015	552 (100.0)	521 (94.4)	289 (52.4)	465 (100.0)	195 (41.9)	187 (40.2)	171 (36.8)	121 (26.0)
	2017	892 (100.0)	862 (96.6)	329 (36.9)	776 (100.0)	463 (59.7)	445 (57.3)	406 (52.3)	333 (42.9)
Central - East	2015	665 (100.0)	579 (87.1)	378 (56.8)	546 (100.0)	202 (37.0)	192 (35.2)	168 (30.8)	90 (16.5)
	2017	843 (100.0)	738 (87.5)	432 (51.2)	678 (100.0)	286 (42.2)	275 (40.6)	234 (34.5)	155 (22.9)
East	2015	1075 (100.0)	565 (52.6)	432 (40.2)	579 (100.0)	210 (36.3)	183 (31.6)	138 (23.8)	80 (13.8)
	2017	1348 (100.0)	843 (62.5)	578 (42.9)	827 (100.0)	348 (42.1)	333 (40.3)	278 (33.6)	185 (22.4)

4.1.4 Discussion

Section 4.1 of this chapter describes the HCV CoC among HIV positive individuals using the cross-sectional methodology. I propose an eight-stage cross-sectional HCV continuum of care for HIV/HCV co-infected individuals, which would allow cross-study comparisons for access and outcomes of HCV treatment in HIV/HCV co-infected individuals. There were 4621 individuals from across Europe co-infected with HIV and HCV at 1/1/2015 who were included in this analysis, and there were major gaps at all stages of the HCV CoC. There were also significant disparities between the different regions in Europe at each stage of the continuum, with South, Central-West and Northern Europe generally performing better than Central-East and Eastern Europe. Less than half of those chronically infected had initiated anti-HCV therapy and only 22.5% had a documented HCV cure, which is partly attributable to the lack of effective HCV therapy available at the time. The CoC was also described at 1/1/2017 and showed improvements in the proportion of individuals with a known HCV-RNA status, treated, and cured compared to the 2015 CoC. This provides evidence that the transition of individuals through the continuum has improved over time, as the proportion of individuals lost at each stage was lower in 2017. A comparison between the 2015 CoC and the 2017 CoC was also done for each region which showed improvements in all regions. However, while improvements in HCV-RNA testing was highest in Eastern Europe, improvements in treatment uptake and SVR was lower in Central-East and Eastern Europe.

4.1.4.1 Importance of standardised cross-sectional CoC

Lourenço et al. make the case for a standardised HIV continuum based on inconsistencies found in continuums from the USA, Canada, France, and Denmark (445). For example, while all reported viral suppression, the definitions varied greatly meaning cross-study comparisons, an essential tool for monitoring, were not feasible (445). The differences highlight the importance of a standardised continuum if comparisons with different populations and time-points are to be made confidently or if the impact of public health programs are to be measured (445). While this point

was emphasised in the HIV continuum, it also stands in the HCV context. Although there were eight stages in this continuum, more or fewer stages could be included depending on the setting. However, it is important to ensure key indicators around diagnosis, treatment, and cure are included to monitor progress towards the WHO 2030 goals for elimination of viral hepatitis as a public health threat (227).

Since the development of the methodology presented in this chapter to describe the cross-sectional HCV CoC, Safreed et al. published a consensus HCV cascade of care in 2019 (446). It was developed by a study group including clinicians, epidemiologists, and public health experts from Europe, North America and Australia. They included 4 stages in the cascade, infected, diagnosed, treated, and cured (446). The CoC was proposed to provide consistent reporting and monitoring of progress towards the WHO goal of HCV elimination by 2030 (227). They piloted their CoC methodology in Denmark, Norway, and Sweden using 2017 data. They reported that 44% of infected people were diagnosed in Denmark, compared to 70% and 80% of individuals diagnosed in Norway and Sweden (respectively). Among those diagnosed, 18% were treated in Norway, 8% in Sweden, and 5% in Denmark. While these findings are dissimilar from the 2017 CoC findings from Northern Europe presented in this chapter (57% ever received HCV treatment), the populations and definitions used differ, so it is not possible to make direct comparisons. This analysis only includes HIV/HCV co-infected individuals, however they were looking at all individuals with HCV. Also, I include individuals who received treatment at any point prior to 2017, while they only included individuals treated during 2017. They found significant differences between the CoC in Denmark, Norway, and Sweden, highlighting the intraregional difference in the HCV epidemic, which I was unable to explore.

4.1.4.2 Definition of stages

The consensus HCV CoC mainly differed from the CoC presented in this chapter because it included an initial stage estimating the prevalence of HCV in the

population (446). This is useful to determine the proportion of HCV positive individuals who have not been diagnosed. As well as not estimating the undiagnosed population, it was not possible to include an accurate measure of 'engagement in care', which other HIV/HCV co-infection continuums have estimated (442). This would be helpful to understand whether patients are not transitioning through the stages due to a lack of engagement or failures in health structures so that interventions and resources can be targeted at the appropriate area. Other descriptions of HCV continuums published prior to the consensus HCV CoC also included information that was beyond the scope of this analysis. For example, Hajarizadeh et al. also include an estimate for the number of people living with HCV in Australia and were therefore able to provide an estimate of the proportion of individuals living with HCV who were undiagnosed (25%) (427). However, they did not include information on individuals' engagement in care (427). The Austrian HIV Cohorts Study developed a continuum with similar stages to the continuum presented in this paper (447). While they also did not estimate the number of people living with HCV, their definition of SVR allowed them to capture reinfections (447). Cachay et al. included stages in their continuum around engagement in care; however, their continuum is based on data from a single clinic, and they also did not include an estimate of the number of people living with HCV (443). However, the cross-sectional continuum proposed in this thesis has some advantages over other descriptions of the HCV CoC, such as including information on the proportion of individuals who completed HCV treatment and the proportion of individuals who were followed-up after stopping treatment, which provides insight into whether poor of engagement with care is the potential reasons for not achieving SVR.

4.1.4.3 HCV-RNA testing

Approximately 1 in 5 anti-HCV positive individuals had no documented HCV-RNA test. This was explored using logistic regression, and after adjustment, those from Central-East or Eastern Europe were found to have a lower odds of being tested compared to those from Southern Europe. PWID, individuals with a CD4 count >500 cells/mm^3,

and individuals with a non-ADI were also more likely to be tested, while individuals with a HIV-RNA >500 (cp/ml) and those with an AIDS event were less likely to be HCV-RNA tested. An HCV-RNA test is relatively expensive (448), and it is possible that in some settings HCV-RNA testing is primarily targeted at individuals where HCV treatment is considered. By 2017 the proportion of individuals HCV-RNA tested increased to 88%, which indicated there have been some improvements in HCV diagnosis among HIV positive individuals between 2015 and 2017.

4.1.4.4 HCV treatment

Among patients known to be HCV-RNA positive, the proportion who had received HCV treatment was highest in Southern and Central-Western Europe and lower in other regions. Although the proportion treated in Northern Europe was similar to Central-East and Eastern Europe, fewer people had been HCV-RNA tested in Central-East and Eastern Europe. Although I focused on which stages might be needed in a hepatitis C continuum, it is worth noting that, for descriptive purposes, this continuum is based at January 2015, before the widespread introduction of DAAs. In the IFN-era, therapy was often deferred due to contraindications, toxicities, and low efficacy (449). Alcohol consumption, current injecting drug use and having a pre-existing psychiatric illness have been identified as the main reasons for not initiating HCV treatment, however, there is a lack of evidence to support excluding patients because of potentially poorer treatment outcomes, with treatment adherence better predicting SVR (450). Between the 2015 and 2017 CoC, there was a 15% increase in the proportion of ever HCV-RNA positive individuals who ever received HCV treatment. However, there are still challenges in the DAA-era, while The European Association for the Study of the Liver (EASL) guidelines for treating HCV recommends the prioritisation of HCV therapy for those with advanced liver fibrosis or from high-risk groups (359), access to treatment is still low in some countries due to high drug prices.

4.1.4.5 SVR

The proportion of individuals with confirmed HCV cure was low across all regions in 2015. These low cure rates should also be viewed in the context that IFN plus RBV was the predominant regimen in this study and that the majority of the study population had genotype 1 or 4, which are difficult to cure genotypes with IFN based regimens (326). At the point of analysis, second-generation DAAs had only been available for a short time, and therefore DAA uptake was still limited. Only 89 (6.6%) of the 1357 individuals with a follow-up HCV-RNA test after completing treatment received IFN-free treatment. By 2017 the SVR rate was 42% which is a 20% increase from 2015 (22%). Among the 2623 individuals with a FU HCV-RNA test, 40.1% received an IFN-free DAA regimen, which is a 33.6% increase from 2015. However, there were regional differences in the proportion of individuals receiving IFN-free DAAs, as only 13.3% of individuals from Eastern Europe with a FU HCV-RNA received IFN-free DAAs, compared with 48.0% of individuals from Southern Europe. This finding was expected, as we have already seen a rapid increase in DAA uptake in 2015 for all EuroSIDA regions except Eastern Europe (368). As DAAs are highly effective for all genotypes (439), SVR rates are expected to continue improving in the DAA era.

4.1.4.6 Strengths and limitations

One of the main limitations of the cross-sectional analysis was the lack of a follow-up HCV-RNA measurement at least 12/24 weeks after completing treatment, making it impossible to determine SVR for all patients. It is possible that HCV-RNA has been measured at a different site than HIV clinics tests and therefore not reported, although substantial efforts have been made to follow-up missing data from all sites as part of the quality assurance (QA) program in EuroSIDA. This study did not estimate the undiagnosed population, which is an important part of the continuum as one of the major breakpoints of the HCV continuum is diagnosis. Although cohorts are more inclusive and generalisable than clinical trials (250), they are still not entirely representative of all HCV infected individuals as there are vulnerable groups or incarcerated populations that are not included in cohorts. Also, EuroSIDA collects

data from centres of excellence, therefore the cross-sectional CoCs might be showing an optimistic picture of the CoC. There is also considerable intra-regional variation in the CoC. Participants are not enrolled into EuroSIDA in proportion to the epidemic, therefore while EuroSIDA collects data from multiple countries, some countries are overrepresented, and findings from that region will be dominated by that country.

Our study also has several important strengths, such as being one of the first studies to suggest a comprehensive cross-sectional continuum of care for HCV and HIV co-infected individuals. The size of the study population, which includes data from clinics all over Europe, is also a strength, as other continuums only include data from a single site, making the results less generalisable.

4.2 Longitudinal HCV CoC

4.2.1 Introduction

The cross-sectional CoC is a useful and convenient tool to visualise the pathway to achieving SVR. It is normally presented as a bar chart, displaying a 'snap-shot' of the current situation. However, while there are many benefits of the traditional CoC framework, there are also some limitations. Using the traditional framework, it is not possible to explore how individuals move through care over time as it only presents where individuals are in their care at one point in time, which does not allow for a non-linear care trajectory (451). Also, the standard method does not allow for the description of LTFU and mortality, as individuals included have to be alive and under FU. It is important to describe individuals who have been dropped from the CoC at each stage to understand what their outcomes are and where interventions should be targeted.

The longitudinal CoC is a helpful way to explore how individuals move through care over time and can overcome some of the limitations of the cross-sectional approach. Lesko et al. developed a novel method for visualising the HIV CoC longitudinally, that follow the same individuals over time as they transition through the stages of care (452). Jose et al. also present a similar method to describe the HIV CoC longitudinally which also uses time-updated factors to describe stages in the continuum over a ten year period (385). Neither Lesko's or Jose's methods exclude individuals who are LTFU or dead from the denominator and can therefore assess both as a relevant endpoint.

4.2.1.1 Aims

There were 3 main aims of this analysis:

1) To explore a methodology for analysing the longitudinal HCV continuum of care

2) To apply the longitudinal methodology to the EuroSIDA study, and explore differences based on the date of enrolment into to study and region
3) To explore factors associated with being HCV-RNA negative and treated (compared to HCV-RNA positive and never treated)

4.2.1.2 What this analysis adds

The time updated CoC methods such as those used by Jose et al. (385) and Lesko et al. (452) to describe the HIV CoC over time have not previously been applied to the HCV model. Creating a methodology for exploring the HCV CoC over time will allow us to better explore the gaps in the HCV continuum compared to using the traditional cross-sectional approach. Individuals do not always make sequential progress through the CoC stages, therefore it is important to explore how individuals may transition back and forth through the stages over time. Also, the main breaks in the CoC are not universal for all regions or patient populations, therefore, this method will allow us to explore regional differences as well as changes over time.

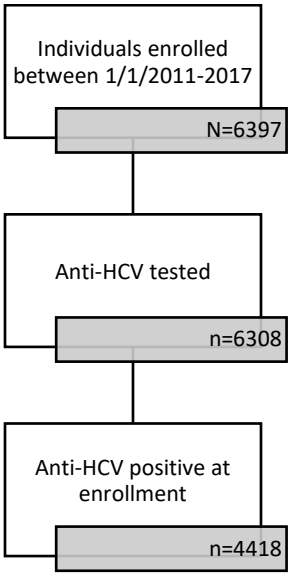
4.2.2 Methods

This analysis was based on data from the EuroSIDA D46 dataset. Cohort details and information on the collection of HCV data have been described in Chapter 2, Section 2.2.

4.2.2.1 Inclusion criteria

There were 6397 individuals who were enrolled into the EuroSIDA study between 1/1/2011 and 1/1/2017. Of these, 6308 were ever anti-HCV tested, and 4418 were anti-HCV positive at baseline, which was defined as the date of enrolment to the EuroSIDA study, and included in this analysis (Figure 4.8). Individuals who did not have at least 2 years of FU before 1/1/2019 (when the D46 dataset was closed) were excluded from this analysis. Individuals who did not have any data after being enrolled into the study were also excluded. An end date of 2 years after enrolment was specified for all individuals who were included in the analysis regardless of death or LTFU, as death or LTFU after baseline did not exclude individuals from this analysis.

Figure 4.8: Flowchart for inclusion in longitudinal analysis



4.2.2.2 Definition of longitudinal Continuum of Care stages

For the longitudinal CoC, I included all individuals who were enrolled in the EuroSIDA study between 1/1/2011 and 1/1/2017 and were anti-HCV positive (Stage 1). All individuals were followed for 2 years, and for each month, they were categorised into 1 of 7 stages (Figure 4.8). These stages were defined based on the individuals HCV status and treatment history as well as whether they were LTFU or died. LTFU was defined as not having a CD4 count, HIV-RNA, or visit data for 15 months. This was due to the HIV treatment guidelines specifying that HIV positive individuals are expected to attend a HIV clinical every 12 months (317), however, these visits may be delayed for a number of reasons, so I increased the window to 15 months to allow for any deferrals. The first stage (HCV-RNA unknown) included all individuals who were not HCV-RNA tested, LTFU, or dead. Individuals HCV-RNA positive were split by whether they had ever received HCV treatment (Stages 2 and 3). HCV-RNA negative individuals were also split into those never treated and treated (Stage 4 and 5, respectively). To explore the changes in DAA uptake over time, Stage 3 and Stage 5 were further split based on the individuals most recent HCV treatment regimen (IFN based vs IFN-free DAA regimen).

The proportion of person-month of FU (PMFU) spent in each stage at each month for the 2 years of FU was calculated. The results were then presented as a stacked area chart to describe how individuals transition through stages during 2 years of FU from enrolment into the study. To explore changes in the way individuals have transitioned through the CoC over time, the stacked area graph was stratified by year of enrolment (2011-2015 vs 2015-2017). These periods of time were compared due to the increase in DAA uptake in 2015 (368). The stacked area chart was also stratified by region and baseline demographics.

Table 4.8: Longitudinal HCV continuum of care definitions

Stage	Definition
Stage 1: HCV-RNA unknown	Anti-HCV positive test (excluding those HCV-RNA tested, HCV genotyped or HCV treated data before index date)
Stage 2: HCV-RNA positive – never treated	HCV-RNA positive test and never received treatment
Stage 3: HCV-RNA positive –treated*	HCV-RNA positive test and previously received treatment
Stage 4: HCV-RNA negative – never treated	HCV-RNA negative test and never received treatment
Stage 5: HCV-RNA negative –treated*	HCV-RNA negative test and previously received treatment
Stage 6: LTFU	15 months without CD4, HIV-RNA, or visits data
Stage 7: Dead	Died

*Split by treatment regimen for certain analysis

4.2.2.3 Variables included in this analysis

The baseline variables used in the different analyses have been described below in Table 4.9.

Table 4.9: Definitions of baseline variables included analysis

Variable	Levels	Definitions and comments
Age (years)	Continuous (per 1 year older) and categorised as ≤50 and >50 years old	
Sex	Male, female	
Region	South, Central - West, North, Central - East, Eastern Europe	Defined in Chapter 2, Section 2.2
Ethnicity	White, Global Majority, unknown	
HIV risk group	MSM, PWID, heterosexual, and other	'Other' includes those with unknown risk group
CD4 count (cells/mm^3)	Continuous and categorised as ≤500, >500 (cells/mm^3), and unknown	Most recent measurement prior to index date/baseline (within one year), if not available then measurement up to 6 months after index date/baseline included
CD4 nadir (cells/mm^3)	Continuous and categorised as ≤50, 50-200, and >200 (cells/mm^3), and unknown	Lowest CD4 count prior to index date/baseline, if not available then measurement up to 6 months after index date/baseline included
HIV-RNA (cp/ml)	≤500, >500, unknown	Most recent measurement prior to index date/baseline (within one year), if not available then measurement up to 6 months after index date/baseline included
AIDS-defining event	Yes, no	Defined using CDC's 1993 definition (421)
nADI	Yes, no	Non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, end-stage renal disease, pancreatitis (422)
Fibrosis	F0/1, F2, F3, F4, unknown and <F3, ≥F3*	Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels measured 1 year prior to baseline
HCV genotype	G1, G2, G3, G4, unknown, and G1, other/unknown	
On cART	Yes, no	Individual on cART (≥3 drugs) treatment at baseline

Prior HCV treatment	Yes, no	Individual received any HCV treatment prior to regimen included in analysis
Year of enrolment	<2016, ≥2016	Date individual was enrolled in EuroSIDA study
HBV infection	Yes, no, unknown	Defined using HBsAg surface antigen test or HBV DNA

*Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

4.2.2.4 Statistical analysis

4.2.2.4.1 Baseline characteristics

Baseline characteristics of individuals included in the cross-sectional analysis were described, and were based on the most recent measurement prior to the index data (1/1/2015). Baseline characteristics of individuals included in the longitudinal analysis were also described and were defined based on the most recent measurement before baseline (enrolment to EuroSIDA). Fibrosis stage was defined using a consensus definition (225) and was determined based on the most reliable fibrosis marker measured within one year prior to the index date/baseline. The most reliable fibrosis marker was considered to be a biopsy result, followed by a Fibroscan result, an APRI score then finally a plasma hyaluronic acid level. Information on how fibrosis data is collected and defined in EuroSIDA has been described in Chapter 2, Section 2.2.7 (245). Categorical characteristics were described with numbers and percentages and numerical variables were described with medians and interquartile ranges. Regional differences in baseline characteristics were compared using chi-squared and Kruskal-Wallis tests for categorical and continuous variables, respectively.

4.2.2.4.2 Factors associated with negative HCV-RNA result

For the longitudinal CoC, determining which individuals were transitioning from HCV-RNA positive – never treated (Stage 2) to HCV-RNA negative – treated (Stage 5) was of particular interest. Logistic regression with Generalised Estimating Equations (GEEs) was used to identify predictors of being HCV-RNA negative – treated. GEEs were used due to the repeated measures from the same individuals. Using GEEs

allows for robust standard errors to be used whilst taking into account correlations between individuals when estimating the effect. Variables found to be significant in univariable analysis ($p<0.1$) were included in the multivariable model. Region was also included in this model a priori.

SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, North Carolina, USA).

4.2.3 Results

Different individuals were included in each analysis, this has been summarised below in Table 4.10.

Table 4.10: Description of individuals included in each analysis

Section	Analysis	n included
4.2.3.1 Baseline characteristics of individuals enrolled between 1/1/2011 and 1/1/2017	Description of individuals eligible	4418
4.2.3.2 Overall CoC	Description of overall longitudinal CoC	4418
	Description by treatment regimen	4418
	Description of individuals who died	155
4.2.3.3 Predictors of HCV-RNA negative - treated	Odds of being HCV-RNA negative - treated (vs HCV-RNA positive - never treated)	27762 vs 34611*
4.2.3.4 CoC by region	Description of longitudinal CoC by region	4418
4.2.3.5 CoC over time	Description of longitudinal CoC by year of enrolment	4418

*Included repeated measures for each individual. Number of observations shown, not individuals

4.2.3.1 Baseline characteristics of individuals enrolled between 1/1/2011 and 1/1/2017

There was a total of 4418 individuals who were anti-HCV positive and enrolled into the EuroSIDA study between 1/1/2011 and 1/1/2017. 1115 (25.2%) individuals were from Southern Europe, 1117 (25.3%) from Central-West, 630 (14.3%) from North, 481 (10.9%) from Central-East, and 1078 (24.4%) from Eastern Europe (Table 4.11). There were 2203 (49.9%) individuals who were enrolled before 2015 and 2215 (50.1%) individuals who were enrolled between 1/1/2015 and 1/1/2017. The majority of individuals included were of white ethnicity (85.7%), male (72.5%), had a median age of 45 years old (IQR: 37-52), and a median CD4 count of 532 cells/mm^3 (IQR: 351-746). The most common mode of HIV transmission was PWID (54.5%), followed by MSM (20.0%), heterosexual (18.4%), and other (7.1%). Most individuals were on cART (83.5%) and had HIV viral load ≤500 cp/ml (79.5%). There were regional differences for all baseline characteristics (p<0.0001). Eastern Europe had a higher proportion of females included (34.3%) than the other regions (<27.8%), and individuals included

from Central-East and Eastern Europe had a lower median age (38 and 36 years old, respectively) compared to other regions (49-50 years old). The CD4 count was 392 cells/mm^3 (IQR: 253-560) in Eastern Europe, 491 (IQR: 323-681) in Central-East, and above 570 cells/mm^3 in North, Central-West and Southern Europe. Only 0.9% of individuals from Eastern Europe were MSM compared to above 15% MSM in all other regions. However, there was a higher proportion of individuals in the heterosexual HIV risk group in Eastern Europe (30.5%) compared to other regions (<16%). The proportion on cART was also lower in Eastern Europe (72.4%) than in other regions (≥82.3%).

The proportion of individuals with a fibrosis marker was highest in Central-Western Europe (94.0%) and lowest in Southern (70.8%) and Northern Europe (71.0%). Of those with a liver fibrosis marker, Sothern Europe had the highest prevalence of stage F3 or F4 fibrosis (23.3%), followed by North (20.8%), East (16.1%), Central-West (15.3%), and Central-Eastern Europe (14.1%). The proportion of individuals HCV genotyped was highest in Southern (79.4%) and Northern Europe (77.0%), and lowest in Eastern Europe (49.3%). Of those with an HCV genotype, genotype 1 was the most common overall (55.6%). However, there was more variation in HCV genotype in Central-East (55.2% genotype 2 – 4) compared to other regions (<45% genotype 2 – 4).

Table 4.11: Baseline characteristics at enrolment to EuroSIDA study in anti-HCV positive individuals enrolled between 1/1/2011 and 1/1/2017, by region of Europe

		Overall	South	Central - West	North	Central - East	East
				n (%)			
Overall		**4418 (100.0)**	**1112 (25.2)**	**1117 (25.3)**	**630 (14.3)**	**481 (10.9)**	**1078 (24.4)**
Sex	**Male**	3201 (72.5)	803 (72.2)	846 (75.7)	488 (77.5)	357 (74.2)	707 (65.6)
	Female	1217 (27.5)	309 (27.8)	271 (24.3)	142 (22.5)	124 (25.8)	371 (34.4)
Ethnicity	**White**	3787 (85.7)	1040 (93.5)	752 (67.3)	452 (71.7)	475 (98.8)	1068 (99.1)
	Global majority	110 (2.5)	7 (0.6)	61 (5.5)	40 (6.3)	2 (0.4)	#VALUE!
	Unknown	521 (11.8)	65 (5.8)	304 (27.2)	138 (21.9)	4 (0.8)	10 (0.9)
HIV risk group	**MSM***	883 (20.0)	185 (16.6)	361 (32.3)	228 (36.2)	99 (20.6)	10 (0.9)
	PWID†	2410 (54.5)	692 (62.2)	438 (39.2)	272 (43.2)	290 (60.3)	718 (66.6)
	Heterosexual	812 (18.4)	169 (15.2)	173 (15.5)	86 (13.7)	55 (11.4)	329 (30.5)
	Other	313 (7.1)	66 (5.9)	145 (13.0)	44 (7.0)	37 (7.7)	21 (1.9)
HIV-RNA (cp/ml)	**≤500**	3511 (79.5)	957 (86.1)	1042 (93.3)	585 (92.9)	370 (76.9)	557 (51.7)
	>500	612 (13.9)	48 (4.3)	51 (4.6)	39 (6.2)	66 (13.7)	408 (37.8)
	Unknown	295 (6.7)	107 (9.6)	24 (2.1)	6 (1.0)	45 (9.4)	113 (10.5)
AIDS event	**No**	3496 (79.1)	851 (76.5)	858 (76.8)	533 (84.6)	381 (79.2)	873 (81.0)
	Yes	922 (20.9)	261 (23.5)	259 (23.2)	97 (15.4)	100 (20.8)	205 (19.0)
Non-ADI‡	**No**	4088 (92.5)	978 (87.9)	998 (89.3)	593 (94.1)	465 (96.7)	1054 (97.8)
	Yes	330 (7.5)	134 (12.1)	119 (10.7)	37 (5.9)	16 (3.3)	24 (2.2)
Year of enrolment	**<2015**	2203 (49.9)	597 (53.7)	552 (49.4)	248 (39.4)	264 (54.9)	542 (50.3)
	≥2015	2215 (50.1)	515 (46.3)	565 (50.6)	382 (60.6)	217 (45.1)	536 (49.7)
Fibrosis§	**F0/1**	2764 (62.6)	552 (49.6)	839 (75.1)	332 (52.7)	337 (70.1)	704 (65.3)
	F2	148 (3.3)	52 (4.7)	51 (4.6)	22 (3.5)	15 (3.1)	8 (0.7)
	F3	206 (4.7)	53 (4.8)	55 (4.9)	32 (5.1)	23 (4.8)	43 (4.0)
	F4	426 (9.6)	130 (11.7)	106 (9.5)	61 (9.7)	35 (7.3)	94 (8.7)
	Unknown	874 (19.8)	325 (29.2)	66 (5.9)	183 (29.0)	71 (14.8)	229 (21.2)
HCV genotype	**G1**	1603 (36.3)	494 (44.4)	386 (34.6)	305 (48.4)	126 (26.2)	292 (27.1)
	G2	103 (2.3)	17 (1.5)	28 (2.5)	28 (4.4)	4 (0.8)	26 (2.4)
	G3	742 (16.8)	200 (18.0)	147 (13.2)	99 (15.7)	83 (17.3)	213 (19.8)
	G4	433 (9.8)	172 (15.5)	140 (12.5)	53 (8.4)	68 (14.1)	#VALUE!
	Unknown	1537 (34.8)	229 (20.6)	416 (37.2)	145 (23.0)	200 (41.6)	547 (50.7)
On cART	**No**	727 (16.5)	197 (17.7)	118 (10.6)	56 (8.9)	58 (12.1)	298 (27.6)
	Yes	3691 (83.5)	915 (82.3)	999 (89.4)	574 (91.1)	423 (87.9)	780 (72.4)

Prior HCV treatment	**No**	2692 (60.9)	523 (47.0)	542 (48.5)	383 (60.8)	376 (78.2)	868 (80.5)
	Yes	1726 (39.1)	589 (53.0)	575 (51.5)	247 (39.2)	105 (21.8)	210 (19.5)
HBV infection	**No**	3389 (76.7)	899 (80.8)	959 (85.9)	401 (63.7)	366 (76.1)	764 (70.9)
	Yes	236 (5.3)	40 (3.6)	66 (5.9)	21 (3.3)	39 (8.1)	70 (6.5)
	Unknown	793 (17.9)	173 (15.6)	92 (8.2)	208 (33.0)	76 (15.8)	244 (22.6)
				Median (IQR)			
Age		45 (37-52)	49 (44-53)	50 (44-55)	49 (42-54)	38 (32-44)	36 (33-41)
CD4 count (cells/mm^3)		532 (351-746)	583 (387-804)	615 (437-837)	574 (390-791)	491 (323-681)	392 (253-560)
CD4 nadir		192 (82-306)	194 (91-308)	136 (27-261)	225 (131-330)	207 (80-314)	210 (106-312)

Evidence of regional differences for all variables (p<0.0001)

*MSM: Men who have sex with men, †PWID: People who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

§Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels

n with CD4 count = 4145, n with CD4 nadir = 4315

4.2.3.2 Overall CoC

The 4418 individuals included in this analysis contributed 110450 person-months of FU (PMFU) over two years (Figure 4.9). Of the 110450 PMFU, individuals spent most time HCV-RNA negative – ever treated (32.2%), followed by HCV-RNA positive – never treated (26.4%), HCV-RNA unknown (15.2%), HCV-RNA positive – ever treated (11.6%), HCV-RNA negative – never treated (10.7%), LTFU (1.9%), and dead (2.04%). Overall, 42.9% (10.7% + 32.2%) of the PMFU was spent HCV-RNA negative, compared to 38.0% (26.4% + 11.5%) that was spent HCV-RNA positive. Also, more time was spent treated than not treated regardless of HCV-RNA status (43.8% vs 37.1%).

Table 4.12 shows the percentage of PMFU spent in each stage at baseline, 6 months, 12 months, 18 months, and 24 months after enrolling in the EuroSIDA study. From this Table and Figure 4.9, it is clear that the proportion of PMFU spent HCV-RNA positive – never treated decreased over time (from 31.5% at enrolment to 20.7% 24 months later) as the area for this stage in Figure 4.9 decreased as time passed. The proportion of PMFU spent HCV-RNA unknown was 20.5% at baseline and decreased to 11.9% by 24 months after enrolment, which indicates almost 9% of individuals who were not HCV-RNA tested at baseline were tested within 2 years of enrolment. PMFU spent HCV-RNA positive – ever treated also decreased over 2 years of FU (from 15.3% to 9.0%). By 2 years after entering the cohort, the proportion of PMFU spent HCV-RNA negative – treated increased from 22.6% to 38.0%. The proportion of individuals who were LTFU or died also steadily increased over time. The proportion of PMFU spent HCV-RNA negative – never treated did not change much over time, only increasing from 10.1% at enrolment to 11.0% after 2 years of FU.

Figure 4.9: Longitudinal HCV CoC

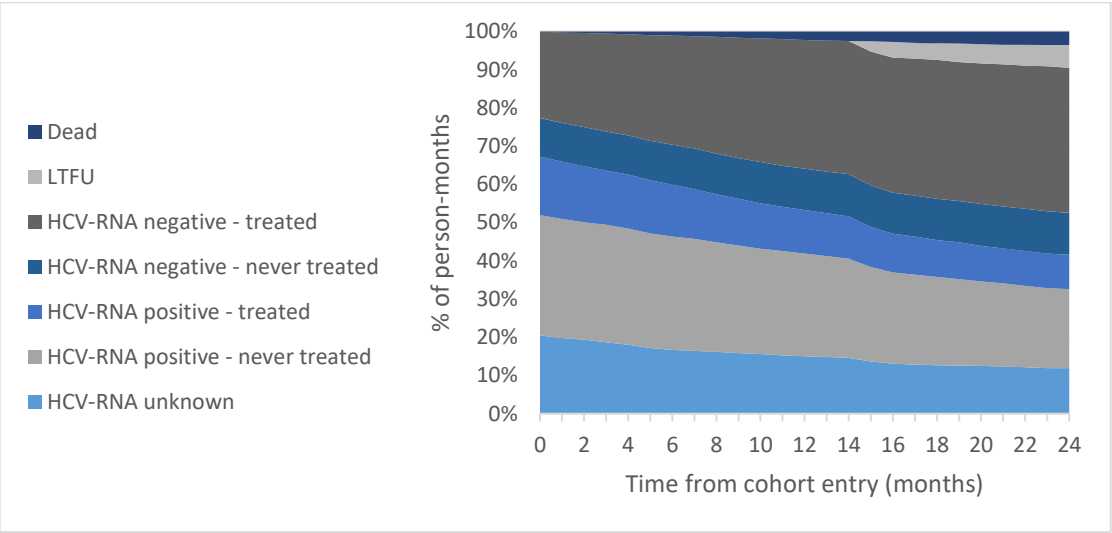


Table 4.12: Percentage of PMFU spent in each stage of CoC

Stage:	Overall	Time from cohort entry (months)				
		0	6	12	18	24
HCV-RNA unknown	15.2%	20.5%	16.7%	15.0%	12.7%	11.9%
HCV-RNA positive - never treated	26.4%	31.5%	29.7%	26.9%	23.1%	20.7%
HCV-RNA positive - treated	11.6%	15.3%	13.5%	11.4%	9.6%	9.0%
HCV-RNA negative - never treated	10.7%	10.1%	10.5%	10.9%	10.8%	11.0%
HCV-RNA negative - treated	32.2%	22.6%	28.5%	33.6%	36.3%	38.0%
LTFU	1.9%	0.0%	0.0%	0.0%	4.4%	5.9%
Dead	2.0%	0.0%	1.1%	2.2%	3.0%	3.5%

4.2.3.2.1 Overall CoC, by treatment regimen

To further explore the changes in treatment over time, Stage 3 (HCV-RNA positive – treated) and Stage 5 (HCV-RNA negative – treated) were split by the individuals most recent treatment regimen (IFN based regimen vs IFN-free DAA regimen) (Figure 4.10). Overall, 28.3% of PMFU were spent treated by IFN, while 15.6% was spent treated by DAAs. However, this figure shows that the percentage of PMFU spent treated by DAAs increased over time (from 7.9 to 20.9%) and the proportion of PMFU treated by IFN decreased (from 30.0% to 26.0%). The percentage of PMFU spent HCV-RNA negative - treated - DAAs increased by 5.6% at enrolment to 18.5% after 24 months, while the proportion of time spent HCV-RNA negative - treated - IFN based regimen

remained fairly consistent over time, and only increased by 2.5% (Table 4.13). Overall, the proportion of PMFU spent HCV-RNA positive – treated – DAA was only 2.4%, and remained consistently low over time.

Figure 4.10: Longitudinal HCV CoC, stratified by treatment regimen

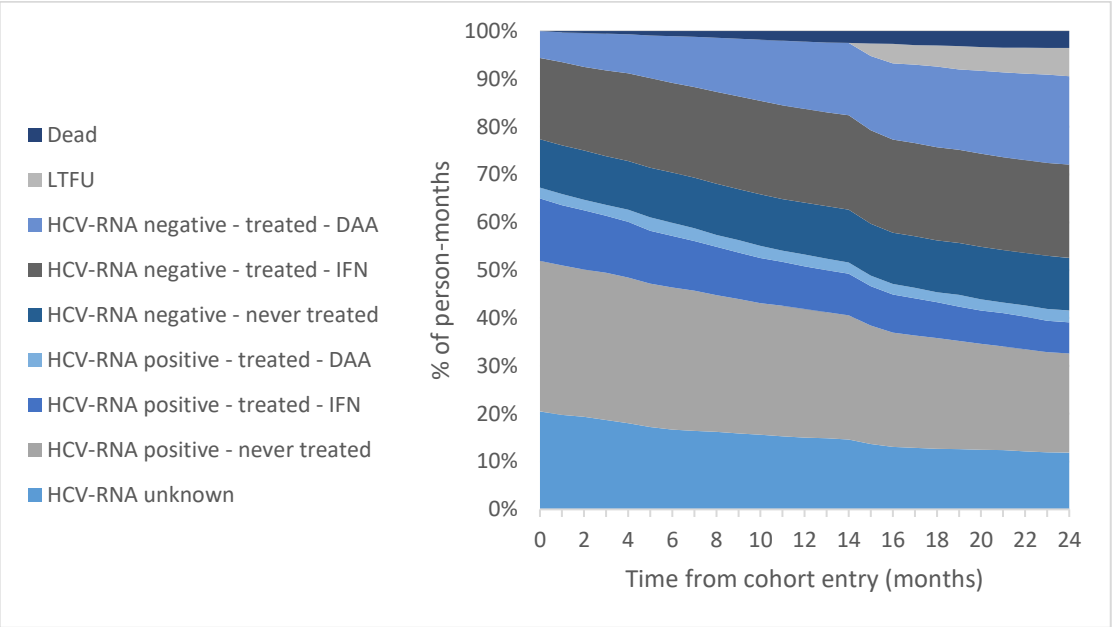


Table 4.13: Percentage of PMFU spent in each stage of CoC, stratified by treatment regimen

Stage:	Overall	Time from cohort entry (months)				
		0	6	12	18	24
HCV-RNA unknown	15.2%	20.5%	16.7%	15.0%	12.7%	11.9%
HCV-RNA positive - never treated	26.4%	31.5%	29.7%	26.9%	23.1%	20.7%
HCV-RNA positive - treated - IFN	9.2%	13.0%	10.8%	9.0%	7.5%	6.5%
HCV-RNA positive - treated - DAA	2.4%	2.3%	2.7%	2.4%	2.1%	2.5%
HCV-RNA negative - never treated	10.7%	10.1%	10.5%	10.9%	10.8%	11.0%
HCV-RNA negative - treated - IFN	19.0%	17.0%	18.8%	19.6%	19.5%	19.5%
HCV-RNA negative - treated - DAA	13.2%	5.6%	9.8%	14.0%	16.8%	18.5%
LTFU	1.9%	0.0%	0.0%	0.0%	4.4%	5.9%
Dead	2.0%	0.0%	1.1%	2.2%	3.0%	3.5%

4.2.3.2.2 Summary of deaths by time-point, region, and CoC stage

Overall, 156 (3.5%) individuals included in this analysis died within 2 years of enrolment. There were 42 deaths 0-6 months after enrolment, 48 deaths 6-12 months after enrolment, 42 deaths 12-18 months after enrolment, and 24 deaths 18-24 months after enrolment (Figure 4.11). Eastern Europe had the highest proportion of deaths (68, 6.3%), followed by Central-East (15, 3.1%), Central-West (32, 2.9%), North (18, 2.9%), and Southern Europe (23, 2.1%). Across all time points, the majority of deaths were from Eastern Europe.

Figure 4.12 shows the number of deaths by the continuum stage prior to death. The majority of deaths occurred in individuals who were HCV-RNA positive (n=65), followed by those with an unknown HCV-RNA status (n=45), HCV-RNA negative (n=39), and LTFU (n=6). Of those who were HCV-RNA positive prior to dying, 83.1% (n=54) had never been treated.

The most common cause of death was AIDS (n=32), the majority of which were due to infections (n=23). There were 21 individuals who died due to liver-related reasons such as cirrhosis (n=10) and liver failure (n=5). NADM was also a common cause of death (n=13), as was substance abuse (n=13), and non-AIDS related infections (n=10). 21 individuals died from other causes such as heart disease (n=2) and stroke (n=2). There were also 46 individuals who died from unknown causes.

Figure 4.11: Percentage of deaths at each time-point, by region

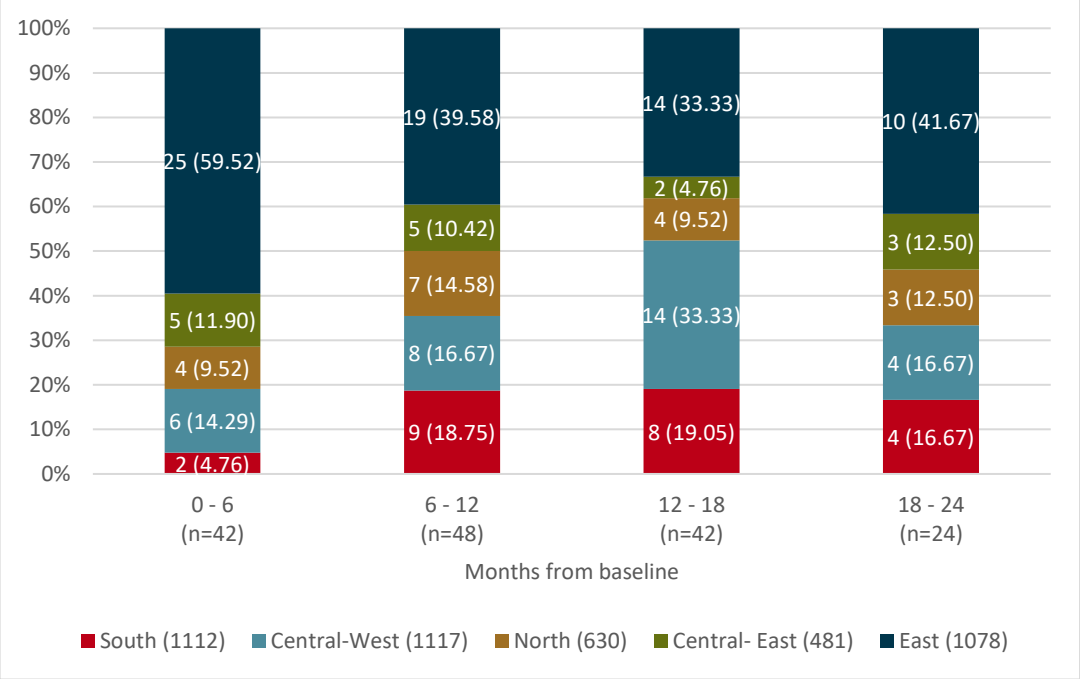
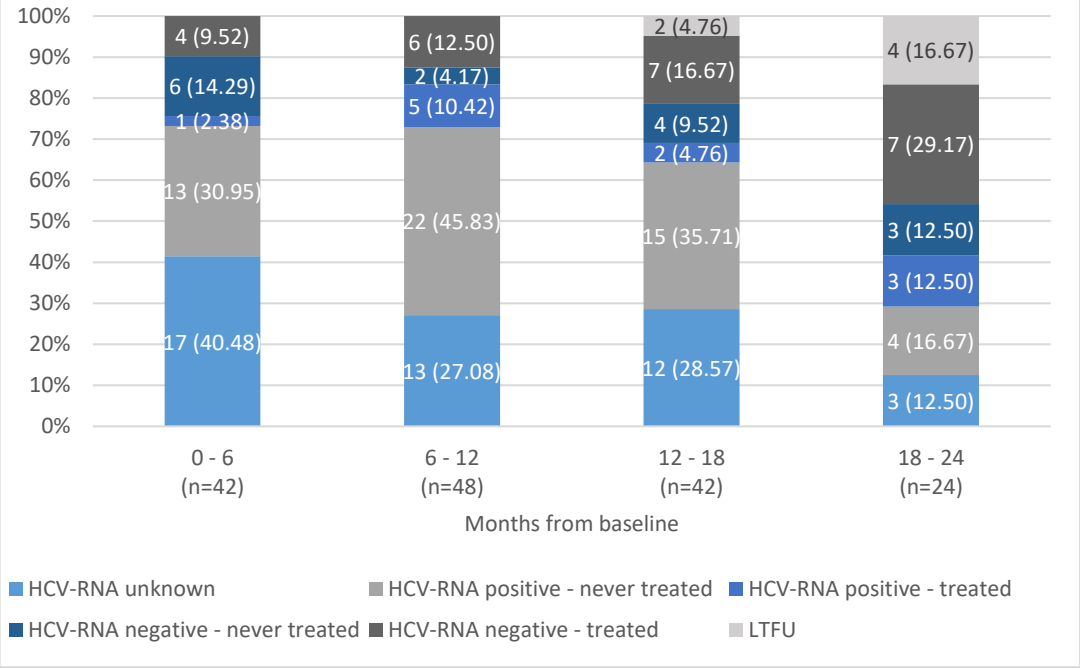


Figure 4.12: Percentage of deaths at each time-point, by CoC stage prior to death



There was 1 individual that died the same month they were enrolled and could not be categorised. Therefore, n = 41 for 0-6 months, not 42

4.2.3.3 Predictors of HCV-RNA negative – treated

Of the 4418 individuals who were included in this analysis, 1534 were ever in Stage 2 (HCV-RNA positive – never treated) and 1806 individuals were ever in Stage 5 (HCV-

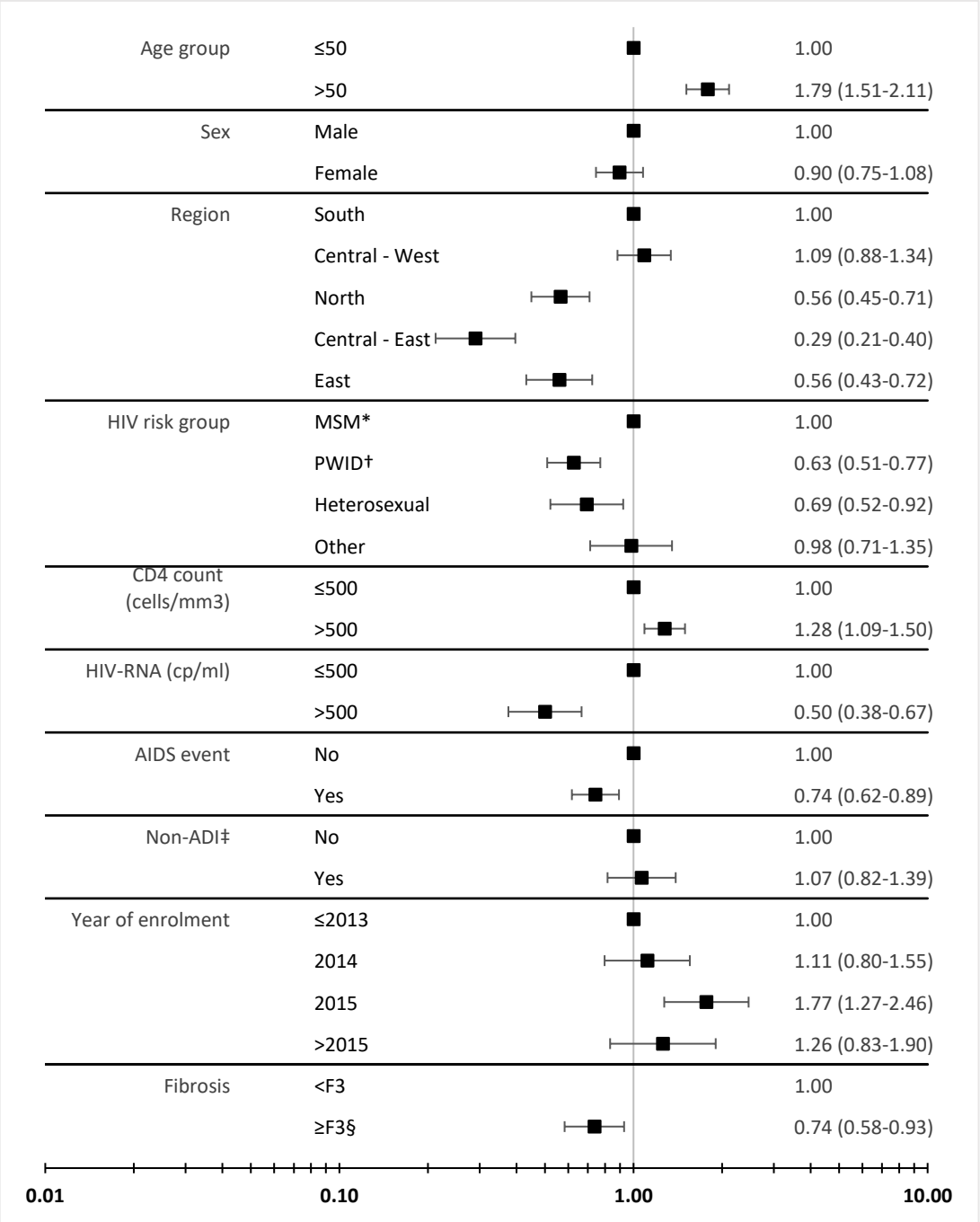
RNA negative – treated). There were 62373 observations included from 2993 individuals ever in either stage, 44.5% of observations were spent in Stage 2 and 55.5% of which were spent in Stage 5. The data was unbalanced as individuals had a varying number of observations. The number of observations ranged from 1 – 25, with an average of 20 observations included for each individual.

In univariable analysis, individuals over 50 years old had a higher odds of starting HCV treatment and being HCV negative compared to individuals under 50 [OR=2.43, 95% CI=2.10-2.82], as did individuals from Central-Western Europe [OR=1.20, 95% CI=0.99-1.45], those with a CD4 count >500 cells/mm^3 [OR=1.64, 95% CI=1.42-1.89], a non-ADI [OR=1.44, 95% CI=1.12-1.85], enrolled into EuroSIDA in 2014, 2015, or 2016 or later [OR=2.00, 95% CI=1.50-2.67, OR=3.18, 95% CI=2.38-4.23, and OR=1.81, 95% CI=1.24-2.64, respectively], and with liver fibrosis ≥F3 [OR=1.30, 95% CI=1.07-1.57]. Females [OR=0.76, 95% CI=0.65-0.89], individuals from North, Central-East and Eastern Europe [OR=0.62, 95% CI=0.50-0.76, OR=0.22, 95% CI=0.16-0.29, and OR=0.32, 95% CI=0.26-0.40, respectively], PWID and heterosexuals [OR=0.52, 95% CI=0.43-0.62 and OR=0.50, 95% CI=0.40-0.63], individuals with a HIV-RNA >500 cp/ml [OR=0.32, 95% CI=0.25-0.41], or an AIDS event [OR=0.86, 95% CI=0.73-1.02] had a lower odds of being HCV-RNA negative - treated. Ethnicity, HCV genotype, cART treatment, and HBV infection were not found to be associated with the odds of being HCV-RNA negative – treated.

After adjustment, being over 50 years old [aOR=1.81, 95% CI=1.54-2.14], having a CD4 count >500 cells/mm^3 [aOR=1.30, 95% CI=1.11-1.52], being enrolled to EuroSIDA in 2015 [aOR=1.73, 95% CI=1.24-2.42], and having fibrosis ≥F3 [aOR=1.26, 95% CI=1.04-1.54] were associated with being HCV negative – treated (Figure 4.13). Individuals from North, Central-East and Eastern Europe [aOR=0.55, 95% CI=0.44-0.69, aOR=0.28, 95% CI=0.21-0.38, and aOR=0.56, 95% CI=0.43-0.72, respectively], PWID and heterosexuals [aOR=0.62, 95% CI=0.51-0.77 and aOR=0.69, 95% CI=0.52-

0.92], with HIV-RNA >500 cp/ml [aOR=0.57, 95% CI=0.43-0.74], and an AIDS event [aOR=0.74, 95% CI=0.61-0.88] had a lower odds of being HCV-RNA negative – treated.

Figure 4.13: Adjusted odds of being HCV-RNA negative - treated



Logistic regression model was also adjusted for unknown CD4 count, unknown HIV-RNA, and unknown fibrosis
*MSM: Men who have sex with men, †PWID: People who inject drugs
‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis
§Either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5) (225) or hyaluronic acid level (>160 ng/mL) (420)

4.2.3.4 Regional CoC

There were 1112 (27800 PMFU) individuals included from Southern Europe, 1117 (27925 PMFU) from Central-West, 630 (15750 PMFU) from North, 481 (12025 PMFU) from Central-East, and 1078 (26950 PMFU) from Eastern Europe. Regional differences in baseline characteristics have been described in 4.2.3.1 and Table 4.11 Overall, the percentage of individuals HCV-RNA negative - treated was 14.1% and 15.1% in Central-East and Eastern Europe, respectively (Table 4.14). However, the percentage of PMFU HCV-RNA negative - treated in Southern (42.2%), Central-West (43.8%), and Northern Europe (36.9%) was higher. PMFU spent with an unknown HCV-RNA value was 37.8% in Eastern Europe and 26.6% in Central-Eastern Europe, however it was only 6.5%, 4.1%, and 2.7% in South, Central-West, and Northern Europe, respectively. Overall the percentage of PMFU LTFU was highest in Eastern Europe (2.7%) and lowest in Northern Europe (1.2%). There was also a higher percentage of death in Eastern Europe (3.9%) compared to other regions, and was lowest in Southern Europe (1.0%).

While the absolute percentage increase of PMFU HCV-RNA negative - treated was roughly 20% from enrolment to 24 months later in South, Central-West, and Northern Europe, there was only a 7.9% increase in Central-East and 5.3% increase in Eastern Europe (Figure 4.14). There was a 15.2% and 16.0% absolute decrease by 24 months after enrolment in the percentage of PMFU HCV-RNA unknown in Central-East and Eastern Europe, respectively. However, by 24 months, the percentage of PMFU HCV-RNA unknown was still much higher in Central-East (20.2%) and Eastern Europe (30.8%) compared to South (4.3%), Central-West (3.2%) and Northern Europe (1.9%).

Figure 4.14: Longitudinal CoC, by region

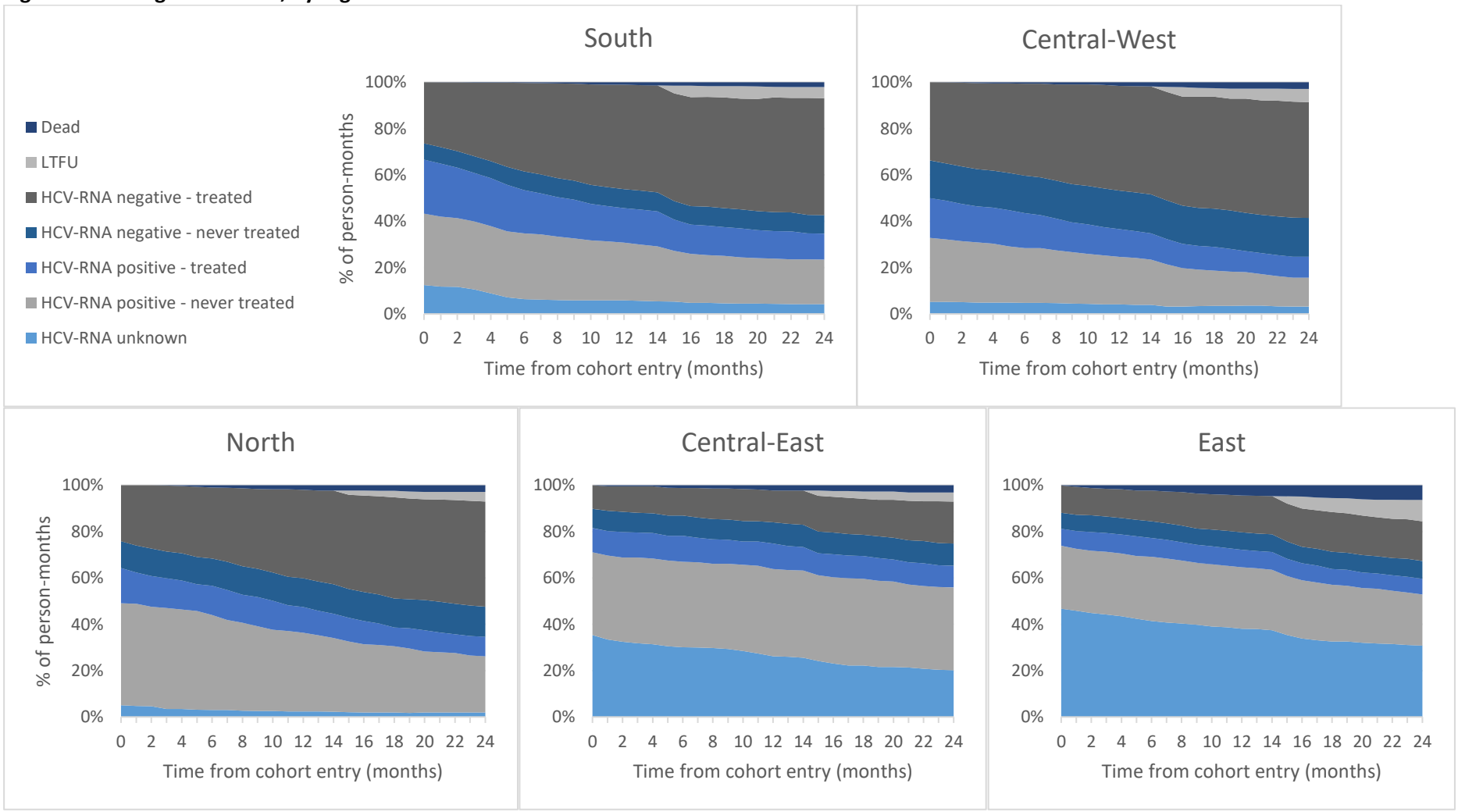


Table 4.14: Percentage of PMFU spent in each stage of CoC, by region

Stage:	South (%)						Central-West (%)						North (%)					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	6.5	12.5	6.4	5.8	4.6	4.3	4.1	5.3	4.8	4.1	3.5	3.2	2.7	5.1	3.0	2.4	1.9	1.9
HCV-RNA positive - never treated	24.5	30.8	28.4	25.0	20.5	19.2	19.9	27.6	23.6	20.5	15.2	12.4	34.2	44.0	41.0	34.0	28.6	24.3
HCV-RNA positive - treated	15.9	23.3	18.6	14.8	12.4	11.2	12.4	17.2	15.0	12.0	10.3	9.0	11.0	15.2	12.7	11.1	8.1	8.4
HCV-RNA negative - never treated	7.9	7.0	8.1	8.2	8.2	7.9	16.4	16.2	16.2	16.7	16.5	16.7	12.4	11.6	11.7	12.4	12.5	13.0
HCV-RNA negative - treated	42.2	26.3	38.2	45.1	47.8	50.5	43.8	33.8	39.7	45.2	48.3	50.0	36.9	24.1	30.6	38.3	43.7	45.4
LTFU	1.9	0.0	0.0	0.0	4.9	4.8	1.8	0.0	0.0	0.0	3.8	5.7	1.2	0.0	0.0	0.0	2.9	4.1
Dead	1.0	0.0	0.3	1.0	1.7	2.1	1.5	0.0	0.6	1.5	2.5	2.9	1.7	0.0	1.0	1.9	2.4	2.9

Stage:	Central-East (%)						East (%)					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	26.6	35.3	30.1	26.2	22.2	20.2	37.8	46.8	41.5	38.0	32.6	30.8
HCV-RNA positive - never treated	36.8	35.8	36.8	37.6	37.4	35.8	25.7	27.1	27.6	26.5	24.5	22.1
HCV-RNA positive - treated	10.2	10.4	11.2	11.0	9.8	9.4	7.5	7.4	8.2	7.6	6.8	6.8
HCV-RNA negative - never treated	9.1	8.3	8.7	9.1	9.1	9.6	7.3	6.9	7.1	7.5	7.5	7.7
HCV-RNA negative - treated	14.1	10.2	11.9	13.7	15.6	18.1	15.1	11.8	13.3	15.9	17.1	17.1
LTFU	1.3	0.0	0.0	0.0	3.1	4.0	2.7	0.0	0.0	0.0	6.1	9.3
Dead	1.9	0.0	1.2	2.3	2.7	3.1	3.9	0.1	2.3	4.5	5.5	6.3

4.2.3.4.1 Regional CoC, by treatment regimen

As described above there were regional differences in the percentage of PMFU treated, however there were also regional differences in PMFU by treatment type (Figure 4.15 and Table 4.15). Overall, the percentage of PMFU spent ever treated with DAAs was 2.7% in Eastern Europe and 3.5% in Central-Eastern Europe, however was over 20% in South, Central-West and Northern Europe. The proportion PMFU ever treated with IFN was higher in Central-East (20.9%) and Eastern Europe (19.9%) compared to the proportion ever treated with DAAs, however was still lower than other regions (34.9%, 34.4%, and 23.9% in South, Central-West, and Northern Europe, respectively). Also, the overall percentage of PMFU HCV-RNA negative - treated - DAAs was around 20% in South, Central-West, and Northern Europe but only 2.5% and 2.1% in Central-East and Eastern Europe, respectively. There was a 17.72%, 16.83%, and 16.19% absolute increase in the PMFU HCV-RNA negative - treated - DAAs in South, Central-West and Northern Europe (respectively) over 24 months, but only increased by 5.82% in Central-Eastern Europe and 3.90% in Eastern Europe over the same time-period.

Figure 4.15: Longitudinal CoC, by region and treatment regimen

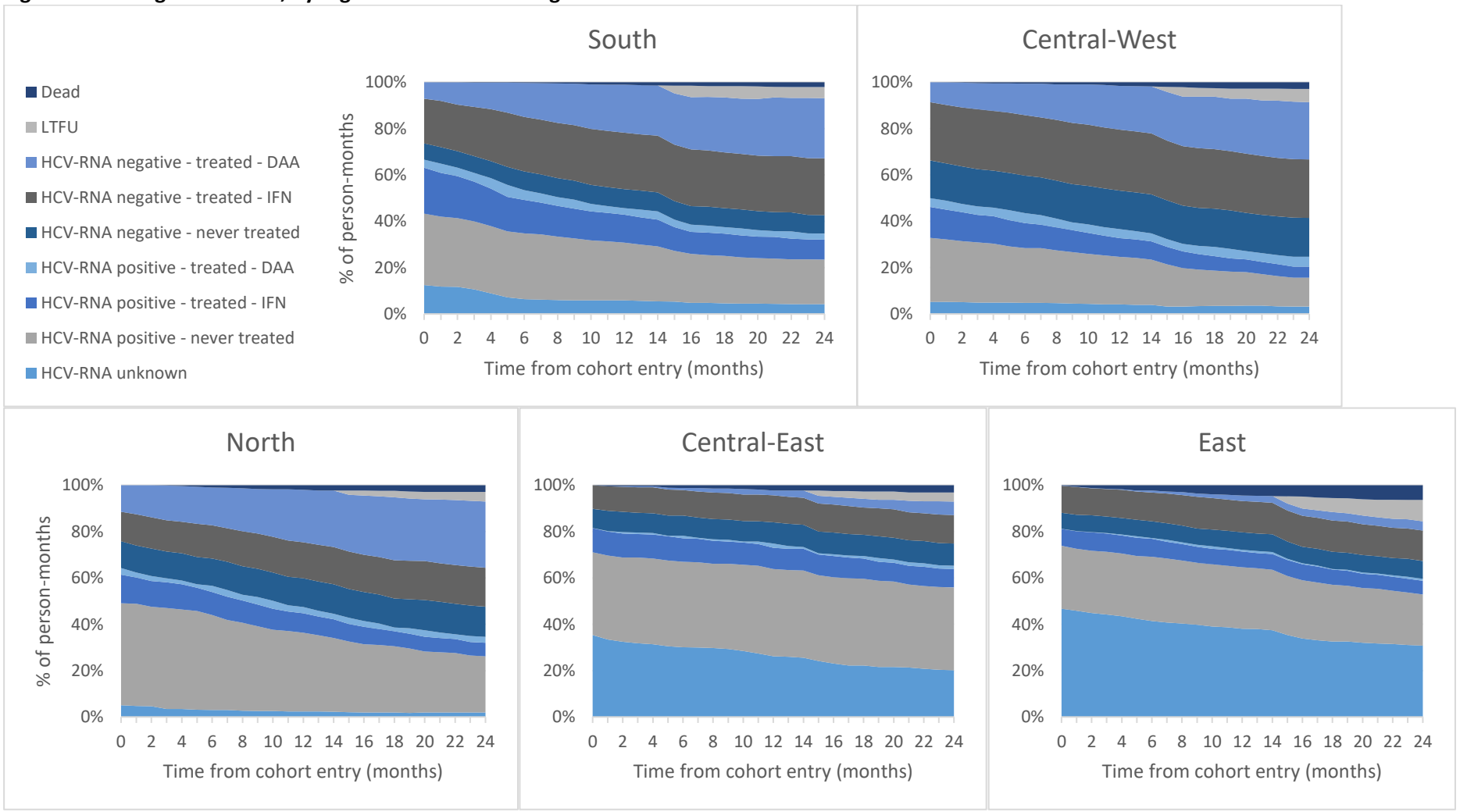


Table 4.15: Percentage of PMFU spent in each stage of CoC, by region and treatment regimen

Stage:	South (%)						Central-West (%)						North (%)					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	6.5	12.5	6.4	5.8	4.6	4.3	4.1	5.3	4.8	4.1	3.5	3.2	2.7	5.1	3.0	2.4	1.9	1.9
HCV-RNA positive - never treated	24.5	30.8	28.4	25.0	20.5	19.2	19.9	27.6	23.6	20.5	15.2	12.4	34.2	44.0	41.0	34.0	28.6	24.3
HCV-RNA positive - treated - IFN	12.5	19.8	14.5	12.1	9.6	8.6	8.6	13.3	10.7	8.1	6.3	4.7	8.5	12.4	10.0	8.4	6.5	5.9
HCV-RNA positive - treated - DAA	3.4	3.5	4.1	2.8	2.8	2.6	3.8	3.8	4.3	3.8	4.0	4.3	2.4	2.9	2.7	2.7	1.6	2.5
HCV-RNA negative - never treated	7.9	7.0	8.1	8.2	8.2	7.9	16.4	16.2	16.2	16.7	16.5	16.7	12.4	11.6	11.7	12.4	12.5	13.0
HCV-RNA negative - treated - IFN	23.4	19.2	23.6	24.4	24.1	24.6	25.8	25.2	26.1	26.3	25.7	25.2	15.4	12.7	14.3	15.6	16.5	16.8
HCV-RNA negative - treated - DAA	18.8	7.1	14.7	20.8	23.7	26.0	18.0	8.6	13.6	18.9	22.6	24.7	21.5	11.4	16.3	22.7	27.1	28.6
LTFU	1.9	0.0	0.0	0.0	4.9	4.8	1.8	0.0	0.0	0.0	3.8	5.7	1.2	0.0	0.0	0.0	2.9	4.1
Dead	1.0	0.0	0.3	1.0	1.7	2.1	1.5	0.0	0.6	1.5	2.5	2.9	1.7	0.0	1.0	1.9	2.4	2.9

Stage:	Central-East (%)						East (%)					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	26.6	35.3	30.1	26.2	22.2	20.2	37.8	46.8	41.5	38.0	32.6	30.8
HCV-RNA positive - never treated	36.8	35.8	36.8	37.6	37.4	35.8	25.7	27.1	27.6	26.5	24.5	22.1
HCV-RNA positive - treated - IFN	9.3	10.4	10.2	9.1	8.7	7.9	6.9	7.3	7.8	6.9	6.6	5.9
HCV-RNA positive - treated - DAA	0.9	0.0	1.0	1.9	1.0	1.5	0.6	0.1	0.4	0.7	0.2	0.8
HCV-RNA negative - never treated	9.1	8.3	8.7	9.1	9.1	9.6	7.3	6.9	7.1	7.5	7.5	7.7
HCV-RNA negative - treated - IFN	11.6	10.2	11.0	11.6	11.9	12.3	13.0	11.7	12.4	13.5	13.5	13.1
HCV-RNA negative - treated - DAA	2.5	0.0	0.8	2.1	3.7	5.8	2.1	0.1	0.8	2.3	3.6	4.0
LTFU	1.3	0.0	0.0	0.0	3.1	4.0	2.7	0.0	0.0	0.0	6.1	9.3
Dead	1.9	0.0	1.2	2.3	2.7	3.1	3.9	0.1	2.3	4.5	5.5	6.3

4.2.3.5 CoC by year of enrolment

There were 2203 individuals who were enrolled between 1/1/2011 and 31/12/2014 (55100 PMFU) and 2215 individuals enrolled between 1/1/2015 and 1/1/2017 (55500 PMFU). There were significant differences in the baseline characteristics of individuals enrolled between 1/1/2011 and 31/12/2014 and 1/1/2015 and 1/1/2017 (Table 4.16). There was a higher percentage of females enrolled between 2011 and 2014 (30.9%) compared to 2015 and 2017 (24.2%). The median age among individuals enrolled between 2011 and 2014 was 44 (IQR: 36-51) while the median age among individuals enrolled between 2015 and 217 was 46 (IQR: 38-53). The median CD4 count was 505 cells/mm^3 (IQR: 330-728) among individuals enrolled between 2011 and 2014 and 560 cells/mm^3 (IQR: 378-770) among individuals enrolled between 2015 and 2017. Also, a higher percentage of MSM were enrolled between 2015 and 2017 (26.8% vs 13.2%), while a higher percentage of PWID were enrolled between 2011 and 2014 (58.0% vs 51.2%).

The majority of PMFU for those enrolled between 1/1/2011 and 1/1/2015 was spent HCV-RNA positive – never treated (29.9%), however this decreased from 34.0% at enrolment to 25.1% 24 months later (Figure 4.16 and Table 4.17). The majority of PMFU was spent HCV-RNA negative – treated (37.4%) for those enrolled between 1/1/2015 and 1/1/2017. The percentage of PMFU spent in this stage increased from 25.9% at baseline to 43.3% 24 months after enrolment. For individuals enrolled before 1/1/2015, the majority of PMFU was spent HCV-RNA positive (42.4%) while those enrolled between 1/1/2015 and 1/1/2017 spent the majority of their PMFU HCV-RNA negative (48.6%). The percentage of PMFU spent LTFU was higher among individuals enrolled between 2015 and 2017 (2.4%) compared to those enrolled between 2011 and 2015 (1.4%).

Table 4.16: Baseline characteristics at enrolment to EuroSIDA study in anti-HCV positive individuals enrolled between 1/1/2011 and 1/1/2017, by year of enrolment

		Overall	2011-2014	2015-2017	p-value
			n (%)		
Overall		4418 (100.0)	2203 (49.9)	2215 (50.1)	
Sex	**Male**	3201 (72.5)	1522 (69.1)	1679 (75.8)	
	Female	1217 (27.5)	681 (30.9)	536 (24.2)	
Ethnicity	**White**	3787 (85.7)	2004 (91.0)	1783 (80.5)	<0.0001
	Global majority	110 (2.5)	43 (2.0)	67 (3.0)	
	Unknown	521 (11.8)	156 (7.1)	365 (16.5)	
Region of Europe	**South**	1112 (25.2)	597 (27.1)	515 (23.3)	<0.0001
	Central - West	1117 (25.3)	552 (25.1)	565 (25.5)	
	North	630 (14.3)	248 (11.3)	382 (17.2)	
	Central - East	481 (10.9)	264 (12.0)	217 (9.8)	
	East	1078 (24.4)	542 (24.6)	536 (24.2)	
HIV risk group	**MSM***	883 (20.0)	290 (13.2)	593 (26.8)	<0.0001
	PWID†	2410 (54.5)	1277 (58.0)	1133 (51.2)	
	Heterosexual	812 (18.4)	446 (20.2)	366 (16.5)	
	Other	313 (7.1)	190 (8.6)	123 (5.6)	
HIV-RNA (cp/ml)	**≤500**	3511 (79.5)	1753 (79.6)	1758 (79.4)	0.0005
	>500	612 (13.9)	331 (15.0)	281 (12.7)	
	Unknown	295 (6.7)	119 (5.4)	176 (7.9)	
AIDS event	**No**	3496 (79.1)	1730 (78.5)	1766 (79.7)	0.3265
	Yes	922 (20.9)	473 (21.5)	449 (20.3)	
Non-ADI†	**No**	4088 (92.5)	2015 (91.5)	2073 (93.6)	0.0073
	Yes	330 (7.5)	188 (8.5)	142 (6.4)	
Fibrosis§	**F0/1**	2764 (62.6)	1361 (61.8)	1403 (63.3)	0.5221
	F2	148 (3.3)	79 (3.6)	69 (3.1)	
	F3	206 (4.7)	101 (4.6)	105 (4.7)	
	F4	426 (9.6)	227 (10.3)	199 (9.0)	
	Unknown	874 (19.8)	435 (19.7)	439 (19.8)	
HCV genotype	**G1**	1603 (36.3)	803 (36.5)	800 (36.1)	0.0298
	G2	103 (2.3)	51 (2.3)	52 (2.3)	
	G3	742 (16.8)	404 (18.3)	338 (15.3)	
	G4	433 (9.8)	196 (8.9)	237 (10.7)	
	Unknown	1537 (34.8)	749 (34.0)	788 (35.6)	
On cART	**No**	727 (16.5)	384 (17.4)	343 (15.5)	0.0812
	Yes	3691 (83.5)	1819 (82.6)	1872 (84.5)	
Prior HCV treatment	**No**	2692 (60.9)	1419 (64.4)	1273 (57.5)	<0.0001
	Yes	1726 (39.1)	784 (35.6)	942 (42.5)	
HBV infection	**No**	3389 (76.7)	1742 (79.1)	1647 (74.4)	0.001
	Yes	236 (5.3)	108 (4.9)	128 (5.8)	
	Unknown	793 (17.9)	353 (16.0)	440 (19.9)	
			Median (IQR)		
Age (years)		45 (37-52)	44 (36-51)	46 (38-53)	<0.0001
CD4 count (cells/mm^3)		532 (351-746)	505 (330-728)	560 (378-770)	<0.0001
CD4 nadir (cells/mm3)		192 (82-306)	191 (90-297)	193 (70-317)	0.8312

*MSM: Men who have sex with men, †PWID: People who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

§Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels

n with CD4 count = 4145, n with CD4 nadir = 4315

Figure 4.16: Longitudinal CoC, by year of enrolment

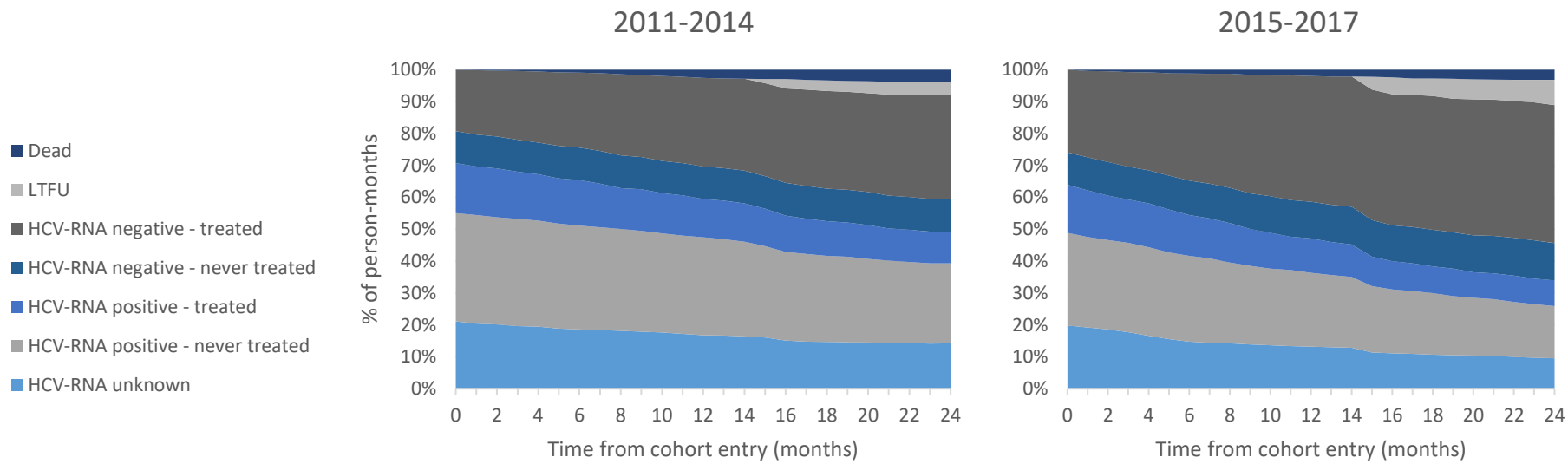


Table 4.17: Percentage of PMFU spent in each stage of CoC, by year of enrolment

Stage:	2011-2014						2015-2017					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	17.0%	21.1%	18.6%	16.8%	14.7%	14.2%	13.4%	19.8%	14.8%	13.2%	10.7%	9.6%
HCV-RNA positive - never treated	29.9%	34.0%	32.6%	30.6%	27.0%	25.1%	22.9%	29.1%	26.9%	23.2%	19.3%	16.3%
HCV-RNA positive - treated	12.5%	15.7%	14.2%	12.1%	10.9%	9.9%	10.8%	15.0%	12.8%	10.7%	8.3%	8.0%
HCV-RNA negative - never treated	10.2%	10.0%	10.2%	10.2%	10.2%	10.3%	11.2%	10.2%	10.8%	11.6%	11.5%	11.7%
HCV-RNA negative - treated	27.0%	19.2%	23.5%	27.8%	30.6%	32.6%	37.4%	25.9%	33.5%	39.4%	41.9%	43.3%
LTFU	1.4%	0.0%	0.0%	0.0%	3.3%	3.9%	2.4%	0.0%	0.0%	0.0%	5.5%	7.9%
Dead	2.2%	0.0%	0.9%	2.5%	3.4%	3.9%	1.9%	0.0%	1.2%	1.9%	2.7%	3.2%

4.2.3.5.1 CoC by year of enrolment, by treatment regimen

A higher percentage of individuals enrolled between 1/1/2015 and 1/1/2017 had ever received HCV treatment (48.1%) compared to those enrolled before 1/1/2015 (39.4%). Figure 4.17 and Table 4.18 describe the CoC by treatment regimen, and show that a similar amount of PMFU was spent ever treated with IFN-based regimens for both enrolment periods (28.8% vs 27.8%), however there was almost a 10% difference in those treated with DAAs (10.7% among individuals enrolled between 2011-2014 vs 20.4% among individuals enrolled between 2015-2017). While the proportion of individuals enrolled between 1/1/2011 and 31/12/201 who were HCV-RNA negative and treated with DAAs was lower overall, it increased from 2.5% at enrolment to 14.0% 24 months after enrolment. This increase in the HCV-RNA negative - treated - DAA stage was also reflected in those enrolled between 2/1/2015 and 1/1/2017 as there the PMFU increased from 8.7% to 22.9%.

Figure 4.17: Longitudinal CoC, by year of enrolment and treatment regimen

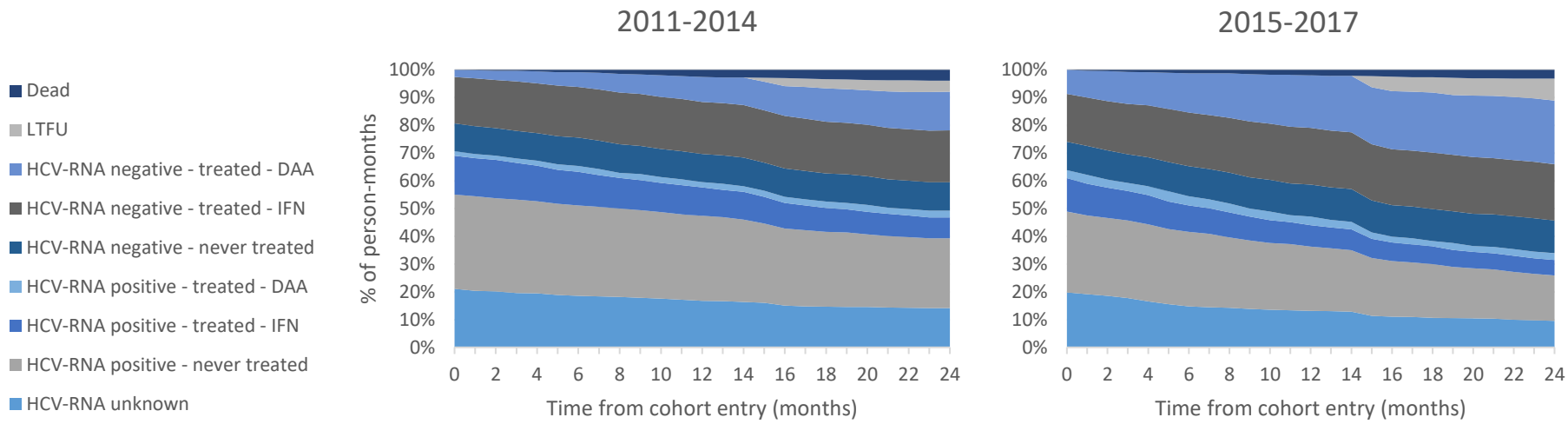


Table 4.18: Percentage of PMFU spent in each stage of CoC, by year of enrolment and treatment regimen

Stage:	2011-2014						2015-2017					
	Overall	Time from cohort entry (months)					Overall	Time from cohort entry (months)				
		0	6	12	18	24		0	6	12	18	24
HCV-RNA unknown	17.0%	21.1%	18.6%	16.8%	14.7%	14.2%	13.4%	19.8%	14.8%	13.2%	10.7%	9.6%
HCV-RNA positive - never treated	29.9%	34.0%	32.6%	30.6%	27.0%	25.1%	22.9%	29.1%	26.9%	23.2%	19.3%	16.3%
HCV-RNA positive - treated - IFN	10.4%	14.0%	12.1%	10.3%	8.6%	7.5%	8.1%	12.1%	9.5%	7.7%	6.4%	5.6%
HCV-RNA positive - treated - DAA	2.1%	1.7%	2.1%	1.8%	2.3%	2.5%	2.7%	2.9%	3.3%	3.1%	1.9%	2.5%
HCV-RNA negative - never treated	10.2%	10.0%	10.2%	10.2%	10.2%	10.3%	11.2%	10.2%	10.8%	11.6%	11.5%	11.7%
HCV-RNA negative - treated - IFN	18.4%	16.7%	18.2%	18.7%	18.7%	18.7%	19.7%	17.2%	19.4%	20.4%	20.3%	20.3%
HCV-RNA negative - treated - DAA	8.6%	2.5%	5.3%	9.0%	12.0%	14.0%	17.7%	8.7%	14.2%	19.0%	21.6%	22.9%
LTFU	1.4%	0.0%	0.0%	0.0%	3.3%	3.9%	2.4%	0.0%	0.0%	0.0%	5.5%	7.9%
Dead	2.2%	0.0%	0.9%	2.5%	3.4%	3.9%	1.9%	0.0%	1.2%	1.9%	2.7%	3.2%

4.2.4 Discussion

In this section, a novel technique used to describe the longitudinal HIV CoC (385) was adapted and applied to the HCV context for the first time. I developed a 7 (or 9 if split by HCV treatment type) stage longitudinal CoC. Using this method, it is possible to explore how the individuals transition through care over time after enrolment into the EuroSIDA study and overcome some of the limitations of the cross-sectional approach (as described in Section 4.2.1). A closed population was followed for 2 years which allowed us to explore LTFU and mortality, which was not possible with the traditional cross-sectional CoC. This tool will allow the assessment of improvements in services over time and highlight gaps where individuals are not accessing appropriate care.

There were considerable regional differences in the longitudinal CoC, which corresponds with the findings from the cross-sectional CoC. However, it is not possible to directly compare the cross-sectional and longitudinal CoC. While repeating the cross-sectional CoC analysis showed an improvement from the 1/1/2015 index data to the 1/1/2017 index date, the longitudinal method was able to provide a clearer picture of how the continuum changed over time. Overall, 15% of PMFU was spent with an unknown HCV-RNA status, however this ranged from <7% in South, Central-West, and Northern Europe to >27% in Central-East and Eastern Europe, potentially reflecting differences in testing strategies across Europe. The overall percentage of individuals treated with DAAs was >20% in South, Central-West, and Northern Europe and <4% in Central-East and Eastern Europe. The change over time in treatment with DAAs was also substantially lower in Central-East and Eastern Europe. These findings highlight regional disparities in HCV diagnosis and access to DAA treatment. Also, not only is access to DAAs is lower in Central-East and Eastern Europe, but uptake over time of DAA is also slower.

4.2.4.1 Strengths and limitations

There were also some limitations of longitudinal analysis, for example, the 'HCV-RNA positive - treated' stage included any individuals who started a HCV treatment regimen, regardless of whether they completed the regimen or the length of treatment. Therefore, some of the 'HCV-RNA positive – treated' individuals may have just started HCV treatment and will go on to reach SVR, as opposed to failing treatment or being reinfected. I wanted to explore how individuals who recently entered the cohort (enrolled before 1/1/2017) transitioned through care. Therefore, I was only able to follow up individuals for 2 years, as each individual included was required to have the potential for 2 years of FU. However, it would have been interesting to include longer follow-up to explore what happens more than 2 years after enrolment. This is the first time this approach has been applied to the HCV context, however more work is required to develop the longitudinal HCV CoC and establish a standardised way for reporting how individuals transition through care over time. Also, as mentioned in the discussion of Section 4.1 (4.1.4.6), EuroSIDA collects data from centres of excellence that may provide a higher standard of care than other centres in the region and may exclude HIV/HCV co-infected individuals who face structural barriers to care. Therefore, these results might be showing an optimistic picture of the CoC.

Our study also has several important strengths. The longitudinal method has several advantages over the cross-sectional approach, and this was one of the first studies to explore a method to describe the HCV continuum longitudinally. The proposed longitudinal CoC allowed description of the movement of individuals through HCV care over time and incorporate LTFU and mortality. This analysis demonstrates an alternative way to explore how HCV positive individuals transition through care. Although the longitudinal CoC uses a more complex analysis, it was presented in a single easy to understand figure like the cross-sectional CoC. Finally, the size of the EuroSIDA study

population and the fact that it includes data from clinics all over Europe is also a strength, as it also enables us to explore regional difference.

4.3 Dissemination of results

The cross-sectional CoC at the 1/1/2015 index date was presented as an oral at the 2017 European Aids Conference (slides in Appendix V) and the manuscript was also published in HIV Medicine in 2019 (Appendix VI). The results in this chapter differ slightly from the published work, as a newer dataset was used for the results presented in this chapter to include more follow-up.

Chapter 5 Effectiveness and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected individuals: Results from a pan-European study

5.1 Introduction

Globally, an estimated 36.7 million individuals were living with human immunodeficiency virus (HIV) in 2015, 2.3 million of whom were also co-infected with hepatitis C virus (HCV) in 2015 (227). If chronic HCV is untreated, individuals have an increased risk of developing life-threatening complications, with approximately 400000 individuals dying from HCV each year, mainly due to hepatocellular carcinoma (HCC) and liver cirrhosis (227). HIV and HCV co-infection is common due to shared routes of viral transmission, such as injecting drug use and sexual transmission in men who have sex with men (MSM), affecting 621000 individuals in the World Health Organisation (WHO) European Region in 2015 (227,453). Being co-infected with HIV (and not receiving antiretroviral therapy (ART)) accelerates HCV disease progression to cirrhosis and liver disease, especially if the individual has a CD4 count less than 200 cells/mm^3 (248,454,455). HIV treatment guidelines now recommend starting ART at HIV diagnosis, but it is also important to identify and treat HCV as early as possible, to prevent the virus from causing complications, and spreading to other individuals (151).

The 2030 agenda for Sustainable Development (described in Chapter 1 Section 1.1.1), included the target to combat hepatitis by 2030, which helped to make hepatitis a global health priority (11). The Global Health Sector Strategy on viral hepatitis calls for the elimination of viral hepatitis as a public health threat by 2030 (231). This would require a reduction in mortality by 65% (from 1.4 million to less than 500000) and a reduction in new infections by 90% (from 6-10 million to less than 1 million) by 2030 (231). These targets include providing HCV treatment to 80% of eligible patients which will lead to cure in more than 90% of patients and have a major impact on HCV-related mortality (456). A progress report on the 2016-2021 Global Health Sector Strategy published in

2019 highlighted universal coverage of prevention, diagnosis, treatment and care for key underserved and overlooked populations as a key point for realising HCV elimination (457). While there is inequity in the services provided for people who inject drugs (PWID), sex-workers, prisoners, and other disenfranchised individuals, PWID (who are usually criminalised) are often the hardest to reach population, with the lowest access to services (457). Globally, over 50% of PWID have chronic HCV (458), almost 25% of individuals newly infected with HCV inject drugs (8), and less than 1% of PWID live in countries with adequate harm reduction services (459). The progress report outlined key underserved and overlooked populations as the main tracers for achieving universal health coverage, however, there are very limited studies that include PWID (457).

5.1.1 Introduction of DAAs

Improvements in the understanding of HCV viral replication has led to the design of direct-acting antivirals (DAAs), which has revolutionised the HCV treatment landscape (223) (see Section 1.2.6). The first DAAs to be approved by the FDA were telaprevir and boceprevir in 2011 (which are no longer on the market), and since, many other DAAs have been approved which interfere with different stages of the HCV replication cycle (351,354,355). In contrast to interferon-based regimens, co-infection with HIV has not been found to reduce SVR rates in the DAA era, as large phase III trials report SVR rates over 95% in HIV/HCV co-infected individuals (351,405,406,460).

5.1.2 Real-world data on DAAs

Randomised controlled trials (RCTs) remain the gold standard for drug approval, however, participants are generally from limited patient populations that do not always reflect the general population that will be receiving the treatment post licencing (386). As mentioned, clinical trials have shown the SVR rate in mono and co-infected individuals to be similar. However, some real-world studies have shown that HIV/HCV co-infected

individuals have a lower rate of SVR (Table 5.1), and the complex comorbidities and potential for interaction with HIV treatment have increased concerns that these high SVR rates cannot be replicated in all real-world settings (461). A study carried out in a community care setting in New York included 253 mono-infected individuals and 74 co-infected individuals treated with DAAs showed that individuals co-infected with HIV/HCV have a lower rate of SVR12 (86% vs 96%, p=0.005) (462). Two studies carried out in Spain also found individuals co-infected with HIV have a worse response to DAA regimens than mono-infected individuals (86.3% vs 94.9% and 92% vs 98%) (463,464). Also, a recent meta-analysis comparing the SVR rate in clinical trials to routine practice in HCV mono-infected individuals with genotype 1 receiving simeprevir, sofosbuvir, and ribavirin, found that the pooled SVR12 rate was higher in RCT (94%) than in observational studies (84%) (465).

However, a study carried out using the Veterans Affair Clinical Case Registry in HIV/HCV co-infected veterans with genotype 1 showed response rates of 86%-92% to DAAs depending on the HCV treatment regimen, with cirrhosis being associated with lower SVR rates (466). Boesecke et al. also found the rate of SVR to be similar between co- and mono-infected individuals in a real-world setting (94% vs 95%, p=0.684) (467). They found that individuals with sub-optimal immune function (CD4 count <350 cells/mm^3) and liver cirrhosis had a lower rate of SVR (82.8%), and suggest these are the main driving forces for the difference between SVR rates for mono-infected and co-infected individuals found in other real-world studies (467). The largest real-world study of DAAs in HIV/HCV co-infected individuals was carried out in Spain and included 2369 individuals (468). They reported an SVR rate of 92% overall, however they also found SVR varied based on the severity of liver disease and HIV immunosuppression, as well as due to the use of suboptimal DAAs and gender (468). Therefore, the majority of real-world studies have confirmed SVR rates similar to those reported in clinical trials (413,466–469).

Table 5.1: Summary of DAA effectiveness in real-world studies in HIV/HCV co-infected individuals

Reference	Country	Year	Genotype	Treatments	n included	SVR12 n (%)
Arias A et al. (464)	Spain	Completed treatment by end of 2015	1a,1b, 3, 4	IFN-free DAA regimens: Sofosbuvir + ledipasvir ± ribavirin Sofosbuvir + daclatasvir ± ribavirin Sofosbuvir + simeprevir ± ribavirin Sofosbuvir + ribavirin Alternatively, HCV genotype 1 patients could be treated with: Ombitasvir + paritaprevir + ritonavir + dasabuvir ± ribavirin	112	103 (92)
Berenguer J et al. (468)	Spain	Nov 2014 - Aug 2016	1-4	IFN-free DAA regimens: Sofosbuvir + ledipasvir ± ribavirin Sofosbuvir + daclatasvir ± ribavirin Sofosbuvir + simeprevir ± ribavirin Sofosbuvir + ribavirin Ombitasvir +paritaprevir + ritonavir + dasabuvir ± ribavirin Ombitasvir +paritaprevir + ritonavir ± ribavirin Simeprevir + daclatasvir Sofosbuvir + simeprevir + daclatasvir Sofosbuvir + ombitasvir +paritaprevir + ritonavir	2369	2180 (92)
Bhattacharya D et al. (466)	USA	Started treatment before 30th Sep 2015	1	IFN-free DAA regimens: Sofosbuvir + ledipasvir ± ribavirin Ombitasvir +paritaprevir + ritonavir + dasabuvir ± ribavirin	905	823 (90.9)
Boesecke C et al. (467)	Germany	Not mentioned, published in 2017	1-4	DAA regimen + pegylated interferon and ribavirin: Sofosbuvir IFN-free DAA regimens: Sofosbuvir + ribavirin Sofosbuvir + simeprevir Sofosbuvir + daclatasvir ± ribavirin Sofosbuvir + ledipasvir Ombitasvir + paritaprevir/ritonavir ± RBV and ± dasabuvir	349	329 (94)
Gayam V et al. (462)	USA	Jan 2014 - Jul 2017	1-4	IFN-free DAA regimens: Sofosbuvir + ribavirin Sofosbuvir + simeprevir Sofosbuvir + ledipasvir	74	64 (86)

				Sofosbuvir + ledipasvir + ribavirin Sofosbuvir + velpatasvir Elbasvir + grazoprevir Daclatasvir + ribavirin Ombitasvir + paritaprevir + ritonavir + dasabuvir Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin		
Milazzo L et al. (470)	Italy	Dec 2014 - Dec 2015	1-4	IFN-free DAA regimens: Ombitasvir + paritaprevir + ritonavir + dasabuvir Sofosbuvir + daclatasvir Sofosbuvir + simeprevir Sofosbuvir + ribavirin Sofosbuvir + ledipasvir	58	53 (91)
Monforte A et al. (471)	Italy	Jan 2013 - 15 Dec 2016	1-4	DAA regimen + pegylated interferon and ribavirin: Telaprevir Boceprevir Simeprevir Sofosbuvir IFN-free DAA regimens: Sofosbuvir + ledipasvir ± ribavirin Dofosbuvir + ribavirin Dofosbuvir + simeprevir ± ribavirin Daclatasvir + simeprevir ± ribavirin Ombitasvir + paritaprevir + ritonavir + ribavirin Ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	585	545 (91.6)
Neukam K et al. (463)	Spain	Oct 2011 - Aug/Sep 2011	1a,1b, 3, 4	DAA regimen + pegylated interferon and ribavirin: Telaprevir Boceprevir Simeprevir Sofosbuvir IFN-free DAA regimens: Sofosbuvir + ledipasvir Sofosbuvir + simeprevir Sofosbuvir + daclatasvir Ombitasvir + paritaprevir + ritonavir Ombitasvir + paritaprevir + ritonavir + dasabuvir	256	221 (86.3)

Piroth L et al. (469)	France	Started treatment before 1st May 2015	1-4, 6	IFN-free DAA regimens: Sofosbuvir + daclatasvir ± ribavirin Sofosbuvir + ribavirin Sofosbuvir + ledipasvir ± ribavirin Sofosbuvir + simeprevir ± ribavirin Daclatasvir + asunaprevir + ribavirin Sofosbuvir + simeprevir + daclatasvir Sofosbuvir + ledipasvir + daclatasvir Ombitasvir + paritaprevir + ritonavir-boosted + ribavirin Ombitasvir + paritaprevir + ritonavir-boosted + dasabuvir + ribavirin	323	302 (93.5)

5.1.3 Safety of DAA treatment

The EXPEDITION-2 study explored the safety of glecaprevir/pibrentasvir in HIV/HCV co-infected individuals (406). They reported a number of grade 1 (mild) AEs and 4 serious AEs that were unrelated to glecaprevir/pibrentasvir. One individual had a grade ≥3 (severe or potentially life-threatening) bilirubin AE, however, they did not find any grade 3 or 4 AEs for elevations of ALT or AST (406). In the C-EDGE trial, there were only 2 serious adverse events, however there were also several common AEs, including fatigue (13%), headache (12%), and nausea (9%) (405). There were 3 individuals with a grade 3 ALT AE, 2 with a grade 4 ALT AE, 1 with a grade 4 AST AE, and 1 individual who had a grade 3 bilirubin AE (405).

Milazzo et al. reported 62% of individuals had at least 1 AE; the most common were fatigue, headache and nausea, however none caused treatment discontinuation (470). There were 11 individuals (10%) with hyperbilirubinemia, 2 of whom were also receiving atazanavir (470). Among the 1505 individuals in the German hepatitis C cohort (GECCO) study, 7 individuals stopped treatment early due to AEs, however they did not report any grade 3 or 4 AEs (467). Piroth et al. reported 94 (30%) individuals had an AE related to HCV treatment (469). There were 11 individuals who stopped treatment early; 2 stopped due to intolerance and 1 due to lack of virological response, however reasons for discontinuation was unknown for the other 8 individuals (469). While the safety of DAAs in co-infected individuals has been described in trials, it is not well documented in larger real-world studies.

5.1.4 Aims

There were three main aims of this analysis:

1. To investigate the effectiveness of DAAs, describing the difference in the virological outcomes of DAA treatment by different risk groups and identifying factors associated with achieving SVR
2. To explore the prevalence and reasons for premature discontinuation of DAAs
3. To explore the prevalence of laboratory adverse events (AEs) during treatment, and examine the impact of DAA treatment regimens, ribavirin (RBV), fibrosis stage and treatment start date on laboratory values

5.1.5 What this analysis adds

Real-world data is important to assess how DAAs perform in individuals from different backgrounds, age groups, and with other medical conditions that would not necessarily be included in clinical trials, as well as to examine the long-term effects of DAA therapy (386). Some real-world studies on DAA effectiveness in HIV/HCV co-infected individuals have been carried out in Europe, however, data from Eastern Europe is still scarce. Flisiak et al. carried out two real-world studies in Poland which showed a high DAA effectiveness rate, however HIV positive individuals were not included (472,473). A study carried out in Hungary, which also showed high SVR rates, only included two HIV positive individuals and was therefore not powered to explore SVR among HIV/HCV co-infected individuals (474). Table 5.1 shows that so far, the majority of real-world studies in HIV/HCV co-infected individuals have been carried out in Western Europe and the USA. Also, while current or former PWID are generally excluded from clinical trials, PWID makes up over half of the individuals included in this analysis. Therefore, this analysis also has the added benefit of including DAA effectiveness and safety data on individuals not well described. As mentioned in the Methods Chapter (Section 2.2.7), Cohort X of the EuroSIDA study exclusively enrolled anti-HCV positive individuals with the aim of exploring the adverse effects and benefits of DAA treatment in co-infection individuals. EuroSIDA systematically collected laboratory data during HCV treatment and information on early

treatment termination. This allows us to thoroughly describe the safety of DAAs, which has not previously been done in other cohort studies.

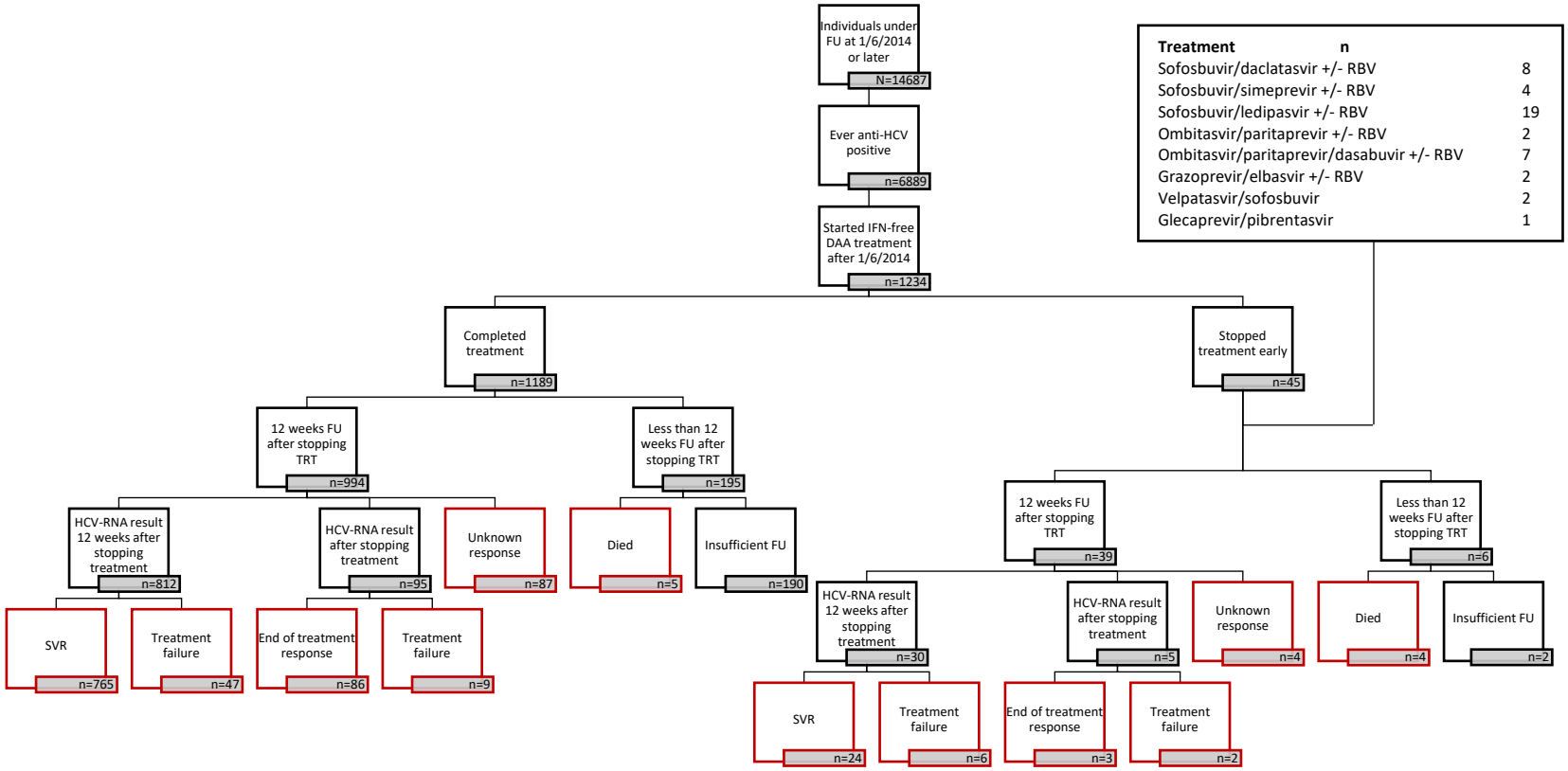
5.2 Methods

This analysis was carried out using data from the EuroSIDA study's (defined in chapter 2) D45 dataset which included data on 22830 individuals from 100 centres in 36 European countries, Israel and Argentina. The cohort and information on the collection of HCV data has been described in detail in Chapter 2, Section 2.2.

5.2.1 Inclusion criteria

Of the 22830 HIV-positive individuals included in the D45 dataset, 14687 were under follow-up (FU) at 1/6/14, 6889 of whom were ever anti-HCV positive, and 1234 of whom received an interferon-free DAA treatment regimen after 1/6/14. This analysis included individuals under follow-up in EuroSIDA that received interferon-free DAA therapy after 1 June 2014, as this is when EuroSIDA began collecting detailed information about HCV treatment, including data on reasons for early discontinuation of HCV therapy and treatment-limiting toxicities of HCV therapy. All reported HCV treatment toxicities were reviewed by a clinician. Individuals who did not have at least 12 weeks of follow-up after stopping treatment were not included in this analysis (unless they died within 12 weeks of stopping treatment). Baseline was defined as the start date of DAA treatment. Figure 5.1 shows a detailed description of how HIV/HCV co-infected individuals were selected for this analysis (those included outlined in red). A different subgroup of these individuals was included for each analysis; this is described in more detail in the results sections.

Figure 5.1: Flowchart for inclusion in analysis



5.2.2 Definition of treatment outcomes

The treatment outcomes were split into 4 categories, SVR (SVR12), treatment failure, end of treatment response, and unknown treatment response. Definitions for the different treatment outcomes can be found in Table 5.2 below. Individuals who achieved SVR or failed treatment were considered to have a known treatment response. Individuals who died during treatment or within 12 weeks of stopping treatment were considered treatment failures, however, individuals who had an unknown treatment response were not.

Table 5.2: HCV treatment outcome definitions

Treatment outcome	Definition
SVR/cure	Individuals with undetectable HCV-RNA at 12 weeks or later after stopping DAA treatment
Treatment failure	Individuals who did not achieve SVR, with detectable HCV-RNA at the first measurement at the end of treatment or later, or individuals who died before SVR could be determined
End of treatment response	Individuals with undetectable HCV-RNA after treatment stopped but prior to 12 weeks after stopping treatment, and no further HCV-RNA at or after 12 weeks
Unknown treatment response	Individuals with no HCV-RNA data after stopping treatment

5.2.3 Variables included in this analysis

The baseline variables used in the different analyses have been described below in Table 5.3.

Table 5.3: Definitions of baseline variables included analysis

Variable	Levels	Definitions and comments
Age (years)	Continuous (per 1 year older) and categorised as ≤50 and >50 years old	
Sex	Male, female	
Region	South/Argentina, Central - West, North, East/Central - East	Defined in Chapter 2 Section 2.2
Ethnicity	White, Global majority, unknown	
HIV risk group	MSM, PWID, heterosexual, and other	'Other' includes those with unknown risk group
CD4 count (cells/mm^3)	Continuous (per 100/mm^3) and categorised as ≤500, >500 (cells/mm^3), and unknown	Most recent measurement prior to baseline (within one year), if not available then measurement up to 6 months of after baseline included

CD4 nadir (cells/mm³)	Continuous (per 100/mm³) and categorised as ≤50, 50-200, and >200 (cells/mm³), and unknown	Lowest CD4 count prior to baseline, if not available then measurement up to 6 months of after baseline included
HIV-RNA (cp/ml)	≤500, >500, unknown	Most recent measurement prior to baseline (within one year), if not available then measurement up to 6 months of after baseline included
Treatment regimen	Sofosbuvir/ledipasvir +/- RBV, sofosbuvir/daclatasvir +/- RBV, ombitasvir/paritaprevir/dasabuvir +/- RBV, ombitasvir/paritaprevir +/- RBV, sofosbuvir/simeprevir +/- RBV, other	The 5 most common treatment regimens are listed, the remaining treatments were categorised as 'other'
Fibrosis	F1, F2, F3, F4, unknown and ≤F3, F4*	Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels measured 1 year prior to baseline
HCV genotype	G1, G2, G3, G4, unknown, and G1, other/unknown	Included HCV genotype data measured at any time-point
Ever received cART	Yes, no	Individual ever received cART (≥3 drugs) treatment prior to baseline
Prior HCV treatment	Yes, no	Individual received any HCV treatment prior to regimen included in analysis
Baseline	Continuous (per 6 months later) and categorised as <2016 and ≥2016	Date individual started their DAA treatment
Treatment duration	Continuous (per 1 week later) and categorised as ≤12 and >12 weeks	Calculated from DAA start date to first treatment stop
Hepatitis B infection (HBV)	Yes, no, unknown	Defined using HBsAg surface antigen test or HBV DNA
AIDS-defining event	Yes, no	Defined using CDC's 1993 definition (421)
Non-AIDS defining illness (non-ADI)	Yes, no	Non-AIDS defining malignancy, cardiovascular disease (CVD), end-stage liver disease (ESLD), HCC, end-stage renal disease (ESRD), and pancreatitis (422)

*Determined by either a biopsy (METAVIR stage F4), FibroScan (>12.5kPa), APRI (score >2), or hyaluronic acid (>150ng/mL)

5.2.4 Statistical analysis

5.2.4.1 Baseline characteristics

Baseline characteristics of individuals with a known response were defined based on the most recent measurement prior to baseline. If an individual did not have a CD4 count or HIV-RNA value within 12 months prior to baseline, then a value up to 6 months after baseline was included instead. Categorical characteristics were described with numbers and percentages, while numerical variables were described with medians and interquartile ranges. Fibrosis stage was defined using a consensus definition (225), and was determined based on the most reliable fibrosis marker measured within one year

prior to the baseline. The most reliable fibrosis marker was considered to be a biopsy result, followed by a Fibroscan result, an APRI score, and plasma hyaluronic acid level. Information on how fibrosis data is collected and defined in EuroSIDA has been described in Chapter 2, Section 2.2.7 (245). The baseline characteristics of individuals who had a known treatment outcome were compared using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables.

5.2.4.2 Stopping early

Not all individuals completed their recommended treatment regimen, and the reasons for stopping treatment early were described. Median treatment times were also calculated and compared between those who completed their treatment regimen and stopped early. Not all individuals had information on whether they stopped treatment earlier than scheduled, therefore the proportion of individuals who stopped early was calculated as a proportion of the individuals with treatment completion data.

5.2.4.3 Factors associated with known treatment response and SVR

Logistic regression was used to calculate the odds of having a known response to DAAs (SVR or treatment failure compared to end of treatment response or unknown treatment response). Logistic regression was also used to determine factors associated with achieving SVR among those with a known treatment response. Variables described in Table 5.3 that were found to be significant in univariable analyses ($p<0.1$) were included in multivariable models. As regional differences were of particular interest it was included in the multivariable models, regardless of whether it was significant in univariable analysis (a priori).

5.2.4.4 Laboratory data

Analysis of laboratory data was carried out on individuals who started treatment between 1 June 2014 and 1 October 2016, as this is when data on laboratory values (haemoglobin, leukocytes, neutrophils, platelet count, s-creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin) were systematically collected during HCV therapy by EuroSIDA.

AEs

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events is a shared tool used to ensure consistency and accuracy when reporting the severity of AEs (475). Version 2.0 was released in 2014 and was used to determine the severity of AEs for different laboratory markers (Table 5.4) (475). The severity of AEs were graded from 1-4, where grade 1 indicates a mild event, grade 2 indicates a moderate event, grade 3 indicates a severe event, and grade 4 indicates a potentially life-threatening event (475). When multiple measurements were recorded during treatment, the most serious AE value was included, which was the lowest value for haemoglobin, leukocytes, neutrophils, platelet count, and the highest value for s-creatinine, ALT, AST, ALP and bilirubin.

Change in laboratory values over time

Linear mixed-effects models (described in Chapter 2, Section 2.3.2.3) were used to explore factors associated with the change in laboratory values from pre-treatment (measured less than 6 months before starting treatment) to end of treatment (max 24 weeks after starting treatment). Changes in haemoglobin, leukocytes, neutrophils, platelet count, s-creatinine, ALT, AST, ALP, and bilirubin were assessed as these laboratory values were collected systematically during HCV treatment by EuroSIDA. The

impact of DAA treatment regimen, RBV, fibrosis stage, and treatment start date on laboratory data was explored. DAA treatment regimen, RBV, fibrosis stage, and treatment start date were included in the models as a fixed effect, however, time from baseline and the intercept were included as random effects, which allow for the explanatory variables to vary between individuals. An unstructured covariance structure was used for all 9 models, which assumes that each variance and covariance is unique, and does not impose a structure on the variance for the intercept or the slope as they are not likely to be similar (476).

SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, North Carolina, USA).

Table 5.4: DAIDS AE grading table (475)

Laboratory test	ULN*	Sex	Grade			
			1	2	3	4
Haemoglobin (g/dL)	n/a	Male	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
		Female	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Leukocytes (cells/mm³)	n/a	Both	2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Neutrophils (cells/mm³)	n/a	Both	800 to 1,000	600 to 799	400 to 599	< 400
Platelet count (cells/mm³)	n/a	Both	100,000 to < 124,999	50,000 to < 100,000	25,000 to < 50,000	< 25,000
S-creatinine (mg/dL)	1.2	Both	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN	> 1.8 to < 3.5 x ULN	≥ 3.5 x ULN
ALT† (IU/L)	40	Both	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST‡ (IU/L)	40	Both	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALP§ (IU/L)	70	Both	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bilirubin (mg/dL)	1	Both	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

Grades: 1 – mild, 2 – moderate, 3 – severe, 4 – potentially life-threatening

*ULN: Upper limit of normal, †ALT: Alanine aminotransferase, ‡AST: Aspartate aminotransferase, §ALP: Alkaline phosphatase

5.3 Results

The results are split into 9 sub-sections which include different analyses. Overall, there were 1042 individuals included (see Figure 5.1), however, different subsets of the 1042 individuals were included in each analysis, which is summarised in Table 5.5.

Table 5.5: Description of individuals included in each analysis

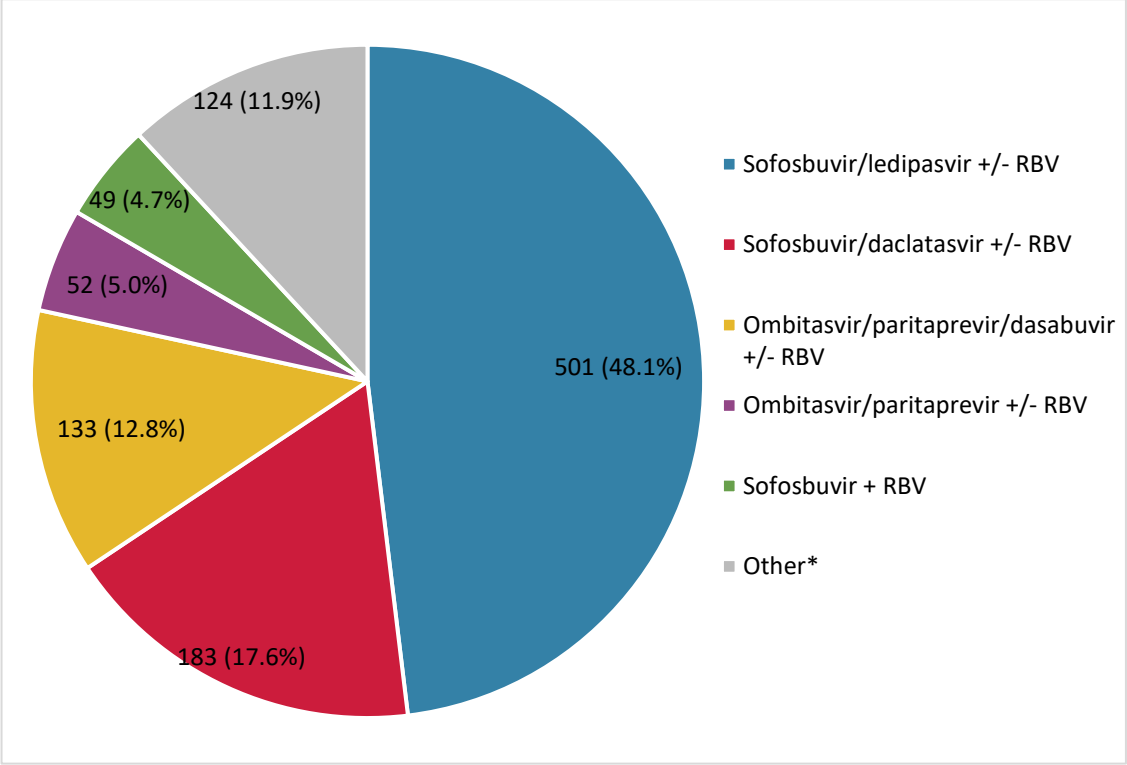
Section	Analysis	n included
5.3.1 Study population and treatment regimens	Description of individuals eligible	1234
	Comparison of those included and excluded	1042 vs 192
5.3.2 Virological response to treatment	Description of treatment outcomes	1042
5.3.3 Predictors of known treatment response	Odds of known response to treatment (vs unknown)	862 vs 180
5.3.4 Baseline characteristics of individuals with a known response to HCV treatment	Comparison between individuals with SVR and treatment failure	789 vs 73
5.3.5 Predictors of SVR	Odds of SVR (vs treatment failure)	789 vs 73
5.3.6 Reasons for stopping treatment early	Individuals with treatment stopping data	935
	Description of reasons for stopping early	43
5.3.7 Laboratory adverse events	Description of individuals eligible	555
	Comparison of those with and without data	511 vs 44
5.3.8 Laboratory values over time	Mixed-effects modelling	545
5.3.9 Sensitivity analysis	Investigation of association between non-ADI and SVR	1042

5.3.1 Study population and treatment regimens

Among the 1234 individuals who started interferon-free DAA treatment between 1/6/2014 and 1/3/2018, 1033 individuals had at least 12 weeks of FU after ending treatment, and 9 individuals died within 12 weeks of stopping treatment, therefore 1042 individuals were included in this analysis and all subsequent results relate to this cohort. Individuals not included due to limited FU after stopping treatment were more likely to be ≤50 years old, from Eastern Europe, receive other treatment regimens, started treatment ≥2016, and less likely to have a non-ADI, fibrosis F3 or F4, genotype 1, or previously received a HCV treatment. Most individuals included in this analysis received

a DAA regimen consisting of sofosbuvir/ledipasvir +/- RBV (n=501, 48.1%), 17.6% (n=183) received sofosbuvir/daclatasvir +/- RBV, 12.8% (n=133) received ombitasvir/paritaprevir/dasabuvir +/- RBV, 5.0% (n=52) received ombitasvir/paritaprevir +/- RBV, 4.7% (n=49) received sofosbuvir + RBV, and the remaining 11.9% (n=124) received other combinations of DAAs +/- RBV (Figure 5.2). Of the 1255 individuals included in this analysis, 379 (36.4%) had RBV included in their DAA regimen. The proportion of individuals with cirrhosis was higher among those treated with RBV (112/379 = 29.6%) compared to those not treated with RBV (88/663 =13.3) (p<0.0001).

Figure 5.2: Treatment regimens of 1042 individuals included in analysis



*Other: sofosbuvir/simeprevir +/- RBV (n=44, 4.2%), grazoprevir/elbasvir +/- RBV (n=40, 3.8%), velpatasvir/sofosbuvir (n=25, 2.4%), glecaprevir/pibrentasvir (n=11, 1.1%), and daclatasvir/simeprevir +/- RBV (n=4, 0.4%)

5.3.2 Virological response to treatment

Among the 1042 individuals included in this analysis, 789 (75.7%, 95% CI=73.1-78.3) individuals achieved SVR; 73 (7.0%, 95% CI=5.5-8.6) were treatment failures (this included 9 deaths within 12 weeks of stopping treatment); 89 (8.5%, 95% CI=6.8-10.2) had a negative HCV-RNA result after stopping treatment (but had no follow-up HCV-RNA result 12 weeks after stopping treatment); and 91 (8.7%, 95% CI=7.0-10.4) had an unknown treatment response. Therefore, 862/1042 (82.7%, 95% CI=80.4-85.0) individuals had a known response to their HCV treatment while 180/1042 (17.3%, 95% CI=15.0-12.6) had an unknown response. Among the 862 individuals with a known response to treatment, 789 (91.5%, 95% CI=89.7-93.4) achieved SVR and 73 (8.5%, 95% CI=6.7-10.3) were treatment failures, 12 of whom had stopped treatment early.

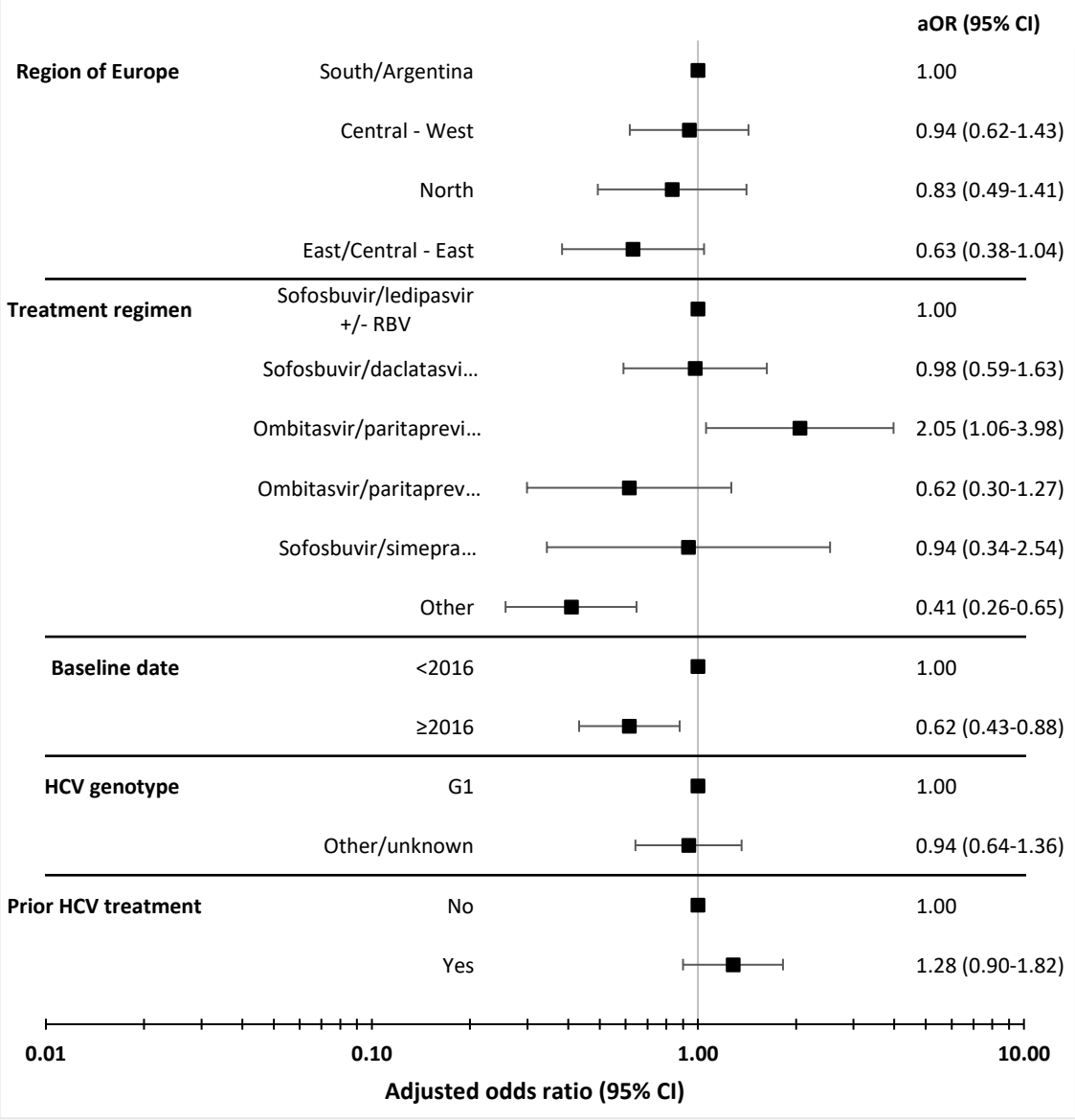
5.3.3 Predictors of known treatment response

In univariable analysis, certain baseline characteristics were associated with a lower odds of having a known response to treatment, such as individuals from East/Central – Eastern Europe (compared to Southern Europe) [odds ratio (OR)=0.50, 95% confidence interval (CI) 0.31-0.79], those who received other treatment regimens (compared to sofosbuvir/ledipasvir +/- RBV) [OR=0.36, 95% CI=0.23-0.55], individuals who started treatment after 2016 [OR=0.51, 95% CI=0.37-0.71], and individuals with HCV genotype 2-4 [OR=0.71, 95% CI=0.51-0.97]. Individuals who previously received HCV treatment were more likely to have a known response to treatment [OR=1.44, 95% CI=1.03-2.02], as were individuals who received ombitasvir/paritaprevir/dasabuvir +/- RBV [aOR=1.86, 95% CI=0.98-3.53], however this finding was only marginally significant.

In multivariable analysis, individuals with an unknown treatment outcome were similar to those with a known treatment outcome, but less likely to have started treatment in

2016 or later [adjusted odds ratio (aOR)=0.62, 95% (CI) 0.43-0.88], less likely to be on 'other' treatment regimens, and individuals on ombitasvir/paritaprevir/dasabuvir +/- RBV had a higher odds of having a known response to treatment [aOR=0.41, 95% CI=0.26-0.65] (Figure 5.3). After adjustment region, HCV genotype, and prior HCV treatment were no longer significantly associated with the odds of having a known HCV treatment response.

Figure 5.3: Multivariable factors associated with odds of having a known treatment response



Logistic regression model adjusted for variables shown

5.3.4 Baseline characteristics of individuals with a known response to HCV treatment

The majority of the 862 individuals with a known response to HCV treatment were male (78.0%), of white ethnicity (89.3%), and had a median age of 51 years old (interquartile range [IQR]: 45-55) (Table 5.6). The most common route of HIV transmission was PWID (54.9%), followed by MSM (23.7%), heterosexual (12.9), and other transmission routes (8.6%). The median CD4 count was 605 cells/mm^3 (IQR: 431-813), and 94.9% of individuals had an HIV-RNA value below 500 cp/ml, 96.9% of whom had ever received cART. Of the 862 individuals with a known response, 772 (89.6%) had been genotyped. Among those genotyped, genotype 1 was the most common (64.2%), followed by genotype 4 (17.5%), genotype 3 (16.5%), and genotype 2 (1.8%). 817 (94.8%) individuals had at least one liver fibrosis marker recorded one year prior to their treatment start data; 25 had a liver biopsy, 491 had a FibroScan, 759 had lab data available to calculate their APRI score, and 0 individuals had plasma hyaluronic acid levels recorded. The most reliable biomarker was used (as described in the methods), therefore of the 817 individuals with a fibrosis marker, 25 were based on a biopsy result, 482 were based on FibroScan, and 310 were based on an APRI score. 24.4% of individuals with a fibrosis marker had cirrhosis (METAVIR stage F4).

The proportion of individuals who achieved SVR was significantly different based on fibrosis stage (p=0.0122), as those with fibrosis F0-F3 had a SVR rate over 93.2%, while those with fibrosis F4 had a SVR rate of 86.4%. Individuals of white ethnicity had an SVR rate of 92.9%, individuals from the global majority had a SVR rate of 88.0%, while those with unknown ethnicity had SVR of 77.6% (p=0.0003). There were 163 (18.9%) individuals who had a previous non-ADI, the most common non-ADI was ESLD (excluding HCC) (n=58), followed by CVD (n=55), non-AIDS defining malignancy (excluding HCC) (n=46), pancreatitis (n=21), HCC (n=17), and ESRD (n=9). The proportion of individuals who achieved SVR was significantly lower among individuals who had a non-ADI compared to those that did not (86.5% vs 92.7%; p=0.0105).

Table 5.6: Baseline characteristics at time starting treatment in individuals with a known SVR status

		Overall	SVR	Treatment failure	p-value
			n (%)		
Overall		862 (100.0)	789 (91.5)	73 (8.5)	
Sex	**Male**	672 (78.0)	612 (91.1)	60 (8.9)	0.3617
	Female	190 (22.0)	177 (93.2)	13 (6.8)	
Ethnicity	**White**	770 (89.3)	715 (92.9)	55 (7.1)	0.0003
	Global majority	25 (2.9)	22 (88.0)	3 (12.0)	
	Unknown	67 (7.8)	52 (77.6)	15 (22.4)	
Region of Europe	**South/Argentina**	341 (39.6)	309 (90.6)	32 (9.4)	0.838
	Central - West	287 (33.3)	264 (92.0)	23 (8.0)	
	North	117 (13.6)	107 (91.5)	10 (8.5)	
	East/Central - East	117 (13.6)	109 (93.2)	8 (6.8)	
HIV risk group	**MSM***	204 (23.7)	190 (93.1)	14 (6.9)	0.2134
	PWID†	473 (54.9)	425 (89.9)	48 (10.1)	
	Heterosexual	111 (12.9)	103 (92.8)	8 (7.2)	
	Other	74 (8.6)	71 (95.9)	3 (4.1)	
HIV-RNA (cp/ml)	**≤500**	818 (94.9)	747 (91.3)	71 (8.7)	0.4232
	>500	10 (1.2)	9 (90.0)	1 (10.0)	
	Unknown	34 (3.9)	33 (97.1)	1 (2.9)	
Non-ADI†	**No**	699 (81.1)	648 (92.7)	51 (7.3)	0.0105
	Yes	163 (18.9)	141 (86.5)	22 (13.5)	
Baseline date	**<2016**	477 (55.3)	430 (90.1)	47 (9.9)	0.1041
	≥2016	385 (44.7)	359 (93.2)	26 (6.8)	
Fibrosis‡	**F0-F3**	408 (47.3)	378 (92.6)	30 (7.4)	0.0372
	F4	90 (10.4)	87 (96.7)	3 (3.3)	
	Unknown	120 (13.9)	111 (92.5)	9 (7.5)	
HCV genotype	**G1**	199 (23.1)	172 (86.4)	27 (13.6)	0.5649
	G2	45 (5.2)	41 (91.1)	4 (8.9)	
	G3	496 (57.5)	459 (92.5)	37 (7.5)	
	G4	14 (1.6)	13 (92.9)	1 (7.1)	
	Unknown	127 (14.7)	116 (91.3)	11 (8.7)	
Ever received cART	**No**	135 (15.7)	122 (90.4)	13 (9.6)	0.735
	Yes	90 (10.4)	79 (87.8)	11 (12.2)	
Prior HCV treatment	**No**	30 (3.5)	27 (90.0)	3 (10.0)	0.5471
	Yes	832 (96.5)	762 (91.6)	70 (8.4)	
HCV-RNA (IU/ml)	**<500000**	501 (58.1)	461 (92.0)	40 (8.0)	0.0167
	≥500000	361 (41.9)	328 (90.9)	33 (9.1)	
	Positive (unknown value)	195 (22.6)	179 (91.8)	16 (8.2)	
			Median (IQR)		
Age (years)		51 (45-55)	51 (45-55)	52 (46-54)	0.2446
CD4 count (cells/mm^3)		605 (431-813)	612 (433-822)	580 (380-747)	0.0925
CD4 nadir (cells/mm^3)		160 (72-265)	160 (70-265)	180 (77-264)	0.5251

*MSM: Men who have sex with men, †PWID: People who inject drugs

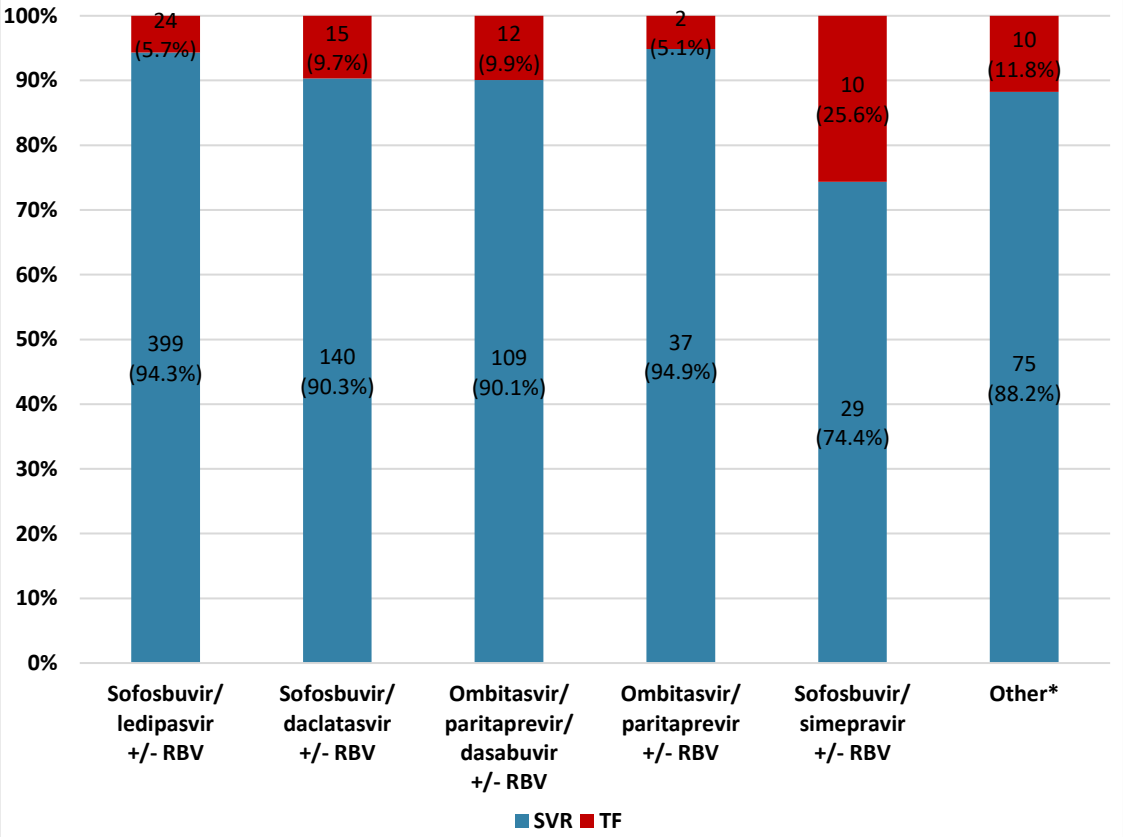
†Non-ADI: non-AIDS defining malignancy, cardiovascular disease (CVD), end-stage liver disease (ESLD), HCC, end-stage renal disease (ESRD), pancreatitis

‡Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels

n with CD4 count = 829, n with CD4 nadir = 858

There was also a significant difference in the proportion of individuals who achieved SVR based on DAA treatment regimen (p=0.0021) (Figure 5.4). SVR was highest among individuals treated with ombitasvir/paritaprevir +/- RBV (94.9%) and was lowest in those treated with sofosbuvir/simeprevir +/- RBV (74.4%). The level of fibrosis also varied between treatment groups (p<0.0001), as 48.7% of individuals treated with sofosbuvir/simeprevir had cirrhosis, compared to only 15.7% of individuals of treated with ombitasvir/paritaprevir/dasabuvir +/- RBV (Table 5.7). The majority of individuals treated with ombitasvir/paritaprevir +/- RBV had genotype 2-4 (76.9%) as opposed to genotype 1 (7.7%). Very few individuals treated with ombitasvir/paritaprevir/dasabuvir +/- RBV had genotype 2-4 (3.3%).

Figure 5.4: Difference in treatment outcome by treatment regimen



*Other: sofosbuvir +/- RBV (n=33, 3.8%), grazoprevir/elbasvir +/- RBV (n=25, 2.9%), velpatasvir/sofosbuvir (n=15, 1.7%), glecaprevir/pibrentasvir (n=8, 0.9%), and daclatasvir/simeprevir +/- RBV (n=4, 0.5%)

Table 5.7: Treatment regimen by baseline fibrosis level and HCV genotype

		Treatment regimen							P-value
		Overall	Sofosbuvir/ ledipasvir +/- RBV	Sofosbuvir/ daclatasvir +/- RBV	Ombitasvir/ paritaprevir/ dasabuvir +/- RBV	Ombitasvir/ paritaprevir +/- RBV	Sofosbuvir/ simeprevir +/- RBV	Other	
		n (%)							
Overall		862 (100.0)	423 (49.1)	155 (18.0)	121 (14.0)	39 (4.5)	39 (4.5)	85 (9.9)	
Fibrosis	**<F4**	618 (71.7)	338 (79.9)	87 (56.1)	96 (79.3)	26 (66.7)	19 (48.7)	52 (61.2)	<0.0001
	≥F4*	199 (23.1)	69 (16.3)	57 (36.8)	19 (15.7)	8 (20.5)	19 (48.7)	27 (31.8)	
	Unknown	45 (5.2)	16 (3.8)	16 (3.8)	6 (5.0)	5 (12.8)	1 (2.6)	6 (7.1)	
Genotype	**G1**	496 (57.5)	294 (69.5)	39 (25.2)	107 (88.4)	3 (7.7)	25 (64.1)	28 (32.9)	<0.0001
	G2-G4	276 (32.0)	79 (18.7)	104 (67.1)	4 (3.3)	30 (76.9)	11 (28.2)	48 (56.5)	
	Unknown	90 (10.4)	50 (11.8)	12 (7.7)	10 (8.3)	6 (15.4)	3 (7.7)	9 (10.6)	

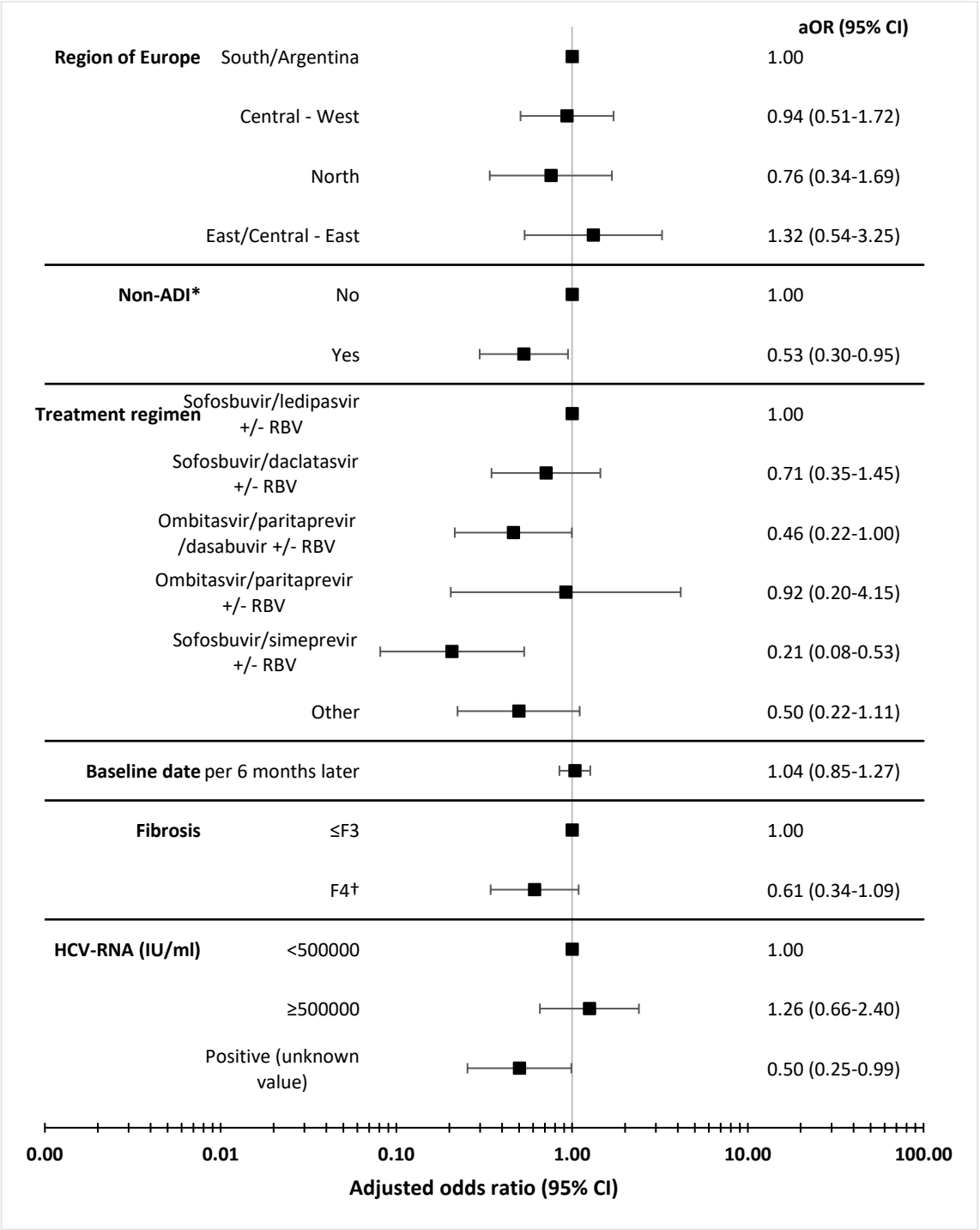
*Either a biopsy (METAVIR stage F4), FibroScan (>12.5kPa), APRI (score >2), or hyaluronic acid (>250ng/mL) at baseline

5.3.5 Predictors of SVR

The odds of achieving SVR was assessed in individuals with a known response to HCV-RNA treatment (n=862). In univariable analysis, non-ADI [OR=0.50, 95% CI=0.30-0.86], receiving sofosbuvir/simeprevir +/- RBV or other treatment regimens (compared to sofosbuvir/ledipasvir +/- RBV) [OR=0.17, 95% CI=0.08-0.40 and OR=0.45, 95% CI=0.21-0.98, respectively], and fibrosis stage F4 (compared to fibrosis ≤F3) [OR=0.47, 95% CI=0.28-0.78] were associated with a lower odds of SVR. There was no evidence of a difference between individuals who had a HCV-RNA result ≥500000 IU/ml or <500000 IU/ml, however those with an unknown level of viremia had a lower odds of achieving SVR compared to those with an HCV-RNA value <500000 IU/ml. There was also borderline evidence that individuals who started treatment later (per 6 months later after 1/6/2014) had a higher odds of SVR (p=0.0652).

After adjustment for these variables (with p<0.1) and region, factors found to decrease the odds of achieving SVR were having a non-ADI [aOR=0.53, 95% CI=0.23-0.95], receiving sofosbuvir/simeprevir +/- RBV [aOR=0.21, 95% CI=0.08-0.53] (compared to sofosbuvir/ledipasvir +/- RBV), and having an unknown level of HCV-RNA viremia [aOR=0.50, 95% CI=0.25-0.99] (Figure 5.5). In post hoc analysis a potential interaction between risk group and region was explored, however this was not significant (p>0.1). Age group, sex, ethnicity, HIV risk group, CD4 count, CD4 nadir, HIV-RNA, AIDS event, treatment duration (≤12 weeks vs >12 weeks), HCV genotype, cART, prior HCV treatment, and HBV co-infection were not included in the model as they either had p>0.1 in the univariable analysis (there was no evidence of an association with SVR), or there was insufficient data to explore the association.

Figure 5.5: Factors associated with odds of achieving SVR



Logistic regression model adjusted for variables shown and unknown fibrosis stage

*Non-ADI: non-AIDS defining malignancy, cardiovascular disease (CVD), end-stage liver disease (ESLD), HCC, end-stage renal disease (ESRD), pancreatitis

†Either a biopsy (METAVIR stage F4), FibroScan (>12.5kPa), APRI (score >2), or hyaluronic acid (>250ng/mL) at baseline

5.3.6 Reasons for stopping treatment early

Of the 1042 individuals included in this analysis, 935 (89.7%) individuals had information on whether they stopped treatment earlier than scheduled. Of these, 43 (4.6%) individuals had one or more components of their HCV regimen stopped early. Of the 43 individuals who stopped treatment early, 24 (55.8%) achieved SVR, 12 (27.9%) were treatment failures (including 4 deaths within 12 weeks of stopping treatment), and 7 (16.2%) had an unknown treatment response. After adjustment, individuals with cirrhosis had a higher odds of stopping treatment early compared to individuals with fibrosis ≤F3 [aOR=2.32, 95% CI=1.16-4.66]. Not all individuals stopped their entire treatment regimen, as 14/43 (32.6%) individuals only stopped RBV early.

The most common reason for stopping treatment early was reported AEs (n=14, 12 of whom were on RBV). There were 11 individuals who only stopped RBV and continued the remainder of the DAA treatment, 9 of whom had a known response to treatment and 8 (88.9%) who achieved SVR12. The most common AE was anaemia (n=8), followed by, rash (n=2), neuropathy (n=1), tiredness, dizziness, anorexia (n=1), intolerance, rash, fatigue, and abdominal pain (n=1), and nausea and vomiting (n=1). Other reasons for stopping treatment early were substance abuse (n=4), physicians decision (n=4), patients decision (n=2), virological failure (n=2), drug interaction (n=2), drug out of stock (n=1), or lost to follow-up (n=1), with 13 individuals having other/unknown reasons for stopping early. Two individuals died during treatment, and two individuals died within 12 weeks of stopping treatment. The median treatment time for those that stopped treatment early was 8 weeks (IQR: 4-12). Those who stopped treatment early due to AEs were treated for a median of 9 weeks (IQR: 4-14), and those with non-AE reasons for stopping treatment were also treated for a median of 8 weeks (IQR: 4-12). Individuals who did not have any reported treatment interruption were treated for a median of 12 weeks (IQR: 12-15).

5.3.7 Laboratory adverse events

555 individuals were eligible for this analysis as they started HCV treatment between 1/6/2014 and 1/10/2016. Of those eligible, 511 (92.1%) had laboratory data available during their treatment regimen and were included in this analysis. Differences between individuals included in this analysis and excluded from this analysis were explored using the chi-squared (or fisher's) test. After adjustment, individuals included in this analysis were less likely to have started HCV treatment after 2016 compared to the 44 individuals without lab data available during their HCV treatment regimen.

Table 5.8 shows the number of individuals with laboratory AEs during HCV treatment (graded 1 to 4) and pre-treatment laboratory abnormalities for different biomarkers. Of the 511 individuals included in this analysis, 363 (71.0%) had at least 1 AE, and overall 770 AEs were recorded among them. The median time to AE was shorter for ALT (4.1 weeks) and AST (4.9 weeks) compared to neutrophils (11.0 weeks) and s-creatinine (9.7 weeks), which occurred later on in the treatment regimen. The majority of 770 AEs during treatment were grade 1 or 2 (651, 84.5%) as opposed to grade 3 or 4 (119, 15.5%). Among the 363 individuals with an AE, 344 had a grade 1 or 2 AE and 87 had a grade 3 or 4 AE. The highest proportion of AEs during treatment was for elevated ALP (54.6%), followed by bilirubin (43.7%), and platelet count (28.6%), with a small proportion of individuals with neutropenia (1.3%) and leukopenia (3.0%). The most common grade 3 or 4 AEs during treatment was raised bilirubin levels (15.3%), followed by reduced platelet count (5.1%) and haemoglobin (1.6%), and increased ALT (1.4%). Among those with a grade 3 or 4 ALT elevation, one individual was HBsAg positive and received lamivudine as the only HBV active treatment. There is no information about the HBV-DNA levels during HCV treatment. Of the 119 grade 3 or 4 AEs that occurred during treatment, 57.1% occurred in individuals on RBV. Also, 56.7% of the 67 individuals with a grade 3 or 4 bilirubin AE were on atazanavir.

There were only 0-2 potentially life-threatening AEs during treatment for each of haemoglobin, leukocyte, neutrophils, platelet count, and s-creatinine and 7 grade 4 ALT AEs, however there were 17 grade 4 bilirubin AEs. The majority of the 17 individuals with bilirubin grade 4 AEs were over 50 years old (n=15), male (n=12), white (n=16), from Southern Europe (n=14), PWIDs (n=11), had HCV genotype 1 (n=14), and received atazanavir (n=12). There were 6 (35.3%) individuals who had cirrhosis and 3 (17.6%) who had liver fibrosis stage F3. The most common treatment regimen was ombitasvir/paritaprevir/dasabuvir +/- RBV (n=6), followed by sofosbuvir/simeprevir +/- RBV (n=5), sofosbuvir/ledipasvir +/- RBV (n=3), other (n=2), and sofosbuvir/daclatasvir +/- RBV (n=1). There were 446 individuals with pre-treatment laboratory data, 335 (74.1%) of whom had an abnormality. The highest proportion of pre-treatment abnormalities were ALT (58.6%), ALP (48.7%) and AST (48.2%) elevations.

Table 5.8: Number of laboratory adverse events during treatment by grade

Biomarker	Baseline		During treatment									
						Grade				Grade 3 or 4 AE		
	n with data	Abnormality	n with data	AEs	Median time to AE (weeks)	1	2	3	4	Overall	On RBV	On ATZ*
Haemoglobin (g/dL)	385	4 (1.0)	451	43 (9.5)	7.1	26 (5.8)	10 (2.2)	6 (1.3)	1 (0.3)	7 (1.6)	4 (57.1)	1 (14.3)
Leukocytes (cells/mm^3)	334	4 (1.2)	365	11 (3.0)	7.9	8 (2.2)	1 (0.3)		2 (0.5)	2 (0.5)	1 (50.0)	
Neutrophils (cells/mm^3)	193	1 (0.5)	227	3 (1.3)	11.0	2 (0.9)			1 (0.4)	1 (0.4)	1 (100.0)	
Platelet count (cells/mm^3)	403	102 (25.3)	493	141 (28.6)	5.1	63 (12.8)	53 (10.8)	24 (4.9)	1 (0.2)	25 (5.1)	11 (44.0)	7 (28.0)
S-creatinine (mg/dL)	364	26 (7.1)	450	39 (8.7)	9.7	19 (4.2)	15 (3.3)	3 (0.7)	2 (0.4)	5 (1.1)	1 (20.0)	1 (20.0)
ALT† (IU/L)	399	234 (58.6)	488	95 (19.5)	4.1	70 (14.3)	18 (3.7)	5 (1.0)	2 (0.4)	7 (1.4)	4 (57.1)	3 (42.9)
AST‡ (IU/L)	392	189 (48.2)	463	74 (16.0)	4.9	62 (13.4)	10 (2.2)		2 (0.4)	2 (0.4)	1 (50.0)	
ALP§ (IU/L)	275	134 (48.7)	315	172 (54.6)	7.7	152 (48.3)	17 (5.4)	3 (1.0)		3 (1.0)	1 (33.3)	
Bilirubin (mg/dL)	367	91 (24.8)	439	192 (43.7)	5.9	71 (16.2)	54 (12.3)	50 (11.4)	17 (3.9)	67 (15.3)	44 (65.7)	38 (56.7)

Grades: 1 – mild, 2 – moderate, 3 – severe, 4 – potentially life-threatening

*ATZ: Atazanavir, †ALT: Alanine aminotransferase, ‡AST: Aspartate aminotransferase, §ALP: Alkaline phosphatase

When multiple measurements were recorded during treatment, the lowest value was included for haemoglobin, leukocytes, neutrophils, platelet count, and the highest value was included for s-creatinine, ALT, AST, ALP and bilirubin

To compare baseline abnormalities and during treatment AEs, I restricted the analysis to those with data both pre-treatment and during treatment data (n=412). Table 5.9 below shows the number of individuals without a pre-treatment abnormality that later had an AE during treatment. Overall, there were 176 AEs, 161 (91.5%) of which were grade 1 or 2 AEs, and 15 (8.5%) grade 3 or 4 AEs. The highest proportion of AEs were bilirubin (23.0%) and ALP (23.0%) elevations. The lowest proportion of AEs were neutrophil (0.6%) and leukocyte (3.2%) reductions, and ALT (3.4%) increases. The grade 3 or 4 AEs during treatment were raised bilirubin (3.0%) and ALT (0.7%) levels, and decreased haemoglobin (1.5%), leukocyte (0.4%), and platelet count (0.4%) levels.

Table 5.9: Summary of laboratory adverse events at baseline and during treatment

Biomarker	n with data	AEs	Grade				Grade 3 or 4
			1	2	3	4	
Haemoglobin (g/dL)	328	29 (8.8)	16 (4.9)	8 (2.4)	4 (1.2)	1 (0.3)	5 (1.5)
Leukocytes (cells/mm^3)	278	9 (3.2)	7 (2.5)	1 (0.4)		1 (0.4)	1 (0.4)
Neutrophils (cells/mm^3)	165	1 (0.6)	1 (0.6)				
Platelet count (cells/mm^3)	271	25 (9.2)	21 (7.7)	3 (1.1)	1 (0.4)		1 (0.4)
S-creatinine (mg/dL)	318	14 (4.4)	11 (3.5)	3 (0.9)			
ALT* (IU/L)	146	5 (3.4)	3 (2.1)	1 (0.7)		1 (0.7)	1 (0.7)
AST† (IU/L)	170	9 (5.3)	7 (4.1)	2 (1.2)			
ALP‡ (IU/L)	100	23 (23.0)	23 (23.0)				
Bilirubin (mg/dL)	234	61 (26.1)	33 (14.1)	21 (9.0)	5 (2.1)	2 (0.9)	7 (3.0)

Grades: 1 or 2 – mild or moderate, 3 or 4 – severe or potentially life-threatening
*ALT: Alanine aminotransferase, †AST: Aspartate aminotransferase, ‡ALP: Alkaline phosphatase

5.3.8 Laboratory values over time

5.3.8.1 Description of longitudinal data

There were 545 individuals with either baseline laboratory data or data during treatment. The number of individuals and observations included in the analysis for each laboratory test varied, ranging from 254 individuals (558 observations) for neutrophils to 535 individuals (1451 observations) for platelet count (Table 5.10). The data was unbalanced, as individuals had a varying number of laboratory tests from baseline to 24

weeks, ranging from 1 test to 17 tests. However, the median number of tests per individual was 2 (IQR: 2-3) for all laboratory tests. The median time between observations also varied between the biomarkers and ranged from a median of 3.6 (IQR: 1.4-6.4) weeks for ALP tests, to 5.7 (IQR: 3.6-9.0) weeks for neutrophil tests.

Table 5.10: Description of longitudinal data included in mixed-effects models

Biomarker	n	Observations	Lab tests per individual		Time between lab test (weeks)	
			Min - Max	Median (IQR)	Min - Max	Median (IQR)
Haemoglobin (g/dL)	504	1314	1 - 17	2 (2-3)	0.1 - 24.0	4.0 (2.0-8.0)
Leukocytes (cells/mm³)	418	1152	1 - 17	2 (2-3)	0.1 - 22.7	3.7 (1.7-6.4)
Neutrophils (cells/mm³)	254	558	1 - 7	2 (2-3)	0.1 - 24.0	5.7 (3.6-9.0)
Platelet count (cells/mm³)	535	1451	1 - 17	2 (2-3)	0.1 - 24.0	3.9 (2.0-7.5)
S-creatinine (mg/dL)	476	1298	1 - 16	2 (2-3)	0.1 - 24.0	4.0 (2.0-7.9)
ALT (IU/L)	529	1440	1 - 16	2 (2-3)	0.1 - 24.0	3.9 (2.0-7.3)
AST (IU/L)	515	1364	1 - 16	2 (2-3)	0.1 - 23.3	4.0 (2.0-7.7)
ALP (IU/L)	378	909	1 - 15	2 (1-3)	0.1 - 24.0	3.6 (1.4-6.4)
Bilirubin (mg/dL)	490	1279	1 - 15	2 (2-3)	0.1 - 24.0	4.0 (2.0-8.0)

*ALT: Alanine aminotransferase, †AST: Aspartate aminotransferase, ‡ALP: Alkaline phosphatase

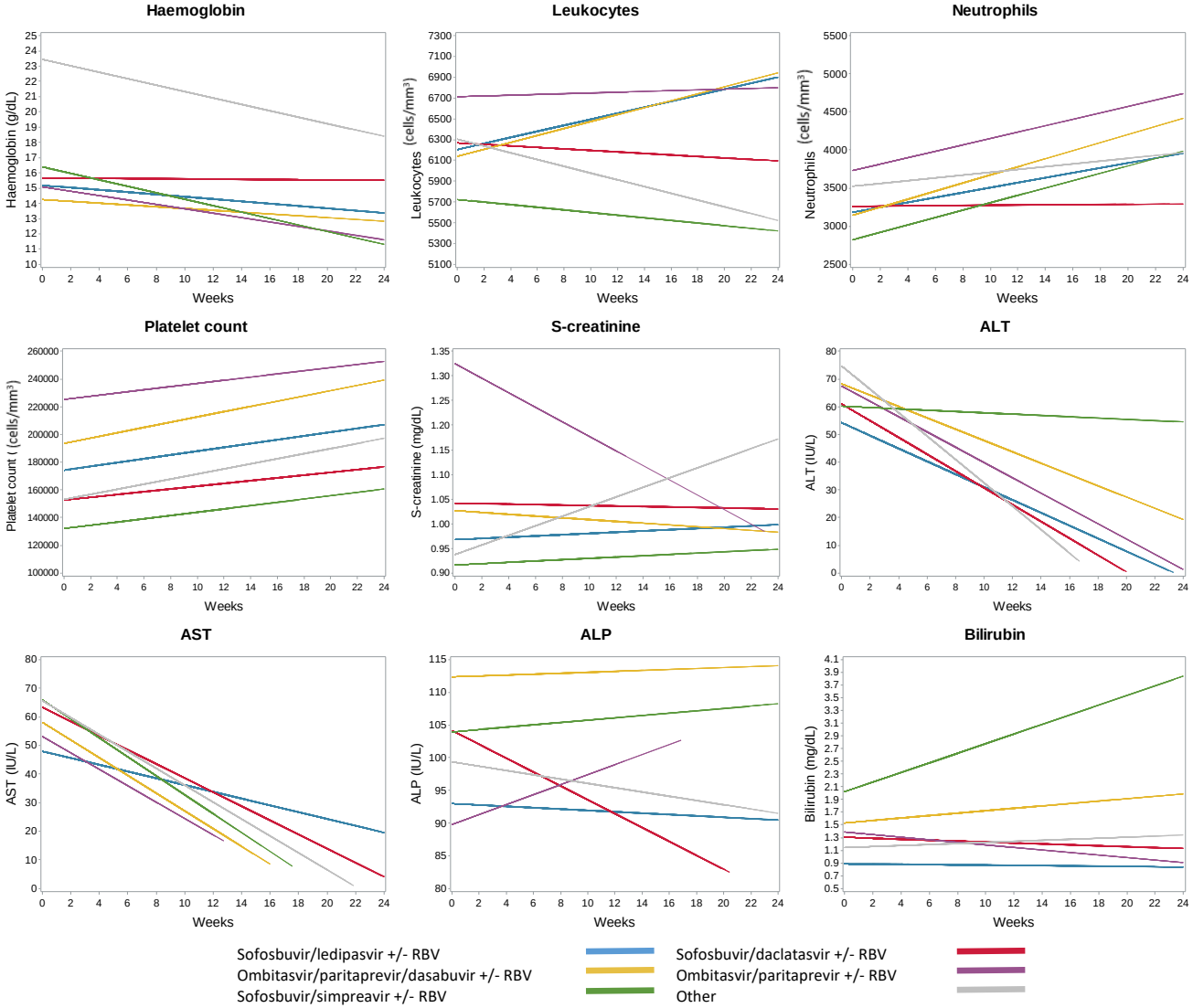
5.3.8.2 Effect of DAA treatment regimens on lab values over time

To explore the effect of different DAA treatment regimens on the estimated laboratory trajectories, nine mixed-effects models were developed (Figure 5.6). There was evidence that DAA treatment regimen was associated with laboratory values for haemoglobin ($p=0.0208$), platelet count ($p<0.0001$), AST ($p=0.0144$), and bilirubin ($p<0.0001$). The difference in treatment regimens is demonstrated in Figure 5.6 by the gaps between each treatment line. Overall, there was a significant decrease in lab value for ALT (-0.33 IU/L per week, 95% CI -0.49--0.18, $p<0.0001$), and AST (-0.17 IU/L per week, 95% CI -0.29--0.05, $p<0.0001$) overtime, and a significant increase in the lab value for neutrophils (4.62 cells/mm^3 per week, 95% CI 1.82-7.43, $p=0.0003$), and platelet count (195.78 cells/mm^3 per week, 95% CI 133.40-258.16, $p<0.0001$) over time. Although there was an overall decrease in ALT levels over time, Figure 5.6 shows the decrease in those treated with sofosbuvir/simeprevir +/- RBV was not as large as those treated with other regimens.

Also, the decrease in AST overtime was lowest in those treated with sofosbuvir/ledipasvir +/- RBV.

Only the change in bilirubin value over time was impacted by DAA treatment regimen (interaction between DAA treatment regimen and time, p=0.0009). This is demonstrated by the non-parallel treatment lines in the bilirubin plot, showing that depending on the treatment regimen, individuals had different changes in their bilirubin levels over time. For example, those treated with sofosbuvir/simeprevir +/- RBV had a baseline bilirubin level of around 2.0 (mg/dL) which increased to around 4.0 (mg/dL) by 24 weeks after starting treatment. However, those treated with ombitasvir/paritaprevir +/- RBV had a lower baseline bilirubin level of 1.4 (mg/dL) that decreased to around 0.8 (mg/dL) by week 24. There was no evidence of a significant difference in the impact of treatment regimens, time, or the interaction between time and treatment regimen for leukocytes, s-creatinine, or ALP.

Figure 5.6: Estimated laboratory values over time, by DAA treatment regimen

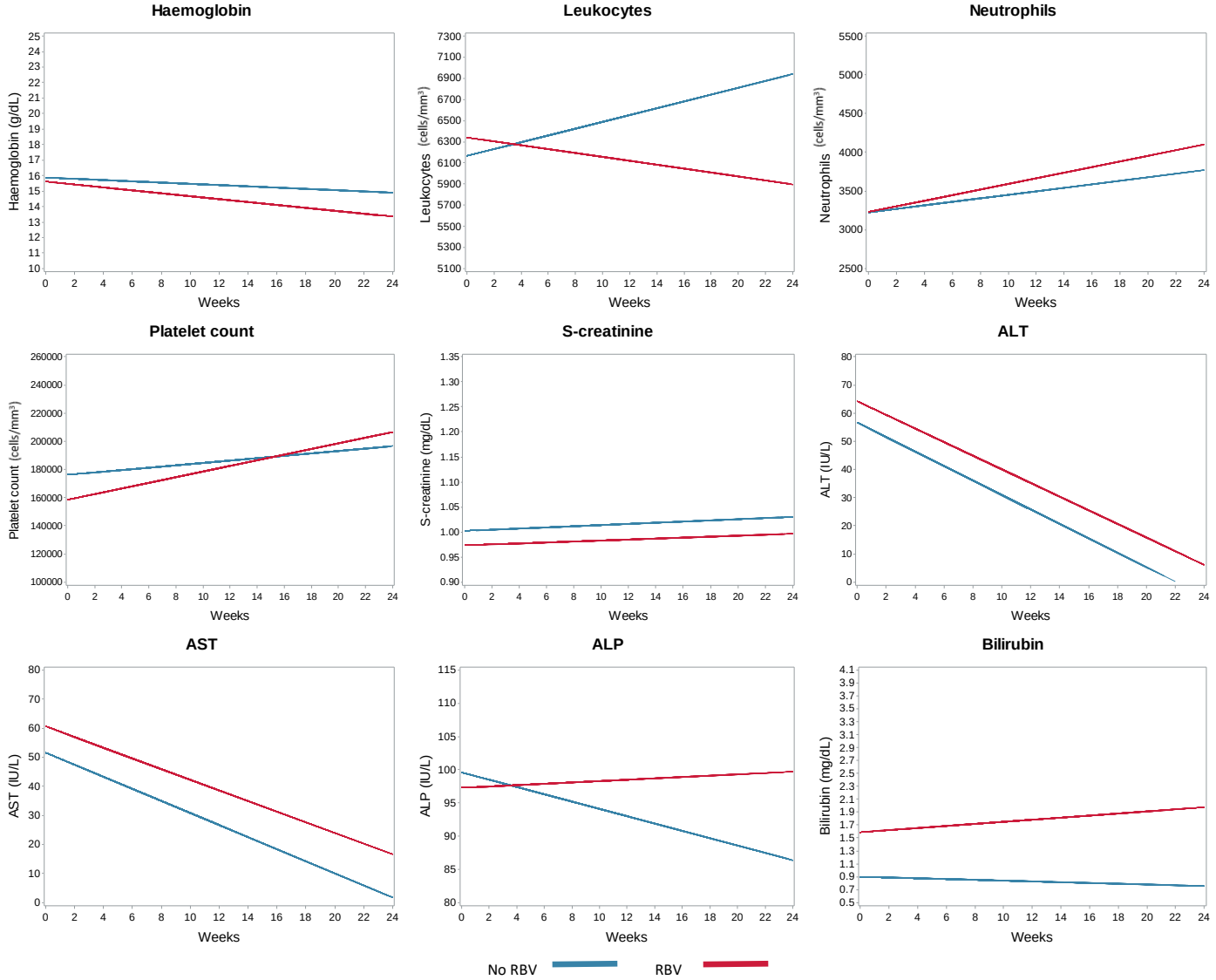


5.3.8.3 Effect of ribavirin on lab values over time

The difference in predicted trajectories for individuals who received RBV as part of their treatment regimen and those who did not can be seen in Figure 5.7. RBV use was significantly associated with platelet count (p=0.0044), AST (p=0.0320), and bilirubin (p<0.0001). Those treated with RBV had a lower baseline platelet count and a higher AST and bilirubin baseline value. Neutrophils (3.25 cells/mm^3 per week, 95% CI 0.71-5.78, p<0.0001) and platelet count (121.16 cells/mm^3 per week, 95% CI 63.69-178.64, p<0.0001) increased over time, while ALT (-0.37 IU/L per week, 95% CI -0.51--0.22, p<0.0001) and AST (-0.30 IU/L per week, 95% CI -0.41--0.19, p<0.0001) decreased over time.

Individuals on RBV had a higher baseline leukocyte level, however by 4 weeks it was the same as those not on RBV, and by 24 weeks it was almost 1000 cell/mm^3 lower (interaction between time and RBV significant, p=0.0005). Those on RBV had a lower platelet count at baseline, however over time their platelet count increased faster than those without RBV included in their treatment regimen, and by 24 weeks, they had a higher platelet count (interaction between RBV and time significant, p<0.0001). Bilirubin levels increase during treatment for those treated with RBV, however slightly decreases for those not on RBV (interaction between time and RBV significant, p<0.0122). There was no evidence of a significant difference in the impact of RBV, time, or the interaction between time and RBV for haemoglobin, s-creatinine or ALP.

Figure 5.7: Estimated laboratory trajectories by RBV

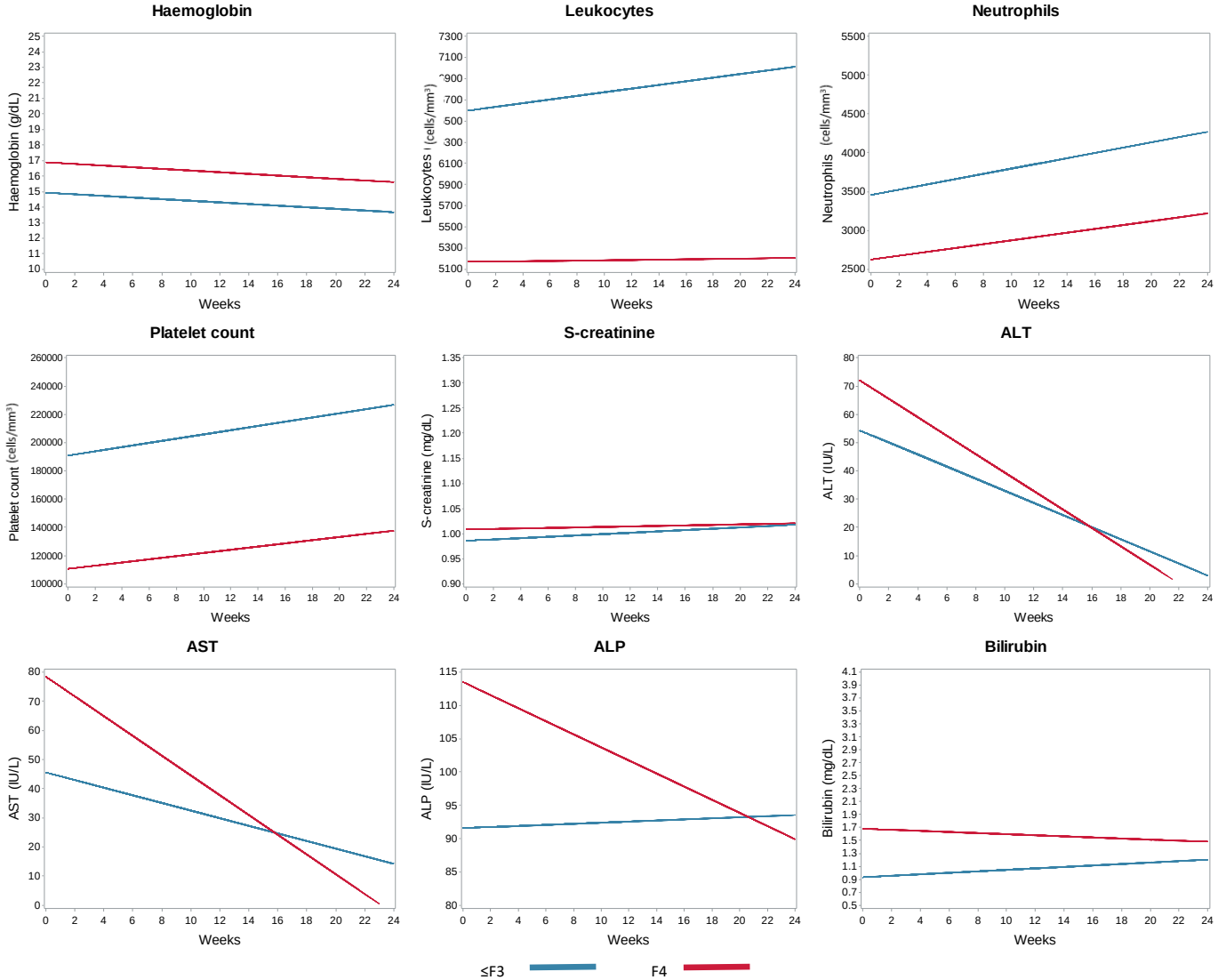


5.3.8.4 Effect of liver fibrosis stage on lab values over time

The impact of fibrosis stage on laboratory values was also explored and can be seen in Figure 5.8. Fibrosis stage was associated with leukocytes, neutrophils, platelet count, ALT, AST, ALP, and bilirubin ($p \leq 0.0001$ for all). Individuals with cirrhosis had a lower baseline neutrophil and platelet count value, and a higher baseline ALT, AST, ALP and bilirubin value. Over time neutrophils (4.85 cells/mm^3 per week, 95% CI 2.51-7.20, $p<0.0001$) and platelet count (213.58 cells/mm^3 per week, 95% CI 159.62-267.55, $p<0.0001$) values increased, however ALT (-0.31 IU/L per week, 95% CI -0.44--0.17, $p<0.0001$) and ALP (-0.19 IU/L per week, 95% CI -0.30--0.08, $p<0.0001$) levels decreased.

Figure 5.8 shows that AST levels for those with cirrhosis decreased quicker than those with fibrosis stage ≤F3. ALP decreased from 114 IU/L at baseline to 90 IU/L by week 24 in cirrhotic individuals, however ALP increased by ≤5 IU/L in those with fibrosis stage ≤F3. The impact of time and fibrosis stage on bilirubin levels can also be seen in Figure 5.8, the bilirubin values decrease between baseline and 24 weeks after starting treatment for those with cirrhosis, and increase for those with fibrosis stage ≤F3. This highlights the interaction between fibrosis stage and time was significant for AST ($p=0.0017$), ALP ($p=0.0189$) and bilirubin ($p=0.0279$).

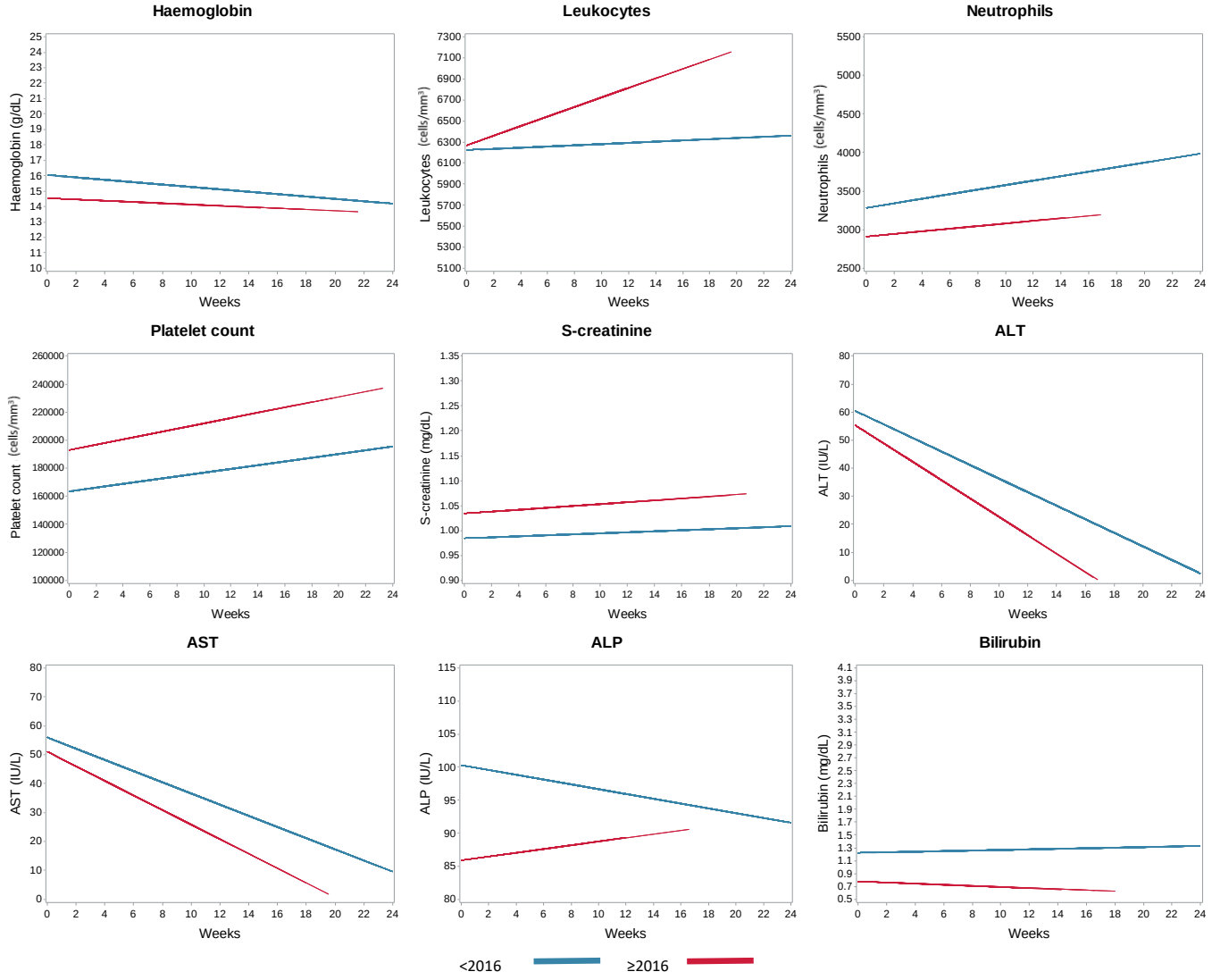
Figure 5.8: Estimated laboratory trajectories by fibrosis stage



5.3.8.5 Effect of DAA start date on lab values over time

The date an individual received treatment was significantly associated with platelet count and bilirubin; those who started treatment before 2016 had a lower baseline platelet count and a higher baseline bilirubin value ($p<0.0001$ and $p=0.0014$, respectively). Leukocytes (0.8395 cells/mm^3 per week, 95% CI -1.3717-3.03, $p=0.0278$) and platelet count (189.54 cells/mm^3 per week, 95% CI 144.82-234.25, $p<0.0001$) increased over time, however ALT (-0.3452 IU/L per week, 95% CI -0.4636--0.2269, $p<0.0001$) and AST (-0.2758 IU/L per week, 95% CI -0.3656—0.1860, $p<0.0001$) decreased over time (Figure 5.9). There was no evidence of a significant difference in the impact of treatment start year, time, or the interaction between treatment start year and time for haemoglobin, neutrophils, s-creatinine or ALP.

Figure 5.9: Estimated laboratory trajectories by baseline date



5.3.9 Sensitivity analysis

5.3.9.1 Effect of non-ADI on treatment outcome

As previously mentioned, the non-ADI variable included individuals with a non-AIDS defining malignancy (n=46), cardiovascular disease (n=55), ESLD (n=58), HCC (n-17), ESRD (n=9), or pancreatitis (n=21). The SVR rate was found to be lower in individuals with non-ADI prior to baseline (p=0.0105), however, when ESLD is excluded from non-ADI, the difference was no longer significant (91.8% vs 90.0%, p=0.4962). The univariable association between non-ADI and SVR was significant [aOR=0.50, 95% CI=0.30-0.86] and included in the multivariable analysis, where it was also marginally significant [aOR=0.56, 95% CI=0.32-1.00]. The univariable association between non-ADI excluding ESLD and SVR, was not significant [OR=0.80, 95% CI=0.43-1.51], however this may be due to reduced power, as the effect is still in the same direction, but the effect is not as large and there is a wider CI.

5.4 Discussion

Results from this analysis confirm that high SVR rates can be achieved in HIV/HCV co-infected individuals treated with interferon-free DAA regimens in a real-world non-trial setting. The SVR rate of 91.5% (95%=CI 89.7-93.4) was similar to rates previously reported in real-world studies (466,468,469) and only slightly lower than rates reported in clinical trials (405,406,477–479). There was no evidence to suggest SVR rate was impacted by HCV genotype, however the majority of the study population had genotype 1 (57.6%). There was also no evidence of regional differences in achieving SVR or having a known response to treatment, as SVR ranged from 90.6% to 93.2% across all European regions, however data from Central-East and Eastern Europe are still limited, and further investigation is warranted. There was also no evidence that PWID HIV transmission group had a lower rate of SVR (n with known treatment outcome: 473, SVR12: 89.9%), which is in accordance with the AASLD-IDSA 2018 HCV guidance update that states active or recent drug use is not a contraindication for HCV treatment (480). The majority of individuals completed their treatment regimen, with only 4.6% known to have stopped one or more drugs of the treatment regimen early. There were a number of individuals who experienced at least 1 grade 3 or 4 laboratory AEs during treatment (n=57), however, the number of individuals who experienced a grade 3 or 4 abnormalities was similar pre-treatment (n=53). There were fewer ALT and AST AEs during treatment than pre-treatment, indicating HCV treatment reduced the number of certain laboratory abnormalities, likely due to a reduction in HCV viraemia reducing hepatic inflammation. There was also evidence of differences in the changes in laboratory values from baseline to end of treatment based on treatment regimen, use of RBV, cirrhosis, and treatment start date.

5.4.1 SVR rate

Several other real-world studies reported similarly high rates of SVR among HIV/HCV co-infected individuals treated with IFN-free DAA regimens (see Table 5.1). For example, a study carried out using the Veterans Affair Clinical Case Registry that

included almost 1000 HIV/HCV co-infected individuals with genotype 1 who started DAA treatment before 30/9/2015 showed SVR rates of 86%-92% depending on the HCV treatment regimen (466). In 2017, the GECCO study reported an SVR rate of 94% in 349 HIV/HCV co-infected patients (467). The ANRS CO13 HEPAVIH French nationwide observational cohort study included 323 co-infected individuals who started DAA treatment before 1/2/2015, they reported an overall SVR rate of 93.5% (469). Also, a small study carried out in Italy found an SVR rate of 91% (n=58) in HIV/HCV co-infected individuals compared to 96% (n=51) in mono-infected individuals, which was not a significant difference (p=0.44) (470).

5.4.2 Factors associated with SVR

We found having a non-ADI before starting DAA treatment was associated with a lower odds of SVR in the adjusted logistic regression model. During sensitivity analysis, the association was found to be possibly driven by individuals with ESLD, as when ESLD was excluded from non-ADI there was no longer an association with treatment outcome (however, there was reduced power which may have impacted the significance). Also, individuals with ESLD were found to have a lower odds of achieving SVR in univariable and multivariable analysis. Also, non-ADI is a composite endpoint that includes any individuals who had a non-ADI prior to starting treatment, and 25 of the 58 individuals who had ESLD also had another non-ADI. These individuals may have more progressed disease and therefore it is possible that the association between ESLD and SVR12 may be partly attributable to confounding by indication.

Being treated with sofosbuvir/simeprevir +/- RBV or ombitasvir/paritaprevir/dasabuvir + RBV was also associated with a lower odds of SVR [aOR=0.21, 95%=CI 0.08-0.53 and aOR=0.46, 0.22-1.00, respectively], compared to sofosbuvir/ledipasvir +/- RBV. The Madrid co-infection registry also found individuals treated with sofosbuvir/simeprevir had a lower rate of SVR (468). A poster

presented at EASL 2016 by McGinnis et al. also found that individuals treated with sofosbuvir/simeprevir +/- RBV had a lower SVR rate, however, they found individuals treated with sofosbuvir/simeprevir +/- RBV had a higher proportion of cirrhosis compared to other treatment regimens (481). Cirrhosis was found to be associated with a lower odds of achieving SVR in the univariable analysis, but after adjustment, the reduction in odds was no longer statistically significant. As mentioned above, ESLD was associated with which indicates that cirrhosis negatively impacts the odds of achieving SVR12. The individuals included in this analysis that were treated with sofosbuvir/simeprevir +/- RBV were more likely to have cirrhosis, which has been shown to reduce the odds of achieving SVR in a number of clinical trials (351) and real-world studies (468), including The GECCO study which found that the SVR12 rate dropped to 86.1% in individuals with liver cirrhosis (from 94% in people without cirrhosis) (467). The Veterans Affair Clinical Case Registry study also found cirrhosis reduced the odds of SVR (466). However, 60% (n=162) of The ANRS CO13 HEPAVIH French nationwide observational cohort study had cirrhosis, and they did not find that cirrhotic status impacted the SVR12 rate (469). Sofosbuvir/simeprevir is no longer recommended by the European treatment guidelines for individuals co-infecting with HIV, however ombitasvir/paritaprevir/dasabuvir is still considered to be an alternative treatment option (317).

We did not find any evidence of an impact of HIV related factors (CD4 count, HIV-RNA, ART usage, or prior AIDS event) on HCV treatment outcomes, which corresponds with data from other studies (466,469). Conversely, the Madrid co-infection registry reported individuals with a prior AIDS event or a CD4 cell count less than 200 cells/mm^3 had a higher odds of treatment failure, indicating individuals with advanced HIV disease may have sub-optimal treatment outcomes, however further studies are required to confirm these results (468).

5.4.3 Reasons for stopping treatment

Of 935 individuals with data on whether they completed treatment, only 43 (4.6%) stopped one or more drugs of their treatment regimen early, 55.8% of whom achieved SVR. The percentage of treatment failures among those who completed their treatment regimen and had a known response to treatment was 7.4% (61/826). However, the percentage of treatment failures among individuals who stopped one or more components of their treatment regimen early and had a known treatment response was 33.3% (12/36). The most common reason for stopping early was toxicity, however most of the reported AEs were common and have been seen in other DAA studies (467,470). Also, of the 14 individuals who stopped treatment early due to toxicity, 13 were on RBV (11 of whom only stopped RBV) and experienced common side effects of RBV such as anaemia, rash and fatigue (326,482). It is important to note that RBV is generally added to a DAA regimen if the individual is considered harder to treat, (for example, if the individual has cirrhosis or decompensated cirrhosis), in which case the individual is likely to be more at risk of an AE (317). Also, there were 4 individuals from Northern Europe who stopped treatment early due to 'substance abuse', however this was because they were no longer able to complete their HCV treatment regimen.

5.4.4 Laboratory AEs

Among the 511 individuals included in the laboratory AE analysis, 363 (71.0%) had at least one AE during treatment, which contributed to 770 AE events. There were 119 (15.5%) grade 3 or 4 AEs, the majority of which were elevated bilirubin (n=67, 56.3%). However this finding was not considered to be significant as almost 90% of individuals with elevated bilirubin were also receiving RBV or a HIV treatment regimen that included the protease inhibitor atazanavir, both of which have been shown to increase the risk of hyperbilirubinemia (483–485). The C-EDGE and EXPEDITION-2 trials in HIV/HCV co-infected individuals reported <1% of individuals had a grade 3 AE but did not mention whether they received atazanavir (405,406). None of the individuals included in the GECCO study reported any grade 3 or 4 laboratory AE

(467). However, a small real-world study carried out in HCV mono-infected and HIV/HCV co-infected individuals in Italy reported hyperbilirubinaemia in 11 (10%) individuals, (they did not stratify by HIV status) (470). The AMBER and HARVEST studies were carried out in Poland in 2016 and 2017 in HCV mono-infected individuals and assessed the effectiveness and safety ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- RBV and of ledipasvir/sofosbuvir +/- RBV, respectively (472,473). The AMBER study reported 13.4% of individuals enrolled (n=209) had a grade 3 or 4 bilirubin AE, while in the HARVEST study, 3.5% of those enrolled experienced a grade 3 or 4 bilirubin AE (472,473). All individuals in the AMBER study with a bilirubin AE were receiving RBV as part of their HCV treatment regimen (472). These findings are not dissimilar to the low rates of laboratory AE reported in clinical trials (477–479), while other real-world studies have not systematically reported on laboratory AE events (466,468,469).

The change in laboratory values from baseline to 24 weeks after starting treatment was also explored. Overall, ALT and AST levels decreased over time regardless of the treatment regimen, however, the decrease in ALT was not as large in individuals treated with sofosbuvir/simeprevir +/- RBV. Also, AST levels did not decrease as much in individuals treated with sofosbuvir/ledipasvir +/- RBV compared to those treated with other regimens. The change in bilirubin over time varied based on treatment regimen, as bilirubin levels of those treated sofosbuvir/simeprevir +/- RBV increased from baseline and decreased among individuals treated with ombitasvir/paritaprevir +/- RBV. ALT, AST and ALP were also found to decrease quicker among individuals with cirrhosis compared to those with fibrosis ≤F3.

5.4.5 Strengths and limitations

Our analysis had several limitations therefore the findings should be interpreted with caution. Firstly, it was not possible to determine SVR for 18% of individuals included in this analysis as there was no HCV-RNA follow-up data. Possible reasons include

that HCV RNA was measured and not reported to EuroSIDA, or that HCV RNA has not been measured locally. The former is less likely given the rigorous quality assurance in place and that missing data has been requested by the coordinating team. Some of these individuals had a known end of treatment response, however, as this is real-world data not all individuals are seen at set time-points to assess SVR, and not all clinics have the resources to test. Not all individuals had data on whether they completed their treatment regimen, however in post hoc analysis among individuals with information on whether they completed treatment, the results were consistent. Also, the number of individuals who stopped due to toxicities may have been underestimated, as some centres included physician's decisions and patient's decisions as reasons for stopping treatment early, which may have overlapped with toxicities. Only lab data during treatment for individuals who start treatment between 1/1/2014 and 1/1/2016 were systematically collected. This means it is not possible to comment on AEs of more recently approved DAA drugs. Also, of the 706 individuals eligible for this analysis, those with laboratory data and assessed for AEs were significantly different from those without lab data and excluded from this analysis. Black individuals were found to have a lower odds of SVR in a real-world study on HCV mono-infected individuals (486), and a clinical trial on HIV/HCV co-infected individuals (477). While there was some evidence to suggest a difference in treatment outcome based on ethnicity (p=0.0032) in my analysis, there was insufficient data to explore this further as the majority of the study population was white (87.5%), 3.2% were from the global majority, and 9.2% had an unknown ethnicity. The difference in SVR rate was mainly driven by the difference between those of white and unknown ethnicity (93.5% vs 77.6%). Also, the EuroSIDA cohort may not be representative of all HIV/HCV co-infected individuals as it mainly collects data from university clinics in large European cities that are focused on clinical research, and therefore may ensure their standard of care is in line with good clinical practice and may differ from other treatment centres.

A major strength of this study is that it collects longitudinal clinical cohort data on a large number of individuals across different regions in Europe in a standardised way,

which allows for comparisons between regions, and examination of changes over time. All individuals DAA treatments and reasons for discontinuation were centrally reviewed. This study is also one of the first to include data from East and Central East Europe which is another major strength of the study, as there are not many real-world studies that include data from this region. Laboratory data during treatment was systematically collected, which allowed me to explore laboratory AEs in a way other real-world studies have not.

5.5 Dissemination of results

The results from this chapter were published in the Journal of Acquired Immune Deficiency Syndromes in 2021 (Appendix VIII)

Chapter 6 HCV reinfection among HIV/HCV co-infected individuals in Europe

6.1 Introduction

The prevalence of HCV is significantly higher among people living with HIV (PLWH), especially certain risk groups such as people who inject drugs (PWID) and men who have sex with men (MSM) (487). Currently, 2.4% of PLWH are co-infected with HCV, however, this increases to 6.4% in MSM and 82.4% among PWID (380). Also, the odds of HCV infection is 6 times higher in people living with HIV compared to HIV negative individuals (380).

The WHO set a target for HCV elimination by 2030, which requires a 90% reduction in new infections and a 65% reduction in mortality compared to 2015 (227). However, reinfection could hinder efforts to achieve elimination if not addressed (487). Reinfection is defined as a reoccurrence of HCV viremia after clearing the virus. In the absence of a vaccine against HCV, those who have spontaneously cleared the virus or have been cured through treatment are still at risk of reinfection, which reverses the health benefits of clearing the virus (372,373). Reinfection is of particular concern among PWID and HIV positive MSM who may have ongoing risk behaviours that put them at risk of reinfection (278). Therefore, efforts to eliminate HCV must address the issue of reinfection, especially among high-risk populations such as PWID and MSM(487).

6.1.1 Reinfection after HCV treatment

IFN-era

There have been several studies exploring reinfection after achieving sustained virological response (SVR) which have been summarised in Table 6.1. A meta-analysis examining HCV recurrence (reinfection or late relapse) 5-years post-treatment in

studies carried out from 1990 to 2015 compared recurrence rates among three groups, low-risk HIV-negative individuals, high-risk HIV-negative individuals, and HIV/HCV co-infected individuals (373). High-risk was defined as either current or former injecting drug user (IDU), imprisonment, or MSM, low-risk was defined as having no risk factors, and HIV/HCV co-infected individuals were included regardless of the presence/absence of risk factors (373). They found that 1.3% (108/7969), 5.4% (42/771), and 10.0% (31/309) of individuals were reinfected among low-risk, high-risk, and co-infected individuals, respectively. These findings were also reflected in the reinfection rate, which was 1.85/1000 (95% confidence interval (CI)=0.71-3.35) person-years of follow-up (PYFU) in low-risk individuals, 22.32/1000 PYFU (95% CI=13.07-33.46) in high-risk individuals, and the highest in HIV/HCV co-infected individuals at 32.02/1000 PYFU (95% CI=0.00-123.49) (373). However, the wide 95% confidence interval for the reinfection rate among HIV co-infected individuals indicates uncertainty around the estimate (373).

Lambers et al. explored HCV reinfection among 56 HIV positive MSM in Amsterdam treated for acute HCV infection between 2003-2011 (488). Among the 56 individuals, 5 relapsed (HCV-RNA positive after a negative end of treatment result, with different genotype to primary infection indicated by phylogenetic analysis) and were excluded from the analysis (488). Among the remaining 51 individuals, the median follow-up (FU) time was 1.3 years (interquartile range (IQR): 0.5-1.6) (488). There were 11 (22%) individuals who were reinfected with HCV, and the median time to reinfection was 8.4 months (IQR: 3.6-19.2) (488). Martinello et al. also carried out a study exploring reinfection after either IFN-based or IFN-free DAA therapy between 2004 and 2015 (489). They included 64 HIV positive MSM who were followed for a median of 1.22 years (IQR: 0.19-2.53). Among the 64 co-infected individuals included, 7 (11%) were reinfected by a median of 35 weeks (IQR: 9-81) from the end of treatment (489). Also, among both HIV negative and HIV positive individuals (n=120) they found the incidence of reinfection to be higher in individuals who reported injection drug use at the end of treatment (15.5 per 100 PYFU) compared to those who did not inject drugs during FU (2.6/100 PYFU) (489).

Another study carried out mainly among PWID (86% of the study population) included 84 HIV positive individuals treated between 2001 and 2013 in Spain (490). There were 4 (5%) individuals who were reinfected, and the median time from SVR to reinfection was 68 months (IQR: 55-76) (490). Marco et al. explored reinfection among individuals who were incarcerated in Spain between 2002 and 2016. They included 602 HIV positive (29%) and HIV negative (71%) individuals who achieved SVR (treated with either IFN-based or IFN-free DAA therapy) (491). Overall, 63 (11%) individuals were reinfected, however the authors report that the reinfection rate was 2.5 fold higher among HIV positive individuals (491). They found that 8 (12.7%) individuals were reinfected within a year of SVR, 40 (63.5%) within 5 years, and 62 (98.4%) within 10 years (491).

Islam et al. carried out an analysis in Canada, which is one of the largest population-level studies on HCV reinfection; they included 5915 individuals who cleared the virus either by IFN-based treatment or spontaneous clearance (492). Overall, the median FU time was 5.4 years (IQR: 2.9-8.7), and the median time to reinfection was 3.0 years (IQR: 1.5-5.4). There were 2225 individuals who achieved SVR, 126 of whom were co-infected with HIV and 2099 who were mono-infected with HCV. The proportion of reinfection was higher among HIV positive individuals (10%) than HIV negative individuals (2%) (492). Another study carried out in Canada among HIV/HCV co-infected individuals included 257 individuals who achieved SVR after treatment between 2003 and 2016 (51 of whom received IFN-free DAAs). They reported that 18 (7%) individuals were reinfected, with a median of 2.5 years (IQR: 1.6-3.2) from SVR to reinfection (493).

DAA era

Analysis of the German Hepatitis C Cohort (GECCO) explored reinfection after treatment with IFN-free DAAs among MSM between 2014 and 2018 (494). Out of the 2298 individuals included in this analysis, 509 individuals were also HIV positive, 38 (7.5%) of who were reinfected by a median of 500 days (494). Among the 38 reinfected co-infected individuals, 36 were MSM, highlighting the increased risk of

repeated HCV infection among HIV positive MSM (494). They also compared their findings with their previous work carried out in the IFN-era and found the incidence of reinfection among MSM to be similar in both treatment eras (377,494).

Rossi et al. carried out a study in Canada that included 4114 individuals who had achieved SVR after an IFN-free DAA treatment regimen between 2014 and 2017. Individuals were followed for a median of 123 days (IQR: 84-357), and 40 (1%) individuals were reinfected (495). This analysis included 403 HIV positive individuals, 24 (6%) of whom were reinfected (495). They reported the reinfection rate to be 1.44/100 PYFU overall, 3.11/100 PYFU among recent PWID, and 5.67/100 PYFU among recent PWID who were co-infected with HIV (495). After adjustment, the only factor they found to be associated with reinfection was current or recent injection drug use, and in a separate analysis among PWID, they found that opioid agonist therapy was associated with a (non-significant) reduction in reinfection (495). Finally, a study in Spain also explored reinfection among HIV positive individuals who achieved SVR after treatment with an IFN-free DAA regimen (496). They included 2359 individuals who achieved SVR between 2014 and 2017, 17 (0.7%) of who were reinfected. The majority of the study were PWID (n=1459) of whom 0.3% (n=5) were reinfected, however among the 177 MSM individuals, 6.8% (n-12) were reinfected (496). However, all 12 of the reinfected MSM reported unprotected anal sex with several partners, 7 reported chemsex, 6 reported fisting, and 4 reported slamming (496).

Table 6.1: Summary of studies on HCV reinfection after SVR among HIV/HCV co-infected individuals

Reference	Country	HIV co-infected?	Year	Treatment	Definition of SVR	n SVR	Reinfected n (%)
Berenguer J et al. (496)	Spain	Yes	2014-2017	IFN-free DAA	1 negative HCV-RNA result: 12 weeks after completion of treatment	2359	17 (0.7)
Currie S et al. (497)	USA	Yes (IDU)*	1997-2007	IFN-based	Documented SVR (not defined further), OR, in those who did not have an SVR, 2 consecutive negative HCV-RNA results: at least 6 months post-HCV antiviral treatment	5	1 (20)
Ingiliz P et al. (498)	Germany	Yes (MSM)	2001-2013	IFN-based	1 negative HCV-RNA result: 12 weeks after treatment with pegylated interferon (with or without ribavirin)	302†	48 (16)†
Ingiliz P et al. (377)	Multi-country	Yes (MSM)	2002-2014	IFN-based	1 negative HCV-RNA result: 12 weeks after the end of an interferon-based treatment and at least one subsequent HCV PCR measurement.	606†	149 (25)†
Ingiliz P et al. (494)	Germany	Yes (MSM)*	2014-2018	IFN-free DAA	1 negative HCV-RNA result: 12 weeks after the end of the respective DAA treatment	509	38 (7)
Islam N et al. (492)	Canada	Yes*	1992-2013	IFN-based	2 consecutive negative HCV-RNA results: at least 28 days apart, 12 weeks after completion of interferon-based treatment	126	12 (10)
Lambers F et al. (488)	Holland	Yes (MSM)	2003-2011	IFN-based	1 negative HCV-RNA result: at the end of treatment	51	11 (22)
Marco A et al. (491)	Spain	Yes (incarcerated)*	2002-2016	IFN-based or IFN-free DAA	Not specified	173	26 (15)
Martin T et al. (499)	UK	Yes (MSM)	2004-2012	IFN-based	1 negative HCV-RNA result: 24 weeks following end of treatment and at least one subsequent HCV-RNA measurement	114	27 (24)
Martinello M et al. (489)	Australia and New Zealand	Yes*	2004-2015	IFN-based or IFN-free DAA	1 negative HCV-RNA result	64	7 (11)
Pineda J et al. (490)	Spain	Yes	2001-2013	IFN-based	1 negative HCV-RNA result: 24 weeks after therapy completion	84	4 (5)
Rossi C et al. (495)	Canada	Yes*	2014-2018	IFN-free DAA	1 negative HCV-RNA result: between 10-52 weeks after end of treatment	403	24 (6)
Young J et al. (493)	Canada	Yes	2003-2016	IFN-based or IFN-free DAA	1 negative HCV-RNA result: 12 weeks after the end-of-treatment date	257	18 (7)

* Sub-study in HIV-positive individual among larger study on both co-infected and mono-infected individuals
† n included pooled with those who spontaneously cleared the virus

6.1.2 Spontaneous clearance

In the absence of HCV treatment, the natural progression of HCV can vary after initial exposure. The majority of individuals with acute HCV will develop chronic HCV, while around 25% will spontaneously clear the virus, usually within the first 6 months of infection (222). Most data have shown spontaneous clearance stops the progression of liver disease (291). However, individuals who spontaneously clear the virus are still at risk of reinfection, despite studies in HIV negative individuals suggesting that previous clearance of HCV can lead to some subsequent immunological control (374,499–502).

While around 25% of HIV negative individuals with acute hepatitis C will spontaneously clear the virus, the proportion of HIV/HCV co-infected individuals who spontaneously cleared the virus is lower at around 10-15% (222,247,503,504). A recent meta-analysis carried out by Aisyah et al. explored factors associated with spontaneous clearance of HCV (505). They included data on 20110 individuals and found that PLWH, males, PWID, excessive alcohol drinkers, individuals of Black or aboriginal ethnicity, and individuals over 45 years old were less likely to spontaneously clear HCV (505). They also reported some genetic factors to be associated with increased odds of spontaneous clearance (IL28B rs12979860/rs8099917/rs8103142) (505). Another predictor of spontaneous clearance was a 2-log drop in HCV-RNA at 4 weeks after initial diagnosis, however, as spontaneous clearance is less likely among HIV positive individuals, a 2-log drop of HCV 4 weeks after presentation is less likely (506)

A cross-sectional analysis carried out by Soriano et al. in the EuroSIDA study showed that among 1940 HIV/HCV co-infected individuals, 444 (23%) individuals spontaneously cleared HCV (507). They found a higher rate of HIV spontaneous clearance compared to other studies in HIV positive individuals. The timing of HCV infection compared to HIV infection was unknown, but the authors hypothesise that

HCV infection preceded HIV infection because it is more transmissible than HIV through percutaneous exposure, as seen in other studies among PWID (508,509), which would explain the higher clearance rate (507). After adjustment they found regional differences in odds of spontaneously clearing HCV, they also reported that females and HBsAg positive individuals had a higher odds of spontaneous clearance, and PWID (compared to MSM) had a lower odds of spontaneous clearance (507).

6.1.3 Reinfection after spontaneous clearance

Peters et al. explored factors associated with reinfection among HIV positive individuals who spontaneously cleared HCV in the EuroSIDA study (510). They included 191 individuals who spontaneously cleared the virus, 35 (18%) of whom were reinfected a median of 3.5 years later (510). They also reported that the odds of recurrence was higher among PWID, and lower among older individuals and individuals on cART (510). Sack-Davis et al. also explored reinfection after spontaneous among the International Collaboration of Incident Human Immunodeficiency Virus and HCV in Injecting Cohorts study, which includes data from countries such as the Netherlands, Australia, America and Canada. They included 118 individuals who were HIV negative and HIV positive, 28 (24%) of whom were reinfected (511). Among the 12 HIV positive individuals they included, 3 (25%) were reinfected (511).

A few studies have looked at reinfection after both spontaneous clearance and SVR in HIV/HCV co-infected individuals. Ingiliz et al. looked at reinfection in HIV-positive MSM in Western Europe from 2002 to 2014 and found the overall reinfection rate to be 7.3/100 PYFU (377). They reported a lower incidence of reinfection among PLWH who spontaneously cleared the virus (4.9/100 PYFU) compared to those who were treated and achieved SVR (7.8/100 PYFU) (377). They also found that spontaneously clearing the initial HCV infection was associated with spontaneous clearance of reinfection (adjusted odds ratio=7.47, 95% CI=1.9–29.2) (377). Martin et al. carried

out a study among HIV positive MSM and reported that the reinfection rate after spontaneous clearance (4.2/100 PYFU) was lower than reinfection after SVR (9.6/100 PYFU) (499). However, the difference in reinfection rates was not statistically significant (p=0.15) and may have been due to significantly different testing frequency, therefore only providing weak evidence that spontaneously clearing the virus may provide protective immunity in some people (499).

Islam et al. found the rate of reinfection to be higher after spontaneous clearance compared to individuals who achieved SVR however, this could be explained by differences between those who spontaneously cleared HCV and achieved SVR (492). Individuals who spontaneously cleared HCV were younger, with a higher proportion of PWID, HIV co-infection, and problematic alcohol use (492). Currie et al. also explored reinfection after both SVR and SC, however, they only included 17 HIV co-infected individuals (5 achieved SVR and 12 spontaneously cleared the virus) and reported 1 reinfection, so were unable to carry out further analysis (497).

Table 6.2: Summary of studies on HCV reinfection after spontaneous clearance among HIV/HCV co-infected individuals

Reference	Country	HIV co-infected?	Year	Definition of spontaneous clearance	Number who spontaneously cleared HCV	Reinfected n (%)
Currie S et al. (497)	USA	Yes (IDU)*	1997-2007	2 consecutive negative HCV-RNA results: without a history of HCV antiviral treatment	12	0 (0)
Ingiliz P et al. (498)	Germany	Yes (MSM)	2001-2013	1 negative HCV-RNA result: 24 weeks after diagnosis without HCV treatment	302*	48 (16)*
Ingiliz P et al. (377)	Multi-country	Yes (MSM)	2002-2014	2 consecutive negative HCV-RNA results: at least 24 weeks apart	606*	149 (25)*
Islam N et al. (492)	Canada	Yes*	1992-2013	2 consecutive negative HCV-RNA results: at least 28 days apart, after HCV diagnosis without treatment	497	79 (16)
Martin T et al. (499)	UK	Yes (MSM)	2004-2012	2 consecutive negative HCV-RNA results: first at least 24 weeks following infection	31	5 (16)
Peters L et al. (510)	Multi-country	Yes	Not specified	1 negative HCV-RNA result: following an anti-HCV positive result	191	35 (18)
Sacks-Davis R et al. (511)	Multi-country	Yes*	1985-2010	2 consecutive negative HCV-RNA results: at least 28 days apart, after HCV diagnosis without treatment	12	3 (25)

* Sub-study in HIV-positive individual among larger study on both co-infected and mono-infected individuals

6.1.4 Aims

There were 2 main aims for this chapter:

1. To examine the proportion of reinfection in HIV/HCV co-infected individuals in Europe after achieving:
    a. Sustained virological response (SVR)
    b. Spontaneous clearance
2. To assess whether the risk of reinfection after achieving SVR varies depending on HIV risk group, treatment regimen (IFN-based regimens vs IFN-free DAAs), regional differences, or sociodemographic variables

6.1.5 What this analysis adds

In the absence of an effective vaccine against HCV, those who have been cured or spontaneous cleared the virus are still at risk of reinfection. The overall risk is generally low, however, reinfection is of particular concern among HIV co-infected individuals, in particular PWID and MSM (377,403). Most clinical trials do not follow up participants after they achieve SVR, therefore analysis of cohort studies like EuroSIDA is important to explore the issue of reinfection and associated factors after clearance, to better target prevention and retreatment initiatives. The majority of studies exploring reinfection after SVR have been carried out in the pre-DAA era, therefore more research is needed on reinfection in the DAA era. Also, there are contradicting results on whether reinfection is more common after SVR or spontaneous clearance (377,492). This analysis will allow us to explore reinfection in both treatment eras, and also whether reinfection is more likely to occur after spontaneous clearance or SVR.

6.2 Methods

This analysis was carried out using data from the EuroSIDA study's (defined in chapter 2) D46 dataset, which included data on 22797 individuals enrolled in the study before 1/1/2019 from 36 European countries, Israel and Argentina.

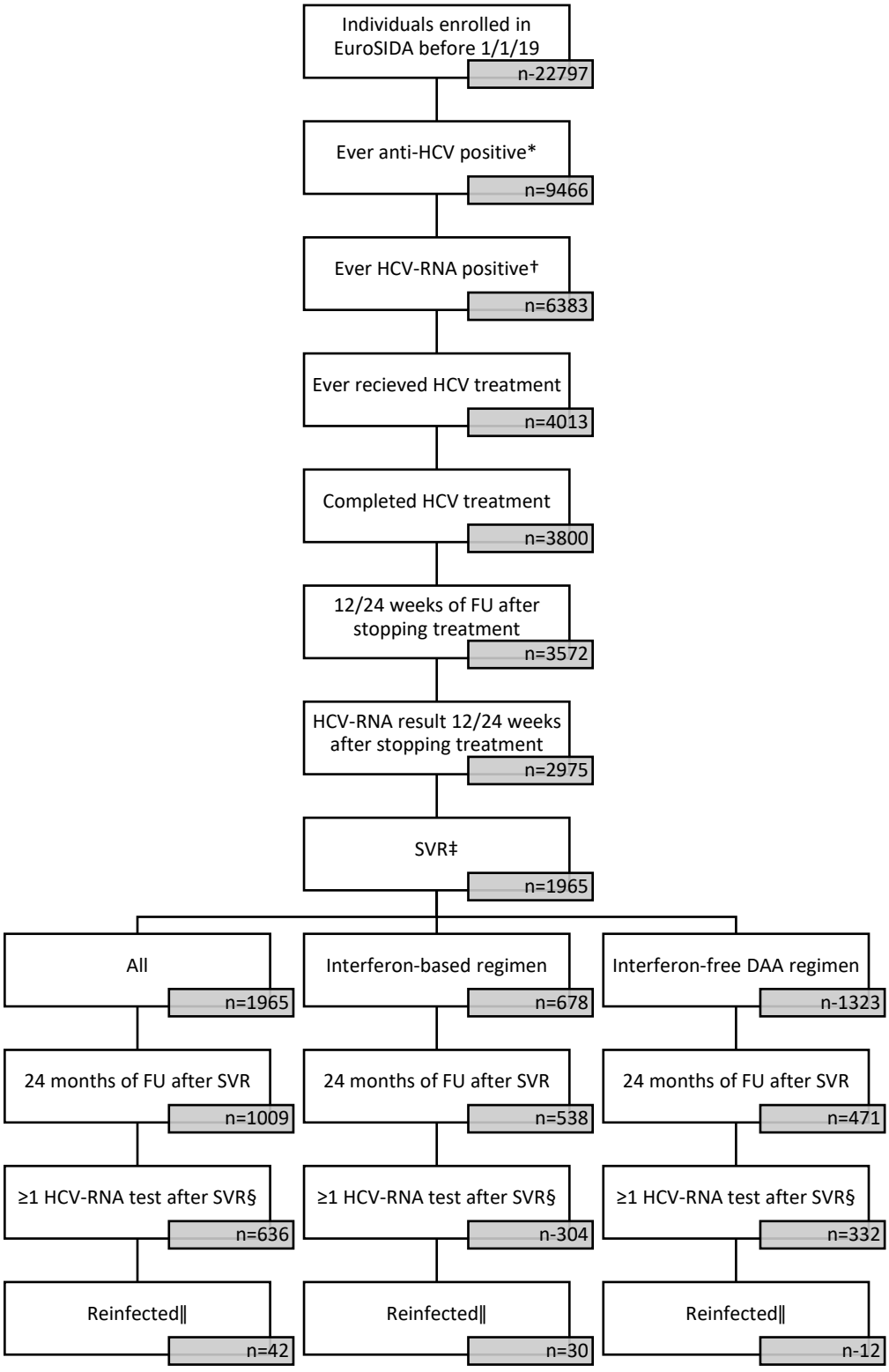
6.2.1 Inclusion criteria

This analysis was carried out in two parts; firstly, reinfection among individuals who received treatment and achieved SVR was described. Secondly, reinfection among those who spontaneously cleared HCV was explored. Below are the inclusion criteria for both analyses:

Reinfection after SVR:

There were 22797 individuals included in the D46 dataset, 9466 of whom were under FU and anti-HCV positive before 1/1/2019 (when the D46 dataset was closed). There were 6838 individuals who were ever HCV-RNA positive, 4013 of whom had ever started HCV treatment, and 3800 that completed treatment. There were 3572 individuals who had sufficient FU after stopping treatment, and 2975 who had an HCV-RNA result to assess SVR. Across both treatment groups, there were 1965 individuals who achieved SVR at least once. There were 1009 individuals who had at least 2 years of FU after achieving SVR, and 636 who had at least 1 HCV-RNA test during that time and were included in this analysis. Baseline was defined as the date of SVR. Figure 6.1 shows a detailed description of how HIV/HCV co-infected individuals were selected for this analysis.

Figure 6.1: Flowchart for inclusion in SVR analysis

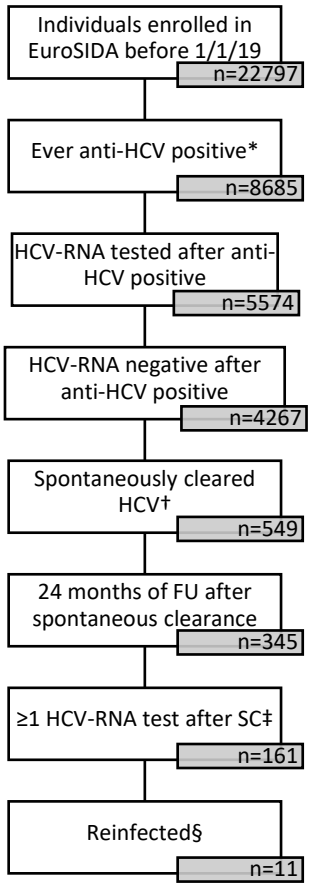


* Anti-HCV positive, HCV-RNA positive, HCV genotyped, or received HCV treated
† HCV-RNA positive, HCV genotyped, or received HCV treated
‡ Negative HCV-RNA result 12 or 24 weeks after treatment end date for IFN-free DAA regimens (SVR12) and IFN-based regimens (SVR24), respectively. Only included those that achieve SVR after ES enrolment date
§ HCV-RNA test or received HCV treated within 24 months of SVR
‖ HCV-RNA positive or received HCV treated within 24 months of achieving SVR

Reinfection after spontaneous clearance:

Among the 22792 individuals enrolled before 1/1/2019, 8685 ever had a positive anti-HCV test result, 549 of whom had spontaneously cleared HCV infection (defined below). There were 345 individuals who had at least 24 months of FU after spontaneous clearance, 161 of which also had at least 1 HCV-RNA test during the 24 months of FU and were included in this analysis. Baseline was defined as the date of spontaneous clearance, which was the second of the two negative HCV-RNA results. A description of how individuals were selected for this analysis can be seen in Figure 6.2.

Figure 6.2: Flowchart for inclusion in spontaneous clearance analysis



* Anti-HCV positive test result

† Two consecutive negative HCV-RNA results 24 weeks apart, after a positive anti-HCV test result and without HCV treatment. Date of spontaneous clearance is the date of second negative HCV-RNA results

‡ HCV-RNA test or received HCV treated within 24 months of spontaneous clearance

§ HCV-RNA positive or received HCV treatment within 24 months of spontaneously clearing HCV

6.2.2 Definitions

SVR

SVR was defined as a negative HCV-RNA result after treatment end date. If the individual received IFN-based regimens then the HCV-RNA result had to be 24 weeks after the end of treatment or later (SVR24), and if the individual received IFN-free DAA regimens then the HCV-RNA result had to be 12 weeks or later (SVR12).

Spontaneous clearance

Spontaneous clearance was defined as two consecutive negative HCV-RNA results at least 24 weeks apart, after a positive anti-HCV test result (as per current EASL guidance) (317). Individuals who were treated before their first anti-HCV positive test were excluded from this analysis, as were individuals who received HCV treatment before the second of the consecutive negative HCV-RNA results.

Reinfection

Reinfection was defined as being HCV-RNA positive or receiving a new HCV treatment regimen within 24 months of SVR or spontaneous clearance. Where individuals had multiple positive HCV-RNA tests or started more than one HCV treatment regimen within two years of SVR or spontaneous clearance, the first test/treatment after clearance was considered to be the date of reinfection.

6.2.3 Variables included in this analysis

The definitions of the different variables included in this analysis have been described below in Table 6.3

Table 6.3: Definition of baseline variables included analysis

Variable	Levels	Definitions and comments
Age (years)	Continuous (per 1 year older) and categorised as ≤45, >45years old	
Sex	Male, female	
Ethnicity	White, Global Majority, unknown	
Region	South (including Argentina and Israel), Central - West, North, Central - East, Eastern Europe	Defined in Chapter 2 Section 2.2
HIV risk group	MSM, PWID, other	Other' includes those with unknown risk group
CD4 count (cells/mm^3)	Continuous and categorised as ≤500, >500 (cells/mm^3), and unknown	Most recent measurement prior to baseline (within one year), if not available then measurement up to 6 months after baseline included
CD4 nadir (cells/mm^3)	Continuous and categorised as ≤50, 50-200, and >200 (cells/mm^3), and unknown	Lowest CD4 count prior to baseline, if not available then measurement up to 6 months after baseline included
HIV-RNA (cp/ml)	≤500, >500, unknown	Most recent measurement prior to baseline (within one year), if not available then measurement up to 6 months after baseline included.
AIDS-defining event	Yes, no	Defined using CDC's 1993 clinical definition (421)
Non-ADI	Yes, no	Non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, end-stage renal disease, pancreatitis (422)
Date of HCV clearance	<2014, ≥2014	
Fibrosis	<F3, ≥F3*	Determined by either a biopsy, FibroScan, APRI, or plasma hyaluronic acid levels measured 1 year prior to baseline
HCV genotype	G1, other, unknown	
Ever received cART	Yes, no	Individual ever received cART (≥3 drugs) treatment prior to baseline
Prior HCV treatment	Yes, no	Individual received any HCV treatment prior to regimen included in analysis

*Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

6.2.4 Statistical analysis

6.2.4.1 Baseline characteristics

As mentioned above, baseline was defined as the date of SVR for those treated, or the second of the consecutive HCV-RNA negative test results for people who spontaneously cleared HCV. Only individuals with 2 years of FU after baseline were included in this analysis. Baseline characteristics of all individuals included in each analysis were described and based on the most recent measurement before baseline. If an individual did not have a CD4 count or HIV-RNA value within 12 months prior to baseline, then a value up to 6 months after baseline was included instead. Numerical variables were described with medians and interquartile ranges, while categorical variables were described with numbers and percentages. Liver fibrosis markers within one year before baseline were included. When individuals had more than one liver fibrosis marker during the year prior to baseline, the most reliable marker was included (biopsy, Fibroscan, APRI score, then finally hyaluronic acid). The consensus definition published by Mauss et al. was used to determine the stage of liver fibrosis (225). Characteristics were compared using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables.

6.2.4.2 Reinfection after SVR and SC

The percentage of individuals who were reinfected after achieving SVR was described. This was then explored by region and by treatment regimen and compared using a chi-squared test. The percentage of individuals who were reinfected after spontaneous clearance was also calculated. However, due to the small numbers, it was not possible to explore the percentage of reinfection by different subgroups.

6.2.4.3 Factors associated with HCV reinfection

Logistic regression was used to determine the adjusted odds of being reinfected with HCV (HCV-RNA positive or received HCV treatment) in the 2 years following SVR among individuals who had sufficient FU. Variables described in Table 6.3 that were significant in univariable analysis ($p<0.1$) were adjusted for in the multivariable model.

SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, North Carolina, USA).

6.3 Results

The results have been split into 2 sections, Section 6.3.1 which explores reinfection after achieving SVR, and Section 6.3.2 which looks at reinfection after spontaneous clearance. Table 6.4 below shows the number of individuals included in each analysis.

Table 6.4: Description of individuals included in each analysis

Section	Analysis	n included
6.3.1 Reinfection after SVR		
6.3.1.1 Study population	Description of individuals eligible Comparison of those included vs excluded	1965 636 vs 1329
6.3.1.2 Baseline characteristics	Comparison between individuals reinfected vs not reinfected	42 vs 594
6.3.1.3 Factors associated with reinfection	Odds of reinfection	42 vs 594
6.3.2 Reinfection after spontaneous clearance		
6.3.2.1 Study population	Description of individuals eligible Comparison of those include vs excluded	549 79 vs 470
6.3.2.2 Baseline characteristics	Comparison between individuals reinfected vs not reinfected	4 vs 75
6.3.3 Sensitivity analysis		
6.3.3.1 Reinfection after SVR analysis	Compared different lengths of FU	1457 vs 1239 vs 1009 vs 512
6.3.3.2 Reinfection after spontaneous clearance analysis	Compared different spontaneous clearance definition	737 vs 592 vs 549

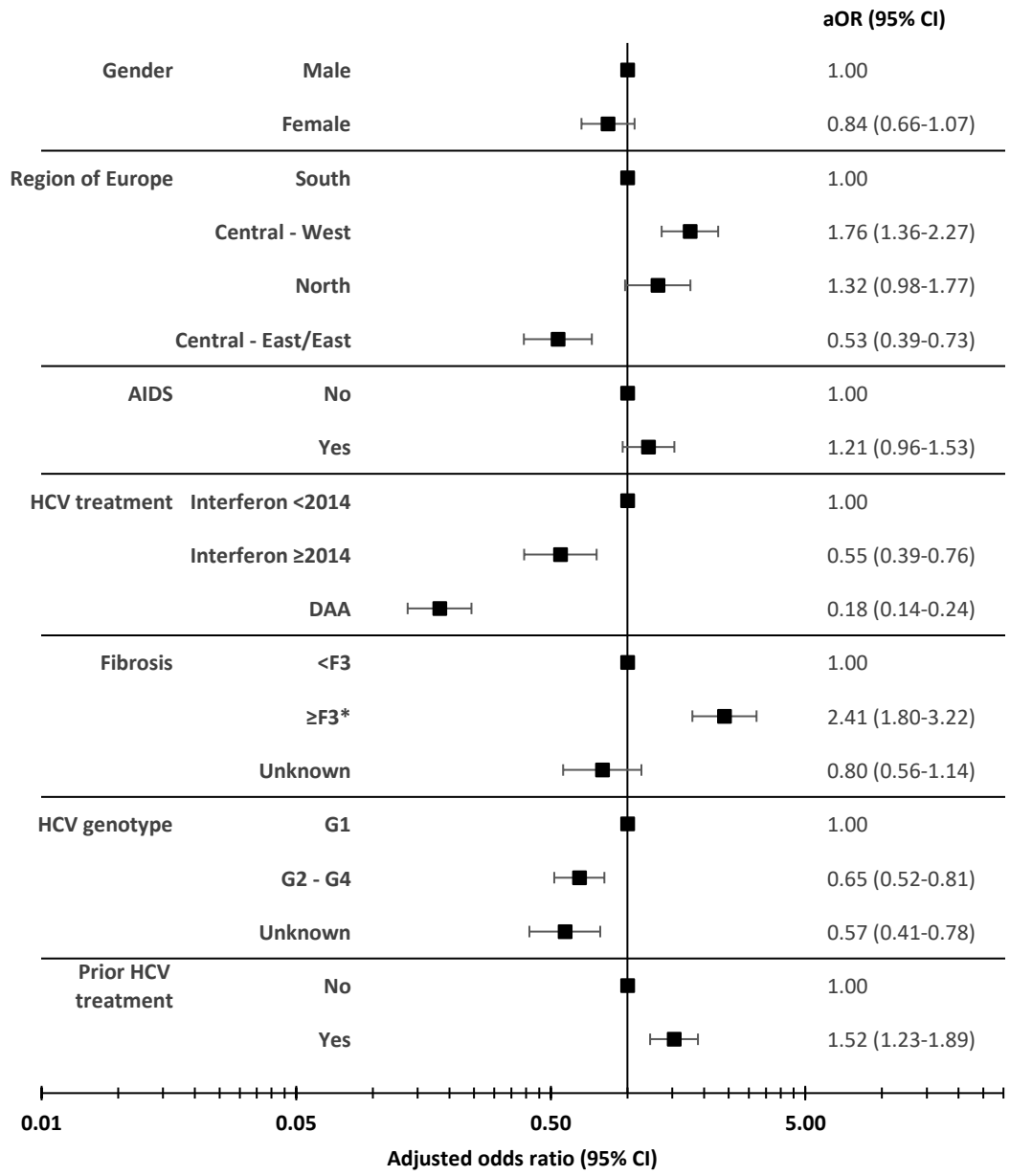
6.3.1 Reinfection after SVR

6.3.1.1 Study population

As described above in Section 6.2.1, there were 1965 individuals who achieved SVR at least once after enrolment into the EuroSIDA study and prior to 1/1/2019, 1009 (51.3%) had 24 months of FU after achieving SVR, and 636 (32.4%) of whom had at least 1 HCV-RNA test during the 24 months of FU and were included in this analysis. There were 1329 individuals who had achieved SVR but were excluded from this analysis for not having sufficient FU and a FU HCV-RNA test after SVR. After adjustment, the odds of being included in this analysis was higher among those from Central Europe [adjusted odds ratio (aOR)=1.76, 95% CI=1.36-2.27], those with fibrosis ≥F3 [aOR=2.41, 95% CI=1.80-3.22], and prior HCV treatment [aOR=1.52, 95%

CI=1.23-1.89] (Figure 6.3). Those from Central-East/Eastern Europe had a lower odds of being included [aOR=0.53, 95% CI=0.39-0.73], as did individuals who started an IFN-based regimen ≥2014 or a DAA regimen [aOR=0.55, 95% CI=0.39-0.76 and aOR=0.18, 95% CI=0.14-0.24, respectively], and those with genotype 2-4 [aOR=0.65, 95% CI=0.52-0.81].

Figure 6.3: Adjusted odds of inclusion in SVR analysis



Model also adjusted for unknown fibrosis and unknown genotype

* Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

6.3.1.2 Proportion of reinfection

As mentioned, individuals were only included if they had 24 months of FU after achieving SVR and at least one HCV-RNA test during FU. Among the 636 individuals included, 42 (6.6%, 95% CI=4.7-8.5) were reinfected within 24 months of achieving SVR. Table 6.5 below shows the number of HCV-RNA tests during 24 months of FU after achieving SVR. Overall, the median number of HCV-RNA tests following SVR was 1 (interquartile range [IQR]: 1-2), however, the number of tests ranged from 0 to 19. There was 1 individual who had 0 HCV-RNA tests after SVR, however, as they started a new HCV treatment regimen within 24 months of achieving SVR, they were considered to be reinfected and included in this analysis. The median number of tests among reinfected individuals (2, IQR: 1-4) was slightly higher than the median number of tests among those not reinfected (1, IQR: 1-2). While a higher proportion of individuals who achieved SVR before 2014 had 4 or more HCV-RNA tests (11.2% vs 5.7%), there was no difference in the median number of tests between those that achieved SVR before or after 2014 (median tests=1, IQR: 1-2 for both groups).

Among the 42 individuals who were reinfected within 2 years of baseline, the median time from SVR to reinfection was 14 months (IQR: 7-20). The individual who did not have a FU HCV-RNA test started a new HCV treatment 3 months after SVR. Those who were treated with an IFN-based regimen were reinfected by a median of 17 months (IQR: 6-21), while those treated with an IFN-free DAA regimen were reinfected by a median of 10 months (IQR: 8-14).

Table 6.5: Number of HCV-RNA tests during 24 months FU after SVR

Number of tests	Overall	Not reinfected (n=594)	Reinfected (n=42)	<2014 (n=178)	≥2014 (n=458)
			n (%)		
0	1 (0.2)		1 (2.4)	1 (0.6)	
1	341 (53.6)	325 (54.7)	16 (38.1)	101 (56.7)	240 (52.4)
2	185 (29.1)	180 (30.3)	5 (11.9)	45 (25.3)	140 (30.6)
3	63 (9.9)	58 (9.8)	5 (11.9)	11 (6.2)	52 (11.4)
≥4	46 (7.2)	31 (5.2)	15 (35.7)	20 (11.2)	26 (5.7)

6.3.1.3 Baseline characteristics of individuals included in analysis

The majority of the 636 individuals included were from Southern Europe (33.6%), followed by Central-West (33.8%), North (19.2%), and Central-East/Eastern Europe (13.4%) (Table 6.6). The median age was 49 years old (IQR: 43-54), and the majority of those included were male (78.1%), and of white ethnicity (86.8%). The most common route of HIV transmission was PWID (50.9%), followed by MSM (25.0%), heterosexual (12.7%), and other or unknown transmission groups (11.3%). The median CD4 cell count was 573 cells/mm^3 (IQR: 412-790), 92.8% of individuals had an HIV viral load below 500 (cp/ml), and 93.7% of individuals were ever on cART. The majority of individuals had a known HCV genotype (n=553, 86.9%), and of those genotyped, genotype 1 was the most common (63.3%). There were 571 (89.8%) individuals who had a liver fibrosis marker result within 1 year of baseline, the majority of whom had fibrosis <F3 (79.3%).

There were significant differences in the proportion of reinfection between baseline characteristics ($p<0.05$). The median age among those reinfected was 47 (IQR: 39-51) years but was higher in individuals not reinfected (49 years, IQR: 43-54). Also, the median CD4 count was lower among individuals who were reinfected (496 cells/mm^3, IQR: 334-709) compared to those not reinfected (582 cells/mm^3, IQR: 425-799). The proportion of reinfection was highest among the MSM risk group (11.9%) and lower among PWID (4.9%), heterosexuals (3.7%), and other risk groups (5.6%). Those who achieved SVR before 2014 had a higher proportion of reinfection (14.0%) compared to individuals who achieved SVR after 2014 (3.7%).

Table 6.6: Baseline characteristics among individuals included, by reinfection status

		Overall	Not reinfected	Reinfected	P-value
			n (%)		
Overall		636 (100.0)	594 (93.4)	42 (6.6)	
Sex	**Male**	497 (78.1)	459 (92.4)	38 (7.6)	0.0521
	Female	139 (21.9)	135 (97.1)	4 (2.9)	
Ethnicity	**White**	552 (86.8)	515 (93.3)	37 (6.7)	0.7742
	Global Majority	14 (2.2)	14 (100.0)		
	Unknown	70 (11.0)	65 (92.9)	5 (7.1)	
Region of Europe	**South**	214 (33.6)	207 (96.7)	7 (3.3)	0.0544
	Central - West	215 (33.8)	195 (90.7)	20 (9.3)	
	North	122 (19.2)	115 (94.3)	7 (5.7)	
	East/Central - East	85 (13.4)	77 (90.6)	8 (9.4)	
HIV risk group	**MSM***	159 (25.0)	140 (88.1)	19 (11.9)	0.0306
	PWID†	324 (50.9)	308 (95.1)	16 (4.9)	
	Heterosexual	81 (12.7)	78 (96.3)	3 (3.7)	
	Other	72 (11.3)	68 (94.4)	4 (5.6)	
HIV-RNA (cp/ml)	**≤500**	590 (92.8)	552 (93.6)	38 (6.4)	0.5960
	>500	31 (4.9)	28 (90.3)	3 (9.7)	
	Unknown	15 (2.4)	14 (93.3)	1 (6.7)	
AIDS	**No**	464 (73.0)	433 (93.3)	31 (6.7)	0.8975
	Yes	172 (27.0)	161 (93.6)	11 (6.4)	
Non-ADI‡	**No**	552 (86.8)	514 (93.1)	38 (6.9)	0.6378
	Yes	84 (13.2)	80 (95.2)	4 (4.8)	
HCV treatment	**Interferon**	304 (47.8)	274 (90.1)	30 (9.9)	0.0015
	DAA	332 (52.2)	320 (96.4)	12 (3.6)	
Year SVR	**<2014**	178 (28.0)	153 (86.0)	25 (14.0)	<.0001
	≥2014	458 (72.0)	441 (96.3)	17 (3.7)	
Fibrosis	**<F3**	453 (71.2)	423 (93.4)	30 (6.6)	0.5574
	≥F3§	118 (18.6)	112 (94.9)	6 (5.1)	
	Unknown	65 (10.2)	59 (90.8)	6 (9.2)	
HCV genotype	**G1**	350 (55.0)	327 (93.4)	23 (6.6)	0.7875
	G2 - G4	203 (31.9)	188 (92.6)	15 (7.4)	
	Unknown	83 (13.1)	79 (95.2)	4 (4.8)	
Ever received cART	**No**	40 (6.3)	38 (95.0)	2 (5.0)	1.0000
	Yes	596 (93.7)	556 (93.3)	40 (6.7)	
Prior HCV treatment	**No**	388 (61.0)	361 (93.0)	27 (7.0)	0.6521
	Yes	248 (39.0)	233 (94.0)	15 (6.0)	
			Median (IQR)		
Age (years)		49 (43-54)	49 (43-54)	47 (39-51)	0.0397
CD4 count (cells/mm^3)		573 (412-790)	582 (425-799)	496 (334-709)	0.0291
CD4 nadir (cells/mm^3)		163 (73-271)	163 (69-271)	165 (106-234)	0.6325

*MSM: Men who have sex with men, †PWID: People who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

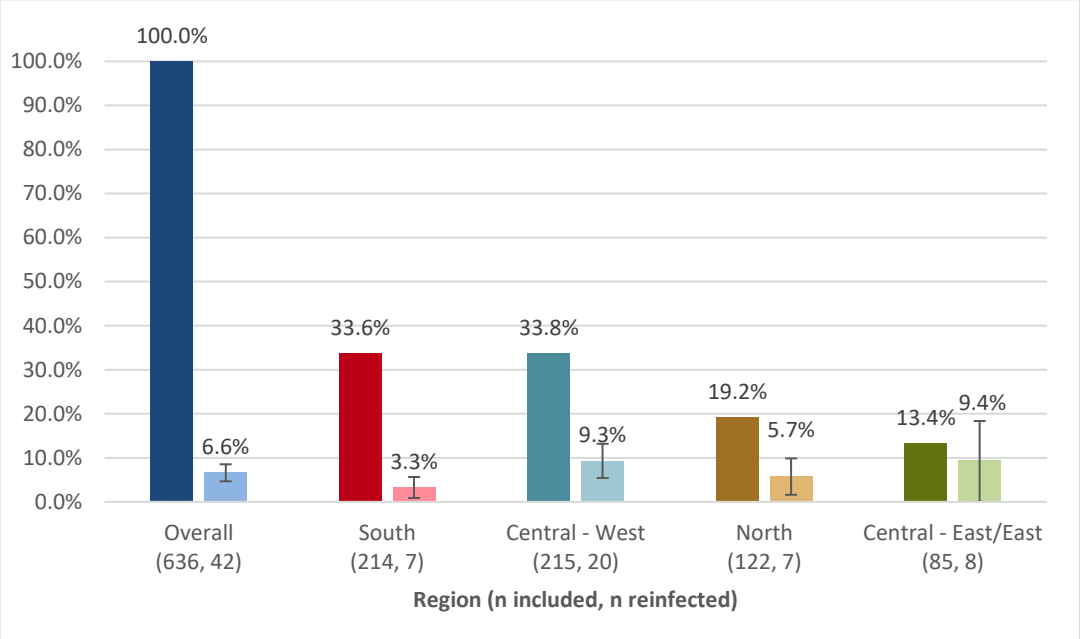
§Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

n with CD4 count = 634, n with CD4 nadir = 639

6.3.1.3.1 Percentage of reinfection by region

There were also differences in the proportion of individuals reinfected within 24 months of achieving SVR between regions (p=0.0544) (Figure 6.4). Central-East/Eastern Europe had the highest proportion of reinfections (9.4%), followed by Central-West (9.3%), and Northern Europe (5.7%), with reinfection lowest in Southern Europe (3.3%).

Figure 6.4: Percentage of individuals reinfected after SVR by region

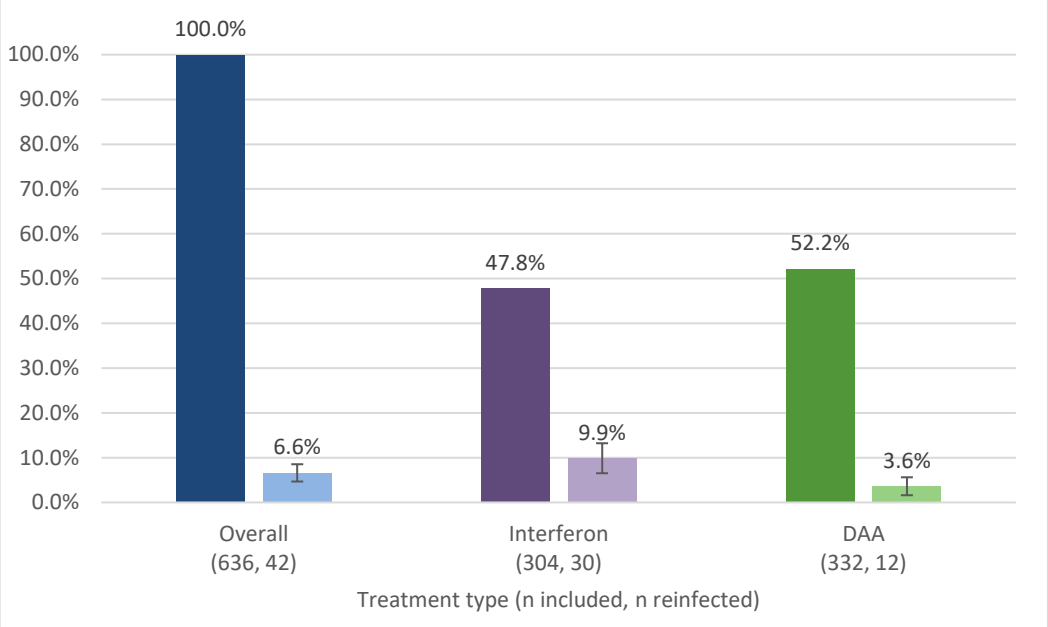


The darker shade bar is the proportion included, while the lighter shade bar is the proportion reinfected within each region

6.3.1.3.2 Proportion of reinfection by treatment

The majority of individuals included in this analysis were treated with an IFN-free DAA regimen (n=332, 52.2%) as opposed to an IFN-based regimen (n=304, 47.8%) (Table 6.6). The proportion of reinfected individuals among those treated with an IFN-based regimen was 9.9%, which was significantly (p=0.0015) higher than the proportion of reinfection among those treated with an interferon-free DAA regimen (3.6%).

Figure 6.5: Proportion of individuals reinfected after SVR by treatment



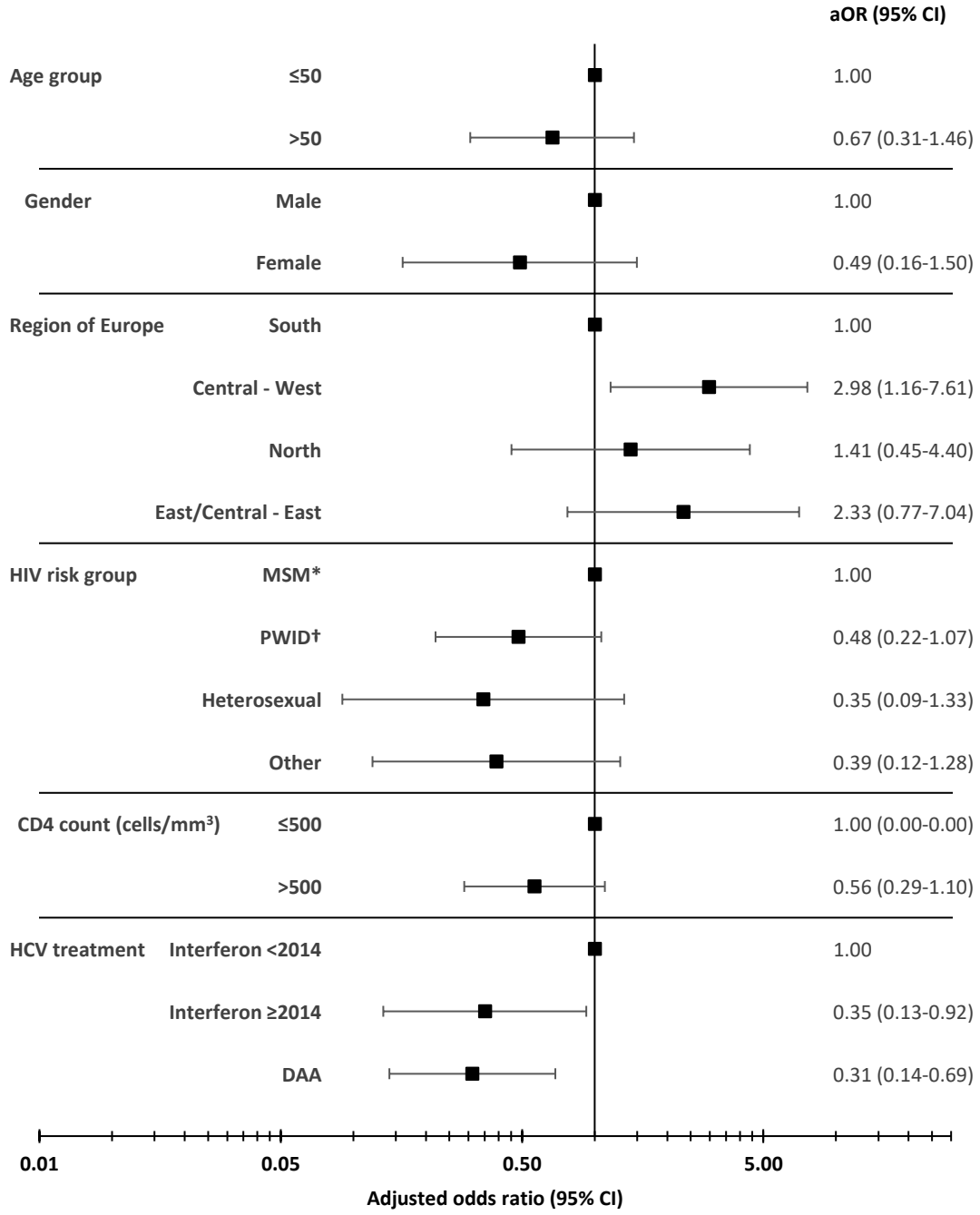
The darker shade bar is the proportion included, while the lighter shade bar is the proportion reinfected within each treatment regimen

6.3.1.4 Factors associated with reinfection

In univariable analysis, individuals >50 years old had a lower odds of reinfection compared to individuals ≤50 [odds ratio (OR)=0.46, 95% CI=0.23-0.91], as did females [OR=0.36, 95% CI=0.13-1.02], PWID and heterosexuals (compared to MSM) [OR=0.38, 95% CI- 0.19-0.77, OR=0.28 and 95% CI=0.08-0.99, respectively], individuals with a CD4 count ≤500 cells/mm^3 [OR=0.55, 95% CI=0.29-1.02], and those who received an IFN-base regimen ≥2014 and IFN-free DAA regimen [OR=0.31, 95% CI=0.12-0.79 and OR=0.24, 95% CI=0.12-0.49, respectively]. Year of SVR and treatment type were highly correlated, therefore the variables were combined (IFN <2014 vs IFN ≥2014 vs DAAs). Individuals from Central-West, and Central-East/Eastern Europe had a higher odds of reinfection compared to individuals from Southern Europe [OR=3.03, 95% CI=1.26-7.33, OR=3.07, 95% CI=1.08-8.76, respectively].

Figure 6.6 shows the results of the adjusted logistic regression model, which identifies characteristics associated with HCV reinfection after SVR. After adjustment, those from Central-West still had a higher odds of reinfection compared to those from Southern Europe [aOR=2.98, 95% CI=1.16-7.61]. Individuals who received an IFN-based regimen after 2014 and those that received an IFN-free DAA regiment had a lower odds of reinfection compared to those who received an IFN-based regimen before 2014 [aOR=0.31, 95% CI=0.12-0.79 and aOR=0.24, 95% CI=0.12-0.49, respectively]. Age, gender, HIV risk group, and CD4 count were not found to significantly impact the odds of reinfection after adjustment, although all had wide confidence intervals.

Figure 6.6: Adjusted odds of reinfection after SVR



Model also adjusted for unknown CD4 count
*MSM: Men who have sex with men, †PWID: People who inject drugs

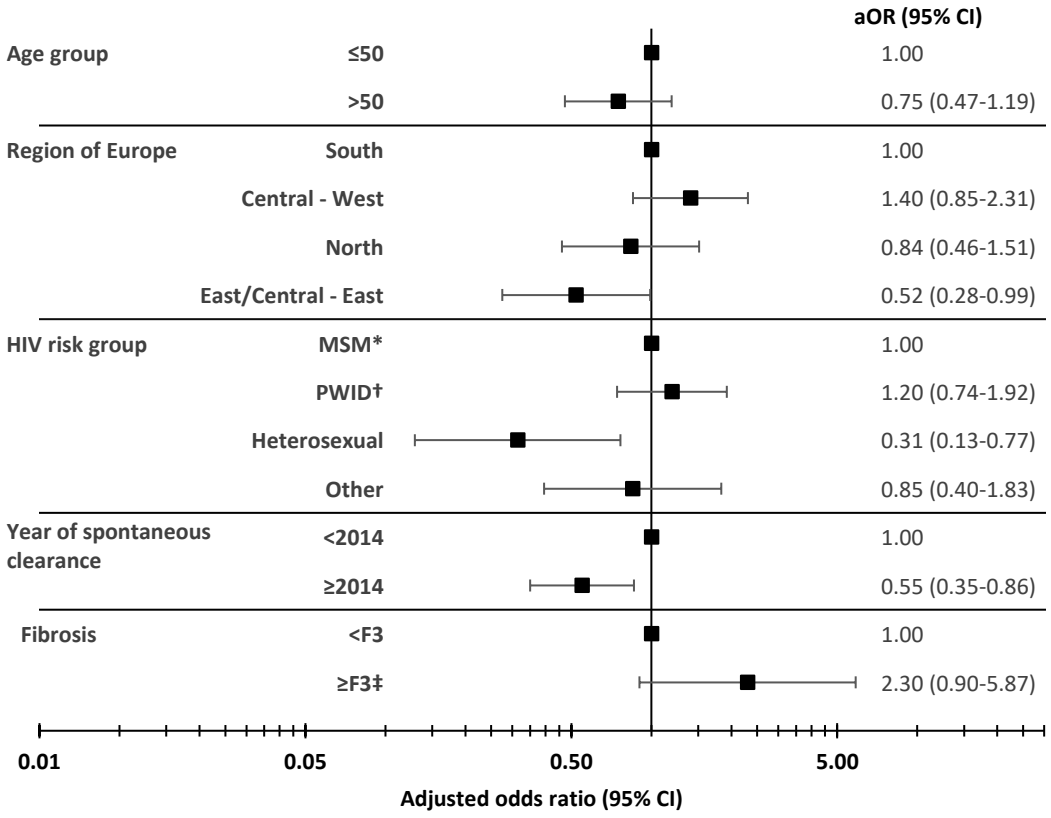
6.3.2 Spontaneous clearance

6.3.2.1 Study population

There were 549 individuals who spontaneously cleared HCV (2 consecutive negative HCV-RNA results 24 weeks apart, without treatment), 345 (62.8%) of whom had 24

months of FU, and 161 (29.3%) who were also HCV-RNA tested during that time and included in this analysis. There were 388 (70.7%) individuals who spontaneously cleared HCV but were excluded from this analysis. After adjustment, individuals included in this analysis had a lower odds of being from East/Central-Eastern Europe [aOR=0.52, 95% CI=0.28-0.99], heterosexual [aOR=0.31, 95% CI=0.13-0.77], or spontaneously clearing HCV after 2014 [aOR=0.55, 95% CI=0.35-0.86], compare to those excluded.

Figure 6.7: Adjusted odds of inclusion in spontaneous clearance analysis



Model also adjusted for unknown CD4 fibrosis
*MSM: Men who have sex with men, †PWID: People who inject drugs
‡Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

6.3.2.2 Proportion of reinfection

Among the 161 individuals included in this analysis, 11 (6.8%, 95% CI=2.9%-10.7%) were reinfected within 24 months of spontaneous clearance, and the median time to

reinfection was 12 months (IQR: 6-19). Overall the median number of HCV-RNA tests after spontaneous clearance was 1 (IQR: 1-2), ranging from 1 test to 8 tests (Table 6.7). Although all individuals had at least 1 HCV-RNA test, one of the reinfected individuals did not have a positive HCV-RNA result. However, this individual received a new HCV treatment regimen 5 months after the negative HCV-RNA results, indicating they had been reinfected even though the positive test result was missing. Among the 11 individuals who were reinfected, the median number of tests was 1 (IQR: 1-7) while the median number of HCV-RNA tests among the 150 individuals who were not reinfected was 1 (IQR: 1-2). The spontaneous clearance definition required individuals to have two consecutive negative HCV-RNA results a minimum of 24 weeks apart, and the median time difference between the two consecutive negative HCV-RNA results was 15 months (IQR: 11-41), ranging from 6 to 110 months.

Table 6.7: Number of HCV-RNA tests during 24 months FU after SC

Number of tests	Overall	Not reinfected	Reinfected
		n (%)	
1	94 (58.4)	91 (60.7)	3 (27.3)
2	52 (32.3)	49 (32.7)	3 (27.3)
3	8 (5.0)	7 (4.7)	1 (9.1)
≥4	7 (4.3)	3 (2.0)	4 (36.4)

6.3.2.3 Baseline characteristics of individuals included in analysis

There were 161 individuals who spontaneous cleared HCV and were included in this analysis. Table 6.8 shows the baseline characteristics of those included. The majority of the study participants were male (70.8%), of white ethnicity (87.6%), and had a median age of 45 years old (IQR: 40-51). The majority of individuals who spontaneously cleared HCV were from Central-Western Europe (41.0%), followed by South (28.0%), North (19.3%), and Central-East/Eastern Europe (11.8%). The median CD4 count was 495 (IQR: 364-720). Only 31.1% of individuals were HCV genotyped, of which 50.0% had genotype 1. The majority of individuals had a liver fibrosis marker (70.8%), of which 91.2% had fibrosis stage <F3.

Due to the small number of individuals who were reinfected, differences in baseline characteristics between individuals who were reinfected and not reinfected were not formally compared. All 11 of the individuals who were reinfected were of white ethnicity, did not have a prior non-ADI, and received cART treatment. Eight individuals were male, 5 were MSM, 5 were PWID and 1 was heterosexual. Five of the reinfected individuals were from Central-Western Europe and 2 were from Southern, Northern Europe, and Central-East/Eastern Europe. The median CD4 count was 473 (IQR: 390-778), which was lower than the median CD4 count among individuals not reinfected (498 cells/mm^3, IQR: 358-720). Seven individuals spontaneously cleared the virus before 2014 and 4 cleared the virus 2014 or later.

Table 6.8: Baseline characteristics among individuals included, by reinfection status

		Overall	Not reinfected	Reinfected
			n (%)	
Overall		161 (100.0)	150 (93.2)	11 (6.8)
Sex	**Male**	114 (70.8)	106 (93.0)	8 (7.0)
	Female	47 (29.2)	44 (93.6)	3 (6.4)
Ethnicity	**White**	141 (87.6)	130 (92.2)	11 (7.8)
	Global Majority	4 (2.5)	4 (100.0)	
	Unknown	16 (9.9)	16 (100.0)	
Region of Europe	**South**	45 (28.0)	43 (95.6)	2 (4.4)
	Central - West	66 (41.0)	61 (92.4)	5 (7.6)
	North	31 (19.3)	29 (93.5)	2 (6.5)
	East/Central - East	19 (11.8)	17 (89.5)	2 (10.5)
HIV risk group	**MSM***	38 (23.6)	33 (86.8)	5 (13.2)
	PWID†	103 (64.0)	98 (95.1)	5 (4.9)
	Heterosexual	7 (4.3)	6 (85.7)	1 (14.3)
	Other	13 (8.1)	13 (100.0)	
HIV-RNA (cp/ml)	**≤500**	134 (83.2)	124 (92.5)	10 (7.5)
	>500	27 (16.8)	26 (96.3)	1 (3.7)
AIDS	**No**	108 (67.1)	102 (94.4)	6 (5.6)
	Yes	53 (32.9)	48 (90.6)	5 (9.4)
Non-ADI‡	**No**	146 (90.7)	135 (92.5)	11 (7.5)
	Yes	15 (9.3)	15 (100.0)	
Year of spontaneous clearance	**<2014**	106 (65.8)	99 (93.4)	7 (6.6)
	≥2014	55 (34.2)	51 (92.7)	4 (7.3)
Fibrosis	**<F3**	104 (64.6)	97 (93.3)	7 (6.7)
	≥F3§	10 (6.2)	8 (80.0)	2 (20.0)
	Unknown	47 (29.2)	45 (95.7)	2 (4.3)
HCV genotype	**G1**	25 (15.5)	20 (80.0)	5 (20.0)
	G2 - G4	25 (15.5)	22 (88.0)	3 (12.0)
	Unknown	111 (68.9)	108 (97.3)	3 (2.7)
Ever received cART	**No**	9 (5.6)	9 (100.0)	
	Yes	152 (94.4)	141 (92.8)	11 (7.2)
			Median (IQR)	
Age (years)		45 (40-51)	45 (40-50)	49 (39-56)
CD4 count (cells/mm³)		495 (364-720)	498 (358-720)	473 (390-778)
CD4 nadir (cells/mm³)		125 (56-245)	121 (53-241)	139 (111-389)

*MSM: Men who have sex with men, †PWID: People who inject drugs

‡Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end-stage liver disease, HCC, end-stage renal disease, pancreatitis

§ Determined by either a biopsy (≥METAVIR stage F3), FibroScan (>9.5kPa), APRI (score >1.5), or hyaluronic acid (>160ng/mL)

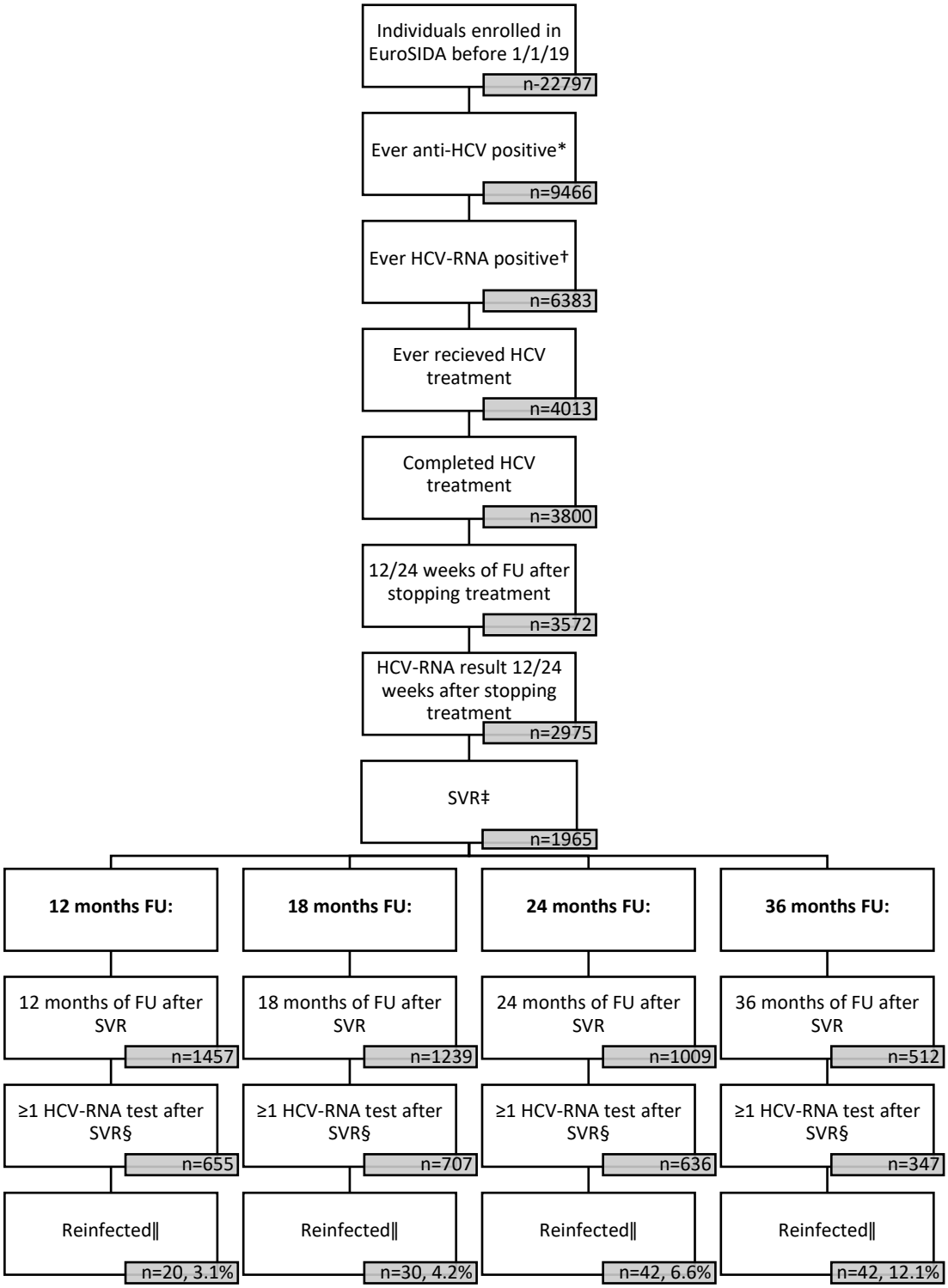
n with CD4 count = 161, n with CD4 nadir = 161

6.3.3 Sensitivity analysis

6.3.3.1 Reinfection after SVR analysis

While 1965 individuals achieved SVR, only 32.4% (n=636) of individuals were included in the analysis as they had 24 months of FU after SVR and had an HCV-RNA test during the 24 months of FU. The impact of the length of FU required for inclusion on the proportion of individuals who achieved SVR was explored (Figure 6.8). The flowchart shows that the shorter the length of FU required, the more individuals included (12 months: n=1457 vs 36 months: n=512). However, the longer the required length of FU, the higher the proportion of individuals with at least 1 HCV-RNA test during FU as 67.8% (n=347/512) of individuals had a FU HCV-RNA test within 36 months of SVR while only 45% of individuals had a FU HCV-RNA test within 12 months of SVR (n=655/1457). Also, the proportion of reinfected individuals was highest when using 36 months of FU (12.1%, 95% CI=8.7-15.5), followed by 24 months (6.6%, 95% CI=4.7-8.5), 18 months (4.2%, 95% CI=2.8-5.7), and 12 months (3.1%, 95% CI=1.7-4.4).

Figure 6.8: Flowchart for inclusion in SVR analysis – by different inclusion criteria



* Anti-HCV positive, HCV-RNA positive, HCV genotyped, or received HCV treated

† HCV-RNA positive, HCV genotyped, or received HCV treated

‡ Negative HCV-RNA result 12 or 24 weeks after treatment end date for IFN-free DAA regimens (SVR12) and IFN-based regimens (SVR24), respectively. Only included those that achieve SVR after ES enrolment date

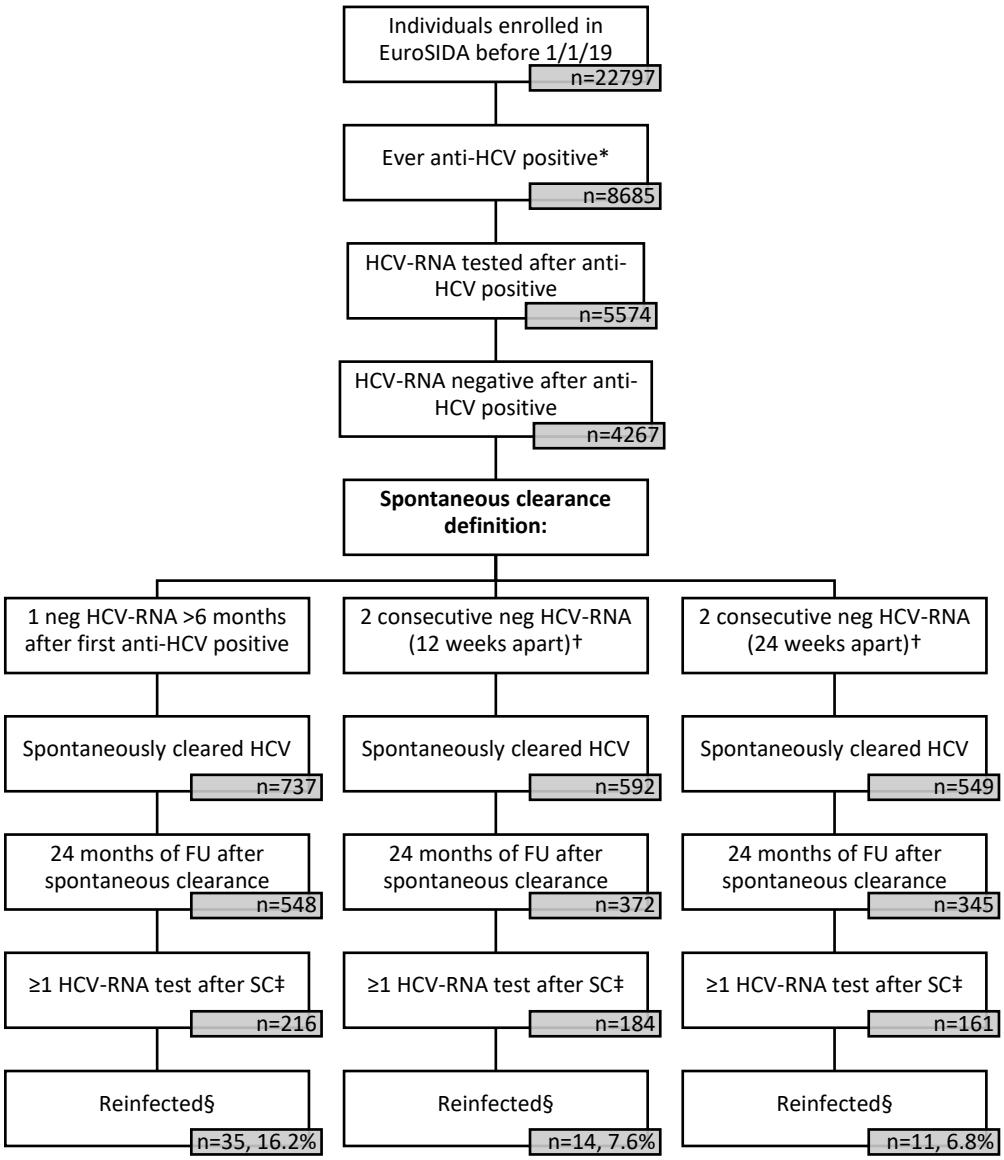
§ HCV-RNA test or received HCV treated

‖ HCV-RNA positive or received HCV treated within 24 months of achieving SVR

6.3.3.2 Reinfection after spontaneous clearance analysis

As previously described in Table 6.2, there are many different ways to define spontaneous clearance of HCV. The definition used in this analysis was two consecutive negative HCV-RNA results at least 24 weeks apart, with no evidence of HCV treatment. However, using different definitions of spontaneous clearance can significantly impact the results (Figure 6.9). The least strict definition explored only required one negative HCV-RNA test result (>6 months after anti-HCV positive) and using this definition a higher number of individuals with sufficient FU would be included (n=216) compared to the stricter definition used (n=161). I also looked at using two consecutive negative HCV-RNA results but only 12 weeks apart instead of 24 weeks apart, and also found a higher number of individuals who spontaneously cleared HCV would be included (n=184). As well as an increased study population, I also found that using a less strict definition of HCV spontaneous clearance such as one negative HCV-RNA test result, or two consecutive negative results 12 weeks apart meant a higher proportion of reinfection (16.2%, 95% CI=11.3-21.1, and 7.6%, 95% CI=3.9-11.4 respectively) compared to the definition used (6.8%, 95% CI=2.9-10.7).

Figure 6.9: Flowchart for inclusion in spontaneous clearance analysis – by difference spontaneous clearance definitions



* Anti-HCV positive test result

† Date of spontaneous clearance is the date of second negative HCV-RNA results

‡ HCV-RNA test or received HCV treated within 24 months of spontaneous clearance

§ HCV-RNA positive or received HCV treatment within 24 months of spontaneously clearing HCV

6.4 Discussion

This chapter describes the risk of reinfection in HIV/HCV co-infected individuals after achieving SVR or spontaneous clearance. Of the 636 HIV/HCV co-infected individuals included in this study who achieved SVR and had at least 24 months of FU after SVR, 6.6% were reinfected within 2 years. There were significant differences in the odds of reinfection based on the region of Europe highlighting the importance of targeted testing and treatment in high-risk regions. Also, the odds of reinfection reduced in the DAA era, contrary to concerns that the introduction of DAAs would increase high-risk behaviour, and in turn, reinfection (487). The proportion of reinfection within 2 years of spontaneous clearance was 6.8%, which is similar to the proportion of individuals reinfected after SVR. However, around 70% of individuals who spontaneously cleared HCV were excluded from this analysis due to insufficient FU.

6.4.1 Reinfection

We found the proportion of individuals reinfected within 24 months of SVR to be 6.6%. These findings are consistent with other studies, such as Rossi et al. who reported a reinfection rate of 6.0% (n=24/403). They found that reinfection was highest among PWID, however they reported that continuous opioid agonist therapy reduced the rate of reinfection (495). Ingiliz et al. also reported a similar proportion of reinfection between 2014 and 2018 among HIV positive individuals after SVR of 7.5% (n=38/509), 95% (n=36) of whom were also MSM (494). While the findings presented in this chapter are similar to these studies, they were carried out among individuals treated with IFN-free DAAs, whereas this analysis included individuals treated with any HCV regimen. Only considering individuals treated with IFN-free DAAs (n=332) in this analysis, the proportion of reinfected individuals is 3.6%. Young et al. included individuals treated with IFN-based and IFN-free treatments and found 6.5% (n=18/257) of individuals were reinfected. As can be seen in Table 6.1, the proportion of HIV co-infected individuals reinfected with HCV after SVR ranged from

0.7%-41%. Therefore, while the findings presented in this chapter are not dissimilar from a number of previously published studies, differences in populations, follow-up time, and definitions make comparisons challenging. This highlights the need for a standardised methodology for analysing the prevalence of HCV reinfection.

Since this analysis was carried out, Chkhartishvili et al. presented data on reinfection after SVR from Georgia between 2015-2017 (512). They included data on 274 individuals who achieved SVR and were tested for reinfection and found that 12 (4.4%) were reinfected by a median of 1.5 (IQR: 0.9-2.2) years (512). There were 85 individuals included from Central-East/Eastern Europe, 9 (9.4%) of whom were reinfected within 2 years of SVR.

The proportion of individuals reinfected after spontaneous clearance was 6.8%. Reinfection after spontaneous clearance has previously been described in the EuroSIDA study by Peters et al., who reported that 18.3% of individuals were reinfected (510). However, the methodology and definitions used in the previous EuroSIDA analysis were different from those used in this analysis, which is the main reason for this difference. For example, the earlier study defined spontaneous clearance as a negative HCV-RNA result after being anti-HCV positive, whereas spontaneous clearance was defined as 2 consecutive negative HCV-RNA results at least 24 weeks apart in this analysis. Had a broader definition of spontaneous clearance been used, which was similar to the definition used by Peters et al., a larger number of individuals would be included in this analysis, and the proportion of reinfected individuals would be 16.2% (Figure 6.9), which is not dissimilar to the results reported by Peters et al..

The proportion of reinfection after SVR (6.6%) was very similar to the proportion of reinfection after spontaneous clearance (6.8%). Martin et al. and Ingliz et al. also included individuals who achieved SVR and spontaneously cleared HCV, they compare both HCV clearance groups and found that the reinfection rate was lower among individuals who spontaneously clearer HCV compared to individuals who achieved SVR (377,499). However, this contradicts with Islam et al., who reported reinfection after spontaneous clearance to be higher than reinfection after achieving SVR (492). However, their finding may be due to differences in the characteristics or testing frequency between individuals who were treated and spontaneously cleared HCV (492).

6.4.2 Factors associated with reinfection after SVR

After adjustment, the odds of reinfection was lower among those that received DAAs or IFN-based regimens after 2014 (compared to individuals who received an IFN-based regimen before 2014), which is in contrast to fears that reinfection would increase in the DAA era due to increased high-risk behaviours. The reduction in reinfection could be due to a lower prevalence of HCV in the population since the increased uptake of DAA treatment in 2014 (368). A recently published report by Doyle et al. explored the impact of curing HCV in HIV positive gay and bisexual men on the prevalence of HCV (513). They found that the incidence and prevalence of HCV drastically decreased with treatment scale-up (513). These findings highlight the effectiveness of treatment as prevention in the HCV setting, which the findings presented in this chapter also support. Hosseini-Hooshyar et al. recently explored HCV reinfection among HIV positive individuals in Australia after unrestricted access to DAA therapy and also reported lower rates of HCV reinfection (514). They also did not find any increase in the levels of high risk injecting or sexual behaviour since the introduction of DAA therapy (514). Ingiliz et al. reported a similar reinfection rate in both the interferon era and DAA era (494). Marco et al. carried out an analysis among incarcerated individuals during the IFN and DAA era and found that

reinfection in the DAA era was much higher (491). However, there were significant differences between the studies, as the analysis in the IFN-era had a much smaller sample size and a much shorter FU time (491). Also, the proportion of reinfection was highest in East/Central-Eastern Europe (9.4%), followed by Central-West (9.3%), North (5.7%), and Southern Europe (3.3%). However, after adjustment only Central-Western Europe had a significantly higher odds of reinfection compared to Southern Europe.

In univariable analysis, the proportion of reinfection after SVR was highest among MSM, which has been reflected in other studies (494,496). This finding is mainly explained by the varying sexual and drug-related risk behaviours among this population (515). Also, several studies have explored HCV infection among HIV negative MSM using pre-exposure prophylaxis (PrEP) and found the prevalence of HCV to be similar among both HIV negative and HIV positive MSM (516–518). The strains of HCV circulating in the HIV negative and HIV positive MSM populations were also found to be similar, indicating sexual transmission of HCV is occurring between both groups (516–518). The HCV epidemic is expanding to HIV negative MSM on PReP, therefore, HCV surveillance and interventions should not be restricted to only HIV positive MSM. After adjustment, there was still a trend of higher reinfection among MSM but the finding was not statistically significant. However, as this is real-world data the testing frequency is not standardised. EASL recommend testing PLWH with ongoing risk behaviours for HCV reinfection after SVR or spontaneous clearance at 3 to 6-month intervals (4 to 8 test over 24 months) (317). However, only 5.2% of non-reinfected individuals who achieved SVR had ≥4 HCV-RNA tests during months of FU, while 35.7% of those reinfected had ≥4 tests. Therefore, some of the associations (or lack of associations) with risk factors and reinfection may be due to increased (or decreased) HCV testing among certain groups.

6.4.3 Strengths and limitations

This analysis had several limitations. Firstly, it was not possible to determine whether all individuals who completed treatment achieved SVR due to missing HCV-RNA data, which could be due to insufficient FU time, individuals being LTFU, or not adequately followed-up after HCV treatment. Also, missing FU HCV-RNA data after achieving SVR or spontaneous clearance meant it was not possible to assess reinfection in all individuals. The EuroSIDA Study did not collect data on HCV risk behaviours and so I was unable to assess their impact on HCV reinfection, which would also have been useful as this has been shown to impact the odds of HCV reinfection in other studies (278). I was also unable to assess the impact of harm reduction services on reinfection due to the lack of validated data on opioid substitution therapy and needle exchange programs. The majority of study participants were also of white ethnicity which meant it was not possible to explore differences in reinfection based on ethnicity. Phylogenetic analysis to check for HCV reoccurrence was not carried out, and it was assumed that all re-emergence of HCV was due to reinfection. It is possible that some late relapses could have been misclassified as reinfection, though this is unlikely as >95% of late relapse occurs within 12 weeks of treatment end date (519). Also, some clinics may have targeted HCV-RNA testing to those at the highest risk of reinfection, or with signs of reinfection. Finally, the EuroSIDA study may not be representative of the HIV/HCV co-infected population, and the frequency of HCV testing may not accurately reflect the testing carried out during routine care (520).

This analysis also had several strengths, mainly that we were able to include a large number of individuals from across Europe that cleared HCV, including a large number of individuals from Eastern Europe where HCV reinfection among PLWH has not previously been described (at the time of this analysis). Since this analysis, a poster presented at the Conference on Retroviruses and Opportunistic Infections described reinfection in Georgia (512). They found that among 420 HIV/HCV co-infected

individuals, 12 (4.4%) were reinfected by a median of 1.5 years (IQR: 0.9-2.2). Only individuals who had at least 2 years of FU to explore reinfection were included. This was because the longer individuals are followed for, the higher the chance of finding reinfection, therefore only including individuals with sufficient FU reduced the potential risk of bias (those followed for longer would have a higher proportion of reinfection). Also, including individuals with insufficient FU after HCV clearance would lead to an underestimation of the proportion of individuals who were reinfected. Also, only individuals with at least 1 HCV-RNA tested during FU were included, however as mentioned above, the difference in testing frequency between different risk groups could still bias the results.

6.5 Dissemination of results

Some of the findings from this chapter were presented as a poster at the 5th International HIV/Viral Hepatitis Co-Infection Meeting (Appendix IX), and as an oral at the International AIDS Society Conference in 2019 (Appendix X). A manuscript is in preparation.

Chapter 7 Discussion

Since the start of this thesis, there have been several changes to the HIV epidemic. According to UNAIDS, there were 36.7 million people living with HIV in 2017, but by 2020 the estimated prevalence had increased to 38 million (3,521). In 2019, 1.7 million individuals were newly infected with HIV, which is a decrease from 2016 when 1.8 million individuals were newly infected (3,521). The Fast-Track Targets were agreed upon in 2016 by the UN General Assembly (see Chapter 1 Section 1.1.1) and aimed to reduce the number of deaths and new infections to less than 500000 by 2020 (13). Unfortunately, these targets were not met, however, there was a substantial increase in the number of people accessing antiretroviral therapy, from 20.9 million in 2016 to 26 million by the end of 2020 (3,521). There have also been improvements to the HIV treatment landscape since the start of this thesis. The most notable improvement is the approval of the long-acting drug cabotegravir in 2020, which is structurally closest to the integrase inhibitor dolutegravir (522). This simplified HIV regimen may be preferred to standard daily oral HIV therapy by PLWH, and potentially also increase treatment adherence (522).

To my knowledge, since the 2017 WHO Global Hepatitis Report, the estimate on the global prevalence of HCV has not been updated (227). As mentioned throughout this thesis, in 2016 the WHO adopted the Global Health Sector Strategy plan to eliminate HCV by 2030 which requires a 90% reduction in HCV incidence and a 65% reduction in HCV-related mortality compared to the 2015 baseline (227,231). This strategy has since been adopted by several national hepatitis elimination plans. In 2019 Razavi et al. explored whether 45 high-income countries were on track to achieve elimination by 2030 (523). They found that 80% of countries were not on track to achieve the WHO targets by 2030, and 67% of countries were off by 20 years (523). However, Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland and the United Kingdom were projected to meet the elimination targets by 2030 (523).

Each results chapter in this thesis provides useful information to help monitor progress towards the WHO goals and highlights areas that need work to achieve elimination by 2030. A summary of the results of each analysis presented in this thesis can be found in the discussion section of each results chapter (Chapter 3-6). Below is a discussion of the limitations, clinical implications of these results, suggestions for further research, and concluding remarks.

7.1 Limitations

Specific limitations relating to each of the four analyses can be found in the discussion section of each results chapter. The general limitations that apply to multiple chapters have been discussed below.

7.1.1 Observational studies

I carried out all the analysis in this thesis using data from the EuroSIDA observational cohort study. EuroSIDA has limited exclusion criteria, which varies depending on the cohort. For example, for Cohort XI which started enrolled in 2019, the only individuals excluded are individuals under 18 years old and individuals who started an integrase inhibitor before 2012. This means a broad spectrum of individuals are included in the study regardless of gender, ethnicity, or risk factor. Data was originally collected every 6 months, however due to PLWH having less frequent clinic visits this was adapted, and data is collected annually since 2017. Also, the enrolment of new cohorts into the study occurs in recruitment waves to ensure participants are not excluded due to irregular FU. Observational cohort studies such as EuroSIDA have many benefits for carrying out clinical research, such as having a large, heterogeneous study population with long FU. They are also very useful for exploring a wide range of disease outcomes.

However, observational cohort studies have several potential biases due to the nature of the study design. The term bias is used in epidemiological studies to describe non-random errors, also known as systematic errors. There are many different types of bias, but they can generally be categorised as selection bias or information bias. Selection bias occurs when there are systematic differences between individuals who took part in the study and those eligible that did not partake in a study or dropped out. As individuals have to be measured over a long period of time, it is possible to lose contact with patients. Those who are lost-to-follow-up (LTFU) may have poorer outcomes than those that are not disengaged from care, which causes attrition bias. This can lead to an over/underestimation of the effect estimates, as those with less favourable outcomes are not included in the analysis. The incidence of LTFU in the EuroSIDA study is generally low, and was estimated to be 3.72 per 100 PYFU in a paper published by Mocroft et al., however they reported considerable differences between countries (393).

Information bias mainly occurs when data is incorrectly recorded. These errors can be due to the patient, the person recording the information, or even the medical instrument or questionnaire used to take the measurements. If the errors occur at random, then this type of information bias is known as non-differential bias. This is more of a problem when the study results show no association as this bias can reduce the true association between an exposure and outcome. Differential bias occurs when the study participants supply different information based on the exposure or outcome. For example, individuals who have the outcome of interest may be more likely to recall risky behaviours, this is also known as recall bias.

Any of these biases may occur when analysing cohort data, therefore it is important to address them using statistical methods or recognise the bias and acknowledge the limitations the results may have.

7.1.2 Unmeasured confounding

In randomised controlled trials (RTC), the issue of confounding is alleviated as individuals are allocated to a treatment regimen or intervention at random. This means that the patient characteristics in different arms are balanced, therefore by design confounding can be controlled for. Different multivariable statistical techniques, which have been used throughout my thesis, can be used to adjust for measured confounding. However, if the confounder is unmeasured or unknown it is not possible to adjust for the potential bias. Although a large range of variables are routinely collected in the EuroSIDA study, problems around unmeasured or unknown confounding are unavoidable with cohort studies. Also, residual confounding can occur due to measurement errors and inaccuracies, which can bias the effect estimates. Therefore, there is no guarantee that the estimates presented in this thesis have not been biased by these limitations.

While an RCT could overcome the issues of unmeasured and residual confounding, it would not be suitable for any of the analyses presented in this thesis. For example, Chapter 6 looks at the risk of reinfection after treatment with IFN-free or IFN-based regimens. It is possible to randomise individuals to receive an IFN-based or IFN-free treatment regimen and FU them for 2 years to determine the proportion of reinfection. However, it would be unethical to randomise individuals to an IFN-based regimen which is known to be much less effective and have worse side effects than an IFN-free treatment regimen. Also, Chapter 5 describes the proportion of individuals who achieve SVR after treatment with an IFN-free DAA regimen. While this could be explored in an RTC (and has been), the purpose of this chapter was to explore whether the results found in RTCs could be reflected in real-world data. This can be said of all chapters, as I was interested in clinical outcomes in a real-world clinical setting. Therefore, while RTC are the gold-standard study design for evidence-

based medicine, a cohort study design provides the best quality evidence for the aims of this thesis.

7.1.3 Generalisability

The EuroSIDA study collects data from all over Europe which helps improve the representativeness of the data and is one of the major strengths of the study. However, there are some limitations regarding the generalisability of the data. Individuals who attend EuroSIDA clinics may differ from individuals who attend non-EuroSIDA clinics. Centres that contribute data to EuroSIDA are generally university affiliated with larger facilities in major cities, which provide an above-average standard of care. Therefore, data collected from centres like this may not be representative of the country, region, or populations with barriers to engagement with health services. Also, data from each centre are grouped into regions, however there may be significant inter-regional differences in the care provided. This makes it difficult to generalise findings to a specific region as it may only reflect individuals within a specific country or centre. Therefore, the differences in the people included in the EuroSIDA study could lead to bias, as individuals selected to participate in the study are not representative of the wider population.

Also, there are countries outside of Europe with a high prevalence of HIV/HCV co-infection. Therefore, while the questions addressed in this thesis are relevant outside of Europe, the findings of this thesis may not be generalizable to other regions as the distribution of the HCV epidemic globally is heterogeneous.

7.1.4 Missing data and data availability

The EuroSIDA study was originally set up and designed to explore HIV, however EuroSIDA has been able to adapt and evolve over the years to meet the current research agenda. Therefore, when HCV co-infection and liver-related death was found to be of increased risk among PLWH, EuroSIDA began collecting data on this. They were able to explore HCV prevalence among those with laboratory data in the plasma repository, however, not all individuals enrolled had lab data stored there. Therefore, historic data on HCV is missing among many individuals. There are several processes adopted by EuroSIDA to reduce the amount of missing data, which have been described in the Methods Chapter (Section 2.2.4) however, recent data is also sometimes missing. Also, due to the differences in resources, equipment and care across the EuroSIDA centres (520), some information cannot be collected at all clinics.

In each analysis presented in this thesis, there have been missing data for key variables such as HCV-RNA and liver fibrosis stage. While there are many ways to address missing data, the ideal scenario is having a complete dataset. In the analyses presented in this thesis, missing data was mainly dealt with by only carrying out complete case analysis, including a missing or unknown category, or using the last value carried forward. If data are missing at random (MAR), meaning the missing data is not related to the outcome, then missing data in predictor variables do not create bias. However, if the MAR assumption cannot be made, then these methods can introduce bias in the results.

The EuroSIDA Study collects large amounts of detailed clinical information, however, there was still a lack of data on a number of important variables. Up to date information on alcohol consumption would have been very useful for my analysis exploring factors associated with advanced fibrosis, as it is known to impact liver

fibrosis. While the EuroSIDA study does collect information on alcohol use, the data is poor quality and not usable. The inadequate information on injection drug use was also a limitation of a number of my analyses. Having up to date information on injection drug habits and access to harm reduction services would have allowed me to better explore the outcomes of PWID. Also, the impact of social and structural determinants of health on clinical outcomes are widely known, however there was no data in the EuroSIDA study to explore this.

7.1.5 Data quality

As with any cohort of this size, there may be data errors due to data entry mistakes or issues with the data management process. This can lead to non-differential or differential information bias depending on whether the errors are random or systematic, respectively. To help combat this, the EuroSIDA coordinating centre conducts quality control checks to ensure the accuracy of the data provided (described in Chapter 2 Section 2.2.4). The statistical centre also carries out data checks once the data has been finalised. There have been changes in the type of data collected by EuroSIDA over the years, most notably, the decisions to solely enrol HCV co-infected individuals in Cohort X. This meant the collection of HCV related variables that had not been previously included, and restructuring of the follow-up forms was required to ensure the integration of HIV and HCV data collection.

7.2 Clinical implications and further research

Despite the limitations mentioned above, there are a number of important implications from my research. In Chapter 3, I described the regional differences in advanced fibrosis over time, including data from regions not previously well described. Overall, 32.1% of individuals had advanced fibrosis between 2010 and

2018, however 67.9% of HCV-RNA positive individuals included in this analysis had never received HCV therapy. This analysis also described risk factors that increase the odds of having advanced fibrosis, to highlight where interventions need to be targeted to reduce the burden of advanced fibrosis. Having a CD4 count >500 cells/mm^3 increased the odds of advanced fibrosis, indicating the importance of also ensuring co-infected individuals engage with HIV care and treatment. The odds of having advanced fibrosis increased with age, and there was also evidence of PWID having a higher odds of advanced fibrosis. This highlights the need for targeted screening and treatment of HCV among older individuals and PWID. Treatment with DAAs was associated with a reduced odds of advanced fibrosis, stressing the importance of DAA uptake to reduce to burden of liver-related complications. There were also regional differences in the change in the burden of fibrosis over time. While the odds of having fibrosis ≥F3 decreased over time in Southern and Central-Western Europe, it increased in Eastern Europe. All individuals with chronic HCV should have access to DAA therapy regardless of their fibrosis stage or HIV status. However as mentioned previously, some countries still have restrictions on DAA access (366). Therefore, these results show the importance of starting ART and engaging with HIV care to ensure HIV virological suppression while waiting for HCV treatment, which can reduce the risk of developing advanced fibrosis. It would be useful to repeat this analysis when more FU data is available to monitor the changing epidemic in different regions, hopefully showing a downward trend in advanced fibrosis in Eastern Europe as DAA treatment uptake increases.

In Chapter 4 I described a new methodology to express the HCV CoC which could be applied to other HIV/HCV cohorts to help standardise reporting of the CoC. The methodology I developed has already been applied to two different cohort studies and presented at international conferences (Austrian cohort presented at CROI (447) and ICONA cohort presented at the International Liver Congress(524)). I applied the methodology to two separate time-points, which highlighted the improvement in the

transition of individuals through care over time. It would be interesting to see how individuals progress through the COC in the future, which can be explored using updated EuroSIDA data that includes further follow-up. Hopefully, as we move further away from IFN-based regimens and towards better access to DAA treatment for all, the CoC continues to improve, with an increase in screening, treatment, and cure, and higher and quick rates of transition through stages.

One of the largest gaps in the cross-sectional CoC was between being diagnosed as HCV-RNA positive and starting HCV treatment, which was seen at both time points. While HCV treatment guidelines recommend the immediate treatment of all individuals (506), this is not always possible in all settings. The cost of treatment is one of the main factors limiting widespread access to DAAs, however, even though the cost of DAAs are is still very high, they have been shown to be highly cost-effective (418,525). The cost of DAAs have decreased as newer DAAs have entered the market, and also due to the high efficacy and availability of generics (526). Regardless, some European countries still do not provide widespread access to DAA treatment to all HCV positive individuals (366). Hopefully, this analysis can be used to encourage policymakers to ensure guidelines around HCV treatment are followed, by taking steps to remove barriers to care and ensuring engagement and retention in care among marginalised populations. Also, further research into why certain individuals are not referred for treatment, or why individuals are not engaging when referred for treatment is needed. This could be explored using mixed methods, including interviews with clinicians and patients. The findings could then be used to plan appropriate interventions to improve access to care. Also, future research on the cost-effectiveness of early treatment of HCV in all settings is vital as many health systems are attempting to reduce costs.

Since the methodology to explore the HCV CoC was developed, Safreed-Harmon et al. published the Consensus Hepatitis C Cascade of Care to a standardised reporting and monitoring of progress towards HCV elimination targets (446). The first stage they included was the prevalence of HCV in the population, followed by the proportion that has been diagnosed (446). The proportion of individuals diagnosed with HCV is still very low globally. In 2016, the diagnosed population ranged from 10% in low-income countries to 40% in high-income countries (228). Also, analysis of 7 HCV elimination initiatives in HIV positive gay and bisexual men and/or PWID carried out in 2018 (n=4894) reported that approximately 50% of patients remained untreated (527). For the impact of these new effective HCV treatments to be felt, diagnostic services need to drastically improve as HCV infection is extremely underdiagnosed. Following the method proposed by Safreed-Harmon et al. would allow us to explore the undiagnosed population, and target interventions to improve diagnostic services. There is currently ongoing research at CHIP to further develop the cross-sectional CoC described here to estimate the undiagnosed population in EuroSIDA. However, based on the results from the cross-sectional CoC presented in this thesis, there have already been improvements in HCV testing from 2015 to 2017. Overall, there was a 5% increase in HCV-RNA testing across regions (from 83% in 2015 to 88% in 2017), however this varied between regions as there was a 10% increase (from 53% in 2015 to 63% in 2017) in Eastern Europe. While the improvement in testing is promising, in 2017 only 63% of HCV positive individuals in East Europe had a HCV-RNA test which is still very low. Also, while the cost of testing remains high, under-diagnosis of HCV will continue to be a barrier to HCV elimination. Improvements in diagnostic testing, such as the development and widespread use of an affordable one-step test that could be carried out at the point of care, would make it easier to identify individuals in need of HCV treatment.

I also developed a methodology to explore the longitudinal HCV CoC, which was based on applications in the HIV CoC (385). This method overcomes the limitations

of the cross-sectional CoC and allows us to consider death and LTFU. This method differed from the previous cross-sectional analysis as it allowed us to follow the same individuals from enrolment into EuroSIDA for 2 years and visualise how they progressed through care. While the cross-sectional and longitudinal CoC are not directly comparable, the results of the longitudinal CoC can complement the cross-sectional results and provide further information on how individuals transition through care. There were significant regional differences in the longitudinal CoC which is consistent with the findings from the cross-sectional CoC. Over 15% of PMFU was spent with an unknown HCV-RNA status over 2 years of FU, however, similar to the cross-sectional CoC results, HCV-RNA testing varied by region. Less than 7% of PMFU was spent with an unknown HCV-RNA status in South, Central-West, and Northern Europe, however this increased to 27% in Central-Eastern Europe, and 38% in Eastern Europe. Also, access to DAAs was lower in Central-East and Eastern Europe, and the increase in DAA uptake was also slower, highlighting disparities in HCV diagnosis and DAA access in Europe, and the need for immediate targeted action to increase HCV testing and DAA therapy in Eastern Europe if the 2030 elimination targets are to be met.

This is a useful tool that provides insight into how individuals transition through care over time and has not yet been utilised in the HCV context. Understanding the time individuals spend in each stage of the continuum, and where they are lost is crucial when planning where interventions should be targeted. This was the first time the methodology devised by Jose et al. has been applied to the HCV landscape (385). This longitudinal approach can be applied to other HCV cohorts in conjunction with the cross-sectional method, as it can overcome some of the limitations of the traditional CoC approach. There are also extensions to this method, as proposed by Lesko et al., which would allow us to adjust for important variables using inverse probability weighting (452). Hopefully, this methodology can also be applied to a longitudinal HCV CoC.

Chapter 5 highlights that DAAs are effective in HIV positive individuals in a real-world setting, which is in agreement with findings from other cohort studies and highlights the importance of treating all HCV-RNA positive PLWH (466,468,469). This analysis included a large proportion of PWID (55%), and there was no evidence to suggest that PWID had lower odds of achieving SVR. This supports the current guidelines that HCV positive individuals should be treated regardless of their risk group, and that appropriate interventions should be carried to prevent disengagement from care (506). There was evidence that ESLD reduced the odds of achieving SVR after adjustment. The results from Chapter 3 showed that treatment with DAAs reduced the odds of having advanced liver fibrosis. Therefore, the findings from both chapters highlight the importance of treating HCV as soon as possible to avoid deterioration of the liver, as it will also increase the chance of treatment failure. While estimates of SVR in real-world studies have previously been published, the data from this chapter is still important as the EuroSIDA cohort is uniquely positioned to also explore regional differences. Also, due to the minimal exclusion criteria, it was possible to explore differences between risk groups and estimate the proportion of PWID who achieve SVR which other studies have not been able to on this scale.

The research findings presented in Chapter 6 also has important clinical implications, as addressing reinfection after cure is one of the final hurdles to achieving HCV elimination. Overall, the rate of reinfection within 2 years of achieving SVR was 6.6%. This highlights the need to ensure individuals at high risk of reinfection are followed up after cure, and that healthcare providers continue to support and frequently test individuals to identify reinfection early. However, as the CoC results have shown, there are huge disparities in access to HCV testing across the different regions in Europe. Therefore, continued testing post SVR may be challenging in certain regions until steps are taken to improve access to frequent HCV-RNA testing. Reinfected individuals need to be treated early to avoid deterioration of health and to prevent onward transmission (506). Also, due to the high cost of DAAs, it would be prudent

to maximise the duration of clearance by ensuring high-risk individuals are engaged with health care services before, during and after treatment. Some analysis has been carried out which highlight the impact of behaviour counselling and harm reduction serviced on reinfection (528), however further research into ways to minimise reinfection is important. The proportion of individuals reinfected after receiving a DAA regimen was lower than the proportion reinfected after receiving an IFN-based regimen. Again, this highlights the importance of widespread access to DAA treatment. There was no evidence to suggest the HIV risk group impacted the odds of reinfection after SVR. Therefore, this research can help to reduce stigma around treating PWID due to fear of reinfection.

There were 636 individuals with sufficient FU after SVR included in this analysis, 43 of whom were reinfected. However, there were even fewer individuals included in the analysis exploring reinfection after spontaneous clearance (n = 161, 11 reinfected). Due to the low number of reinfections after spontaneous clearance, I was unable to use any statistical modelling to explore factors associated with reinfection after spontaneous clearance. Hopefully, further research on factors associated with reinfection after SVR and spontaneous clearance can be carried out on a newer EuroSIDA dataset which includes more FU. However, a multi-cohort study, such as RESPOND, would be better powered to explore factors associated with reinfection in Europe in the DAA era and after spontaneous clearance. There is currently no effective vaccine for HCV infection, therefore continued work towards a vaccine must be intensified to achieve the goal of HCV elimination by 2030 (371)

7.3 Concluding remarks

This thesis aimed to contribute to the epidemiologic data on HIV/HCV co-infected individuals in Europe and to improve our understanding of the priority areas for

action to achieve the goal of elimination by 2030. This thesis also provides important baseline data which will help monitor progress towards achieving this goal.

Around 32% of the individuals included in the Chapter 3 analysis had advanced fibrosis or cirrhosis between 2010 and 2018. Widespread access to DAAs is crucial to prevent serious liver-related complications, however, 67.9% of individuals included in this analysis are in urgent need of medical management as they have never received any HCV treatment. While the introduction of effective, safe, and tolerable treatment has made a significant impact on the burden of fibrosis in Europe, an increase in screening is necessary to really reap the benefits of DAAs. HCV screening and treatment should be targeted to HIV/HCV co-infected individuals over 40 years, PWID, and those with a low CD4 count as they all had a higher odds of advanced fibrosis. The high prevalence of fibrosis ≥F3 and the relationship between CD4 count and advanced fibrosis highlights the need to prioritise HIV and HCV screening, linkage to both HIV and HCV care, and increased treatment access across Europe. All individuals should be prioritised for HCV treatment regardless of fibrosis stage, however if for any reason HCV cannot be treated, the relationship between CD4 count and fibrosis ≥F3 also highlights the importance of encouraging patients to start ART while waiting for HCV treatment, to maintain HIV virological suppression and increase their CD4 cell count (as recommended by HIV treatment guidelines (116)).

The regional differences identified in the cross-sectional CoC (Chapter 4) emphasise the importance of assessing the treatment landscape, developing strategies to reduce prevalence, and establishing better standards of care for individuals with both HIV and HCV, as well as emphasising the importance of in-depth analyses of the reasons for these gaps at the local level. The majority of co-infected individuals are people who inject drugs (227), which means they also face social issues such as stigma and marginalisation which act as barriers to care (529). Therefore, work on removing

barriers to care and establishing a meaningful continuum is essential if the goal of eliminating viral hepatitis as a public health threat by 2030 (227) is to be met.

In Chapter 4 I also presented a longitudinal method for exploring how individuals transition through HCV care. While the cross-sectional CoC is a very useful tool, the longitudinal CoC approach can take the temporal aspect of the HCV CoC into consideration. However, the longitudinal CoC is a more complicated approach than the cross-sectional CoC and may not be as easily implemented in many settings. Therefore, I suggest it is used to complement the traditional cross-sectional CoC for the evaluation of health care disparities and target setting, as it can provide additional insight into how individuals transition through the CoC.

The analysis in Chapter 5 described the effectiveness of interferon-free DAA treatment regimens in a real-world setting found similar rates of SVR to other real-world cohorts and slightly lower rates than clinical trials, despite 55% of the study population being PWID. There was evidence that ESLD reduced the odds of achieving SVR, which highlights the importance of treating HCV as early as possible, before individuals develop liver complications that increase the risk of treatment failure. There was also no evidence of any new serious safety issues. These results demonstrate the effectiveness and safety of DAA therapy in HIV/HCV co-infected individuals, and supports current treatment recommendations to treat all HCV infected individuals, regardless of co-infection with HIV or drug use (365).

In Chapter 6 I explored reinfection 2 years after viral clearance and found that 6.6% of individuals who achieved SVR were reinfected. This indicates the need to improve surveillance of individuals after curing HCV and maintain their engagement with health services. It is also important to target specific interventions to high-risk groups

to reduce the rates of reinfection. This includes harm reduction services for PWID, and behavioural interventions targeted at MSM who engage in high-risk sexual practices associated with HCV (528). It is also vital that HIV negative MSM on PrEP receive frequent testing and access to HCV treatment, as this will also help to reduce HCV reinfection among HIV positive MSM. After adjustment, the odds of reinfection was significantly lower among those that received IFN-free DAA treatment. However, while increased early access to DAA treatment is paramount, it is also important to introduce prevention strategies to curb high-risk behaviours. Testing after HCV clearance was low, especially after spontaneous clearance. However frequent testing to identify reinfection early among individuals at high-risk of reinfection is also essential to reduce HCV reinfection. Reducing the rate of HCV reinfection is urgently needed to reach the goal of elimination by 2030, especially among marginalised and vulnerable groups.

While the results of this thesis have shown that the prognosis of individuals with HCV infection has generally improved since the introduction of DAAs, there are still individuals who do not have access to these life-changing treatments. Interventions targeted at key populations are required, as well as continued monitoring of progress towards the WHO targets. Hopefully, the results presented in this thesis, along with continued activism and advocacy, can improve the clinical care and quality of life of individuals co-infected with HIV and HCV, especially among marginalised populations who experience significant health inequalities.

Appendix I: EuroSIDA Study Group and Steering Committee

The multi-centre study group, EuroSIDA (national coordinators in parenthesis):

South: Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. Greece: (H Sambatakou), Ippokration General Hospital, Athens; G Adamis, N Paissios, Athens General Hospital "G Gennimatas". Israel: (L Tau), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, AIDS Center (Neve Or), Jerusalem. Italy: (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. Portugal: (A Zagalo), Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. Spain: (JM Miro), JM Miró, M. Laguno, E. Martinez, F. Garcia, JL Blanco, M. Martinez-Rebollar, J. Mallolas, Hospital Clinic – IDIBAPS University of Barcelona, Barcelona; S Moreno, S. del Campo, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, J Puig, JM Llibre, JR Santos, Infectious Diseases Unit & IrsiCaixa AIDS Research Institute, Hospital germans Trias I Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz.

Central West: Austria: (B Schmied), Otto Wagner Hospital, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. France: (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; C Pradier, E Fontas, Hôpital de l'Archet, Nice; C Duvivier, Hôpital Necker-Enfants Malades, Paris. Germany: (J Rockstroh), Universitäts Klinik Bonn; G Behrens, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Luxembourg: (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. Switzerland: (A Scherrer), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen.

North: Denmark: G Kronborg, T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; C Pedersen, IS Johansen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, L Wiese, NF Moller, Sjællands Universitetshospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. Finland: (I Aho), Helsinki University Hospital, Helsinki. Iceland: (M Gottfredsson), Landspitali University Hospital, Reykjavik. Ireland: (C Kelly), St. James's Hospital, Dublin. Netherlands: (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (DH Reikvam), A Maeland, J

Bruun, Oslo University Hospital, Ullevaal. Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; CJ Treutiger, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. United Kingdom:A Milinkovic, St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; A Winston, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Central East: Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb. Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Hungary: (J Szlávik), Szent Lásló Hospital, Budapest. Poland: (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, K Maciejewska, B Aksak-Was, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, J Kamerys, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, B Rozplochowski, Poznan University of Medical Sciences, Poznan. Romania: (R Radoi), C Oprea, Carol Davila University of Medicine and Pharmacy Bucharest, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest. Serbia: (G Dragovic),

The Institute for Infectious and Tropical Diseases, Belgrade. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana.

East: Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk. Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi. Latvia: (B Rozentale), Infectology Centre of Latvia, Riga. Lithuania: (V Uzdaviniene) Vilnius University Hospital Santaros Klinikos, Vilnius; R Matulionyte, Centro poliklinika, Vilnius, Vilnius University Hospital Santaros Klinikos, Vilnius. Russia: (A Panteleev), O Panteleev, St Petersburg AIDS Centre, St Peterburg; A Yakovlev, Medical Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara. Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; J Mikhalik, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv.

The following centres have previously contributed data to EuroSIDA: Infectious Diseases Hospital, Sofia, Bulgaria. Hôpital de la Croix Rousse, Lyon, France. Hôpital de la Pitié-Salpétière, Paris, France. Unité INSERM, Bordeaux, France. Hôpital Edouard Herriot, Lyon, France. Bernhard Nocht Institut für Tropenmedizin, Hamburg,

Germany. 1st I.K.A Hospital of Athens, Athens, Greece. Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy. Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy. Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy. Dérer Hospital, Bratislava, Slovakia. Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain. Kiev Centre for AIDS, Kiev, Ukraine. Luhansk State Medical University, Luhansk, Ukraine. Odessa Region AIDS Center, Odessa, Ukraine

EuroSIDA Steering Committee: I Karpov, M Losso, J Lundgren, J Rockstroh, I Aho, LD Rasmussen, V Svedhem, G Wandeler, C Pradier, N Chkhartishvili, R Matulionyte, C Oprea, JD Kowalska, J Begovac, JM Miró, G Guaraldi, R Paredes. Chair: G Wandeler. Co-Chair: R Paredes. Study Co-leads: A Mocroft, O Kirk

EuroSIDA staff: Coordinating Centre Staff: O Kirk, L Peters, A Bojesen, D Raben, EV Hansen, D Kristensen, JF Larsen, AH Fischer.

Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, S Amele, A Pelchen-Matthews, A Roen.

Appendix II: EuroSIDA research proposal form

Template – Project Proposals in EuroSIDA
(1-2 pages)

Project Title:

Name and centre:

Writing Group (lead author on manuscript):

1. **Background/Scientific Rationale**
2. **Objectives**
3. **Significance**
4. **Feasibility**[1]
5. **Possible Limitations**
6. **Study design/data required**
7. **Statistical Analysis**[1]
8. **Timelines (including potential conference)**
9. **Budget (itemised)** [2]

[1] Please contact Amanda Mocroft a.mocroft@ucl.ac.uk for assistance for the feasibility and statistical analysis paragraph.
[2] Please contact Ole Kirk okj@cphiv.dk for assistance in presentation of budget.

Appendix III: HCV treatment form

Confidential

EuroSIDA HCV treatment form

Center/Patient code:

Criteria for completion:

• For patients enrolled in cohort 10, the HCV Treatment form should be completed if HCV treatment was ongoing during enrolment or has commenced after enrolment (baseline).
Please do not complete a HCV Treatment form if treatment was finished before the patient was enrolled in cohort 10.

• For patients enrolled in EuroSIDA before cohort 10, the HCV Treatment form should be completed if HCV treatment was ongoing 1 June 2014 or has commenced after 1 June 2014.
Please do not complete a HCV Treatment form if treatment was finished before 1 June 2014.

eCRF completed by:

---

eCRF completed date:

Data entry instructions

Comma vs. full stop in numbers e.g. 2,5/2.5:
You have to use full stop instead of comma, otherwise an error will be displayed and you will not be allowed to continue.

Test/measurement not performed:
Leave the field(s) blank.

Unknown dates:
(yyyy-mm-??) If only the day is unknown, use the 15th and then the known month and year. (yyyy-mm-15) For example unknown day in September 2007: 2007-09-15.

(yyyy-??-??) If both day and month are unknown, use the 1st July and then the known year. (yyyy-07-01) For example unknown day and month in 2011: 2011-07-01.

(????-??-??) If both day, month and year are unknown, use the 11th November 1911, i.e. 1911-11-11.

Please list all initiated therapy

Drug:

- ☐ INTF: Interferon
- ☐ PINT: Pegylated interferon
- ☐ RIBA: Ribavirin
- ☐ TELA: Telaprevir
- ☐ BOCE: Boceprevir
- ☐ SIMV: Simeprevir
- ☐ FALV: Faldaprevir
- ☐ DACV: Daclatasvir
- ☐ SOFO: Sofosbuvir
- ☐ HARV: Harvoni (sofosbuvir/ledipasvir)
- ☐ VIEK: Viekirax (ombitasvir/paritaprevir/ritonavir)
- ☐ DASA: Dasabuvir
- ☐ Grazoprevir and Elbasvir
- ☐ PBT: Participant in blinded trial
- ☐ --Other, none of the above--

Interferon

Start date (Interferon):	_____
Start dosage in µg (Interferon):	_____ (Please enter total WEEKLY dosage in µg.)
Stop date (Interferon):	_____
Dosage at time of treatment stop in µg (Interferon):	_____ (Please enter total WEEKLY dosage in µg.)
Was treatment interrupted before schedule? (Interferon):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Interferon):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____

If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.

Pegylated interferon

Start date (Pegylated interferon):	_____
Start dosage in µg (Pegylated interferon):	_____ (Please enter total WEEKLY dosage in µg.)
Stop date (Pegylated interferon):	_____
Dosage at time of treatment stop in µg (Pegylated interferon):	_____ (Please enter total WEEKLY dosage in µg.)
Was treatment interrupted before schedule? (Pegylated interferon):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Pegylated interferon):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown

If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Ribavirin	
Start date (Ribavirin):	_____
Start dosage in mg (Ribavirin):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Ribavirin):	_____
Dosage at time of treatment stop (Ribavirin):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Ribavirin):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Ribavirin):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Telaprevir	
Start date (Telaprevir):	_____
Start dosage in mg (Telaprevir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Telaprevir):	_____
Dosage at time of treatment stop (Telaprevir):	_____ (Please enter total DAILY dosage in mg.)

Was treatment interrupted before schedule? (Telaprevir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Telaprevir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Boceprevir	
Start date (Boceprevir):	_____
Start dosage in mg (Boceprevir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Boceprevir):	_____
Dosage at time of treatment stop (Boceprevir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Boceprevir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Boceprevir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Simeprevir	
Start date (Simeprevir):	_____
Start dosage in mg (Simeprevir):	_____ (Please enter total DAILY dosage in mg.)

Stop date (Simeprevir):	_____
Dosage at time of treatment stop (Simeprevir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Simeprevir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Simeprevir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Faldaprevir	
Start date (Faldaprevir):	_____
Start dosage in mg (Faldaprevir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Faldaprevir):	_____
Dosage at time of treatment stop (Faldaprevir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Faldaprevir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Faldaprevir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Daclatasvir	

Start date (Daclatasvir):	_____
Start dosage in mg (Daclatasvir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Daclatasvir):	_____
Dosage at time of treatment stop (Daclatasvir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Daclatasvir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Daclatasvir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____

If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.

Sofosbuvir

Start date (Sofosbuvir):	_____
Start dosage in mg (Sofosbuvir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Sofosbuvir):	_____
Dosage at time of treatment stop (Sofosbuvir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Sofosbuvir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Sofosbuvir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown

If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Harvoni	
Start date (Harvoni):	_____
Stop date (Harvoni):	_____
Was treatment interrupted before schedule? (Harvoni):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Harvoni):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Viekirax	
Start date (Viekirax):	_____
Stop date (Viekirax):	_____
Was treatment interrupted before schedule? (Viekirax):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Viekirax):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Dasabuvir	

Start date (Dasabuvir):	_____
Start dosage in mg (Dasabuvir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Dasabuvir):	_____
Dosage at time of treatment stop (Dasabuvir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Dasabuvir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Dasabuvir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Grazoprevir and Elbasvir	
Start date (Grazoprevir and Elbasvir):	_____
Start dosage in mg (Grazoprevir and Elbasvir):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Grazoprevir and Elbasvir):	_____
Dosage at time of treatment stop (Grazoprevir and Elbasvir):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Grazoprevir and Elbasvir):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (Grazoprevir and Elbasvir):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown

If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	
Participant in blinded trial	
Start date (Participant in blinded trial):	_____
Stop date (Participant in blinded trial):	_____
Other drug	
If other drug, please specify:	_____
Start date (Other):	_____
Start dosage in mg (Other):	_____ (Please enter total DAILY dosage in mg.)
Stop date (Other):	_____
Dosage at time of treatment stop (Other):	_____ (Please enter total DAILY dosage in mg.)
Was treatment interrupted before schedule? (Other):	◯ No ◯ Yes ◯ Unknown
If yes, please indicate reason for discontinuation (other):	◯ Virological failure ◯ Toxicity/intolerance ◯ Out of stock ◯ Other ◯ Unknown
If other, please specify:	_____
If reason for premature discontinuation is toxicity/intolerance, please fill out an Adverse Event Form.	

Adherence	
Receipt of at least 80% of all scheduled drug doses for at least 80% of the treatment period?	◯ No ◯ Yes ◯ Unknown
If no, please provide reason for non-adherence:	◯ Intolerance ◯ Forgot ◯ Drug out of stock ◯ Other
If other, please describe:	_____

Growth factors and blood transfusions	
Has the patient received EPO during treatment?	◯ No ◯ Yes ◯ Unknown
Has the patient received G-CSF during treatment?	◯ No ◯ Yes ◯ Unknown
Has the patient received a blood transfusion during treatment?	◯ No ◯ Yes ◯ Unknown

Laboratory - Blood count	
Haemoglobin	
Haemoglobin DATE - most recent prior to treatment:	_____
Haemoglobin UNIT - most recent prior to treatment:	◯ mmol/L ◯ g/dL ◯ g/L ◯ Other
If other, please specify:	_____
Haemoglobin VALUE - most recent prior to treatment:	_____
Haemoglobin VALUE - most recent prior to treatment:	_____
Haemoglobin VALUE - most recent prior to treatment:	_____
Haemoglobin VALUE - most recent prior to treatment:	_____

Haemoglobin DATE - lowest during treatment:	_____
Haemoglobin UNIT - lowest during treatment:	◯ mmol/L ◯ g/dL ◯ g/L ◯ Other
If other, please specify:	_____
Haemoglobin VALUE - lowest during treatment:	_____
Haemoglobin VALUE - lowest during treatment:	_____
Haemoglobin VALUE - lowest during treatment:	_____
Haemoglobin VALUE - lowest during treatment:	_____
Haemoglobin DATE - most recent prior to treatment stop:	_____
Haemoglobin UNIT - most recent prior to treatment stop:	◯ mmol/L ◯ g/dL ◯ g/L ◯ Other
If other, please specify:	_____
Haemoglobin VALUE - most recent prior to treatment stop:	_____
Haemoglobin VALUE - most recent prior to treatment stop:	_____
Haemoglobin VALUE - most recent prior to treatment stop:	_____
Haemoglobin VALUE - most recent prior to treatment stop:	_____
Leukocytes	
Leukocytes DATE - most recent prior to treatment:	_____
Leukocytes UNIT - most recent prior to treatment:	◯ cells/µL ◯ 10^9/L ◯ Other

If other, please specify:	_____
Leukocytes VALUE - most recent prior to treatment:	_____
Leukocytes VALUE - most recent prior to treatment:	_____
Leukocytes VALUE - most recent prior to treatment:	_____
Leukocytes DATE - lowest during treatment:	_____
Leukocytes UNIT - lowest during treatment:	○ cells/µL ○ 10^9/L ○ Other
If other, please specify:	_____
Leukocytes VALUE - lowest during treatment:	_____
Leukocytes VALUE - lowest during treatment:	_____
Leukocytes VALUE - lowest during treatment:	_____
Leukocytes DATE - most recent prior to treatment stop:	_____
Leukocytes UNIT - most recent prior to treatment stop:	○ cells/µL ○ 10^9/L ○ Other
If other, please specify:	_____
Leukocytes VALUE - most recent prior to treatment stop:	_____
Leukocytes VALUE - most recent prior to treatment stop:	_____
Leukocytes VALUE - most recent prior to treatment stop:	_____
Neutrophiles	
Neutrophiles DATE - most recent prior to treatment:	_____

Neutrophiles UNIT - most recent prior to treatment:	◯ cells/µL ◯ 10^9/L ◯ Other
If other, please specify:	_____
Neutrophiles VALUE - most recent prior to treatment:	_____
Neutrophiles VALUE - most recent prior to treatment:	_____
Neutrophiles VALUE - most recent prior to treatment:	_____
Neutrophiles DATE - lowest during treatment:	_____
Neutrophiles UNIT - lowest during treatment:	◯ cells/µL ◯ 10^9/L ◯ Other
If other, please specify:	_____
Neutrophiles VALUE - lowest during treatment:	_____
Neutrophiles VALUE - lowest during treatment:	_____
Neutrophiles VALUE - lowest during treatment:	_____
Neutrophiles DATE - most recent prior to treatment stop:	_____
Neutrophiles UNIT - most recent prior to treatment stop:	◯ cells/µL ◯ 10^9/L ◯ Other
If other, please specify:	_____
Neutrophiles VALUE - most recent prior to treatment stop:	_____
Neutrophiles VALUE - most recent prior to treatment stop:	_____
Neutrophiles VALUE - most recent prior to treatment stop:	_____
Platelet count	

Platelet count DATE - most recent prior to treatment:	_____
Platelet count UNIT - most recent prior to treatment:	○ 10^3/µL ○ 10^9/L ○ Other
If other, please specify:	_____
Platelet count VALUE - most recent prior to treatment:	_____
Platelet count VALUE - most recent prior to treatment:	_____
Platelet count VALUE - most recent prior to treatment:	_____
Platelet count DATE - lowest during treatment:	_____
Platelet count UNIT - lowest during treatment:	○ 10^3/µL ○ 10^9/L ○ Other
If other, please specify:	_____
Platelet count VALUE - lowest during treatment:	_____
Platelet count VALUE - lowest during treatment:	_____
Platelet count VALUE - lowest during treatment:	_____
Platelet count DATE - most recent prior to treatment stop:	_____
Platelet count UNIT - most recent prior to treatment stop:	○ 10^3/µL ○ 10^9/L ○ Other
If other, please specify:	_____
Platelet count VALUE - most recent prior to treatment stop:	_____
Platelet count VALUE - most recent prior to treatment stop:	_____
Platelet count VALUE - most recent prior to treatment stop:	_____

Laboratory - Clinical chemistry	
S-creatinine	
S-creatinine DATE - most recent prior to treatment:	_____
S-creatinine UNIT - most recent prior to treatment:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
S-creatinine VALUE - most recent prior to treatment:	_____
S-creatinine VALUE - most recent prior to treatment:	_____
S-creatinine VALUE - most recent prior to treatment:	_____
S-creatinine VALUE - most recent prior to treatment:	_____
S-creatinine DATE - highest during treatment:	_____
S-creatinine UNIT - highest during treatment:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
S-creatinine VALUE - highest during treatment:	_____
S-creatinine VALUE - highest during treatment:	_____
S-creatinine VALUE - highest during treatment:	_____
S-creatinine VALUE - highest during treatment:	_____
S-creatinine DATE - most recent prior to treatment stop:	_____

S-creatinine UNIT - most recent prior to treatment stop:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
S-creatinine VALUE - most recent prior to treatment stop:	_____
S-creatinine VALUE - most recent prior to treatment stop:	_____
S-creatinine VALUE - most recent prior to treatment stop:	_____
S-creatinine VALUE - most recent prior to treatment stop:	_____
Alanine Aminotransferase (ALT)	
ALT DATE - most recent prior to treatment:	_____
ALT UNIT - most recent prior to treatment:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
ALT VALUE - most recent prior to treatment:	_____
ALT VALUE - most recent prior to treatment:	_____
ALT VALUE - most recent prior to treatment:	_____
ALT DATE - highest during treatment:	_____
ALT UNIT - highest during treatment:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
ALT VALUE - highest during treatment:	_____
ALT VALUE - highest during treatment:	_____

ALT VALUE - highest during treatment:	_____
ALT DATE - most recent prior to treatment stop:	_____
ALT UNIT - most recent prior to treatment stop:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
ALT VALUE - most recent prior to treatment stop:	_____
ALT VALUE - most recent prior to treatment stop:	_____
ALT VALUE - most recent prior to treatment stop:	_____
Aspartate Aminotransferase (AST)	
AST DATE - most recent prior to treatment:	_____
AST UNIT - most recent prior to treatment:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
AST VALUE - most recent prior to treatment:	_____
AST VALUE - most recent prior to treatment:	_____
AST VALUE - most recent prior to treatment:	_____
AST DATE - highest during treatment:	_____
AST UNIT - highest during treatment:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
AST VALUE - highest during treatment:	_____

AST VALUE - highest during treatment:	_____
AST VALUE - highest during treatment:	_____
AST DATE - most recent prior to treatment stop:	_____
AST UNIT - most recent prior to treatment stop:	◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
AST VALUE - most recent prior to treatment stop:	_____
AST VALUE - most recent prior to treatment stop:	_____
AST VALUE - most recent prior to treatment stop:	_____
Alkaline phosphatase (ALP)	
ALP DATE - most recent prior to treatment:	_____
ALP UNIT - most recent prior to treatment:	◯ g/dL ◯ mmol/L ◯ µkat/L ◯ IU/L ◯ Other
If other, please specify:	_____
ALP VALUE - most recent prior to treatment:	_____
ALP VALUE - most recent prior to treatment:	_____
ALP VALUE - most recent prior to treatment:	_____
ALP VALUE - most recent prior to treatment:	_____
ALP VALUE - most recent prior to treatment:	_____
ALP DATE - highest during treatment:	_____

ALP UNIT - highest during treatment:	◯ g/dL ◯ mmol/L ◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
ALP VALUE - highest during treatment:	_____
ALP VALUE - highest during treatment:	_____
ALP VALUE - highest during treatment:	_____
ALP VALUE - highest during treatment:	_____
ALP VALUE - highest during treatment:	_____
ALP DATE - most recent prior to treatment stop:	_____
ALP UNIT - most recent prior to treatment stop:	◯ g/dL ◯ mmol/L ◯ IU/L ◯ µkat/L ◯ Other
If other, please specify:	_____
ALP VALUE - most recent prior to treatment stop:	_____
ALP VALUE - most recent prior to treatment stop:	_____
ALP VALUE - most recent prior to treatment stop:	_____
ALP VALUE - most recent prior to treatment stop:	_____
ALP VALUE - most recent prior to treatment stop:	_____
Bilirubin (total)	
Bilirubin DATE - most recent prior to treatment:	_____

Bilirubin UNIT - most recent prior to treatment:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
Bilirubin VALUE - most recent prior to treatment:	_____
Bilirubin VALUE - most recent prior to treatment:	_____
Bilirubin VALUE - most recent prior to treatment:	_____
Bilirubin VALUE - most recent prior to treatment:	_____
Bilirubin DATE - highest during treatment:	_____
Bilirubin UNIT - highest during treatment:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
Bilirubin VALUE - highest during treatment:	_____
Bilirubin VALUE - highest during treatment:	_____
Bilirubin VALUE - highest during treatment:	_____
Bilirubin VALUE - highest during treatment:	_____
Bilirubin DATE - most recent prior to treatment stop:	_____
Bilirubin UNIT - most recent prior to treatment stop:	◯ µmol/L ◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
Bilirubin VALUE - most recent prior to treatment stop:	_____

Bilirubin VALUE - most recent prior to treatment stop:	_____
Bilirubin VALUE - most recent prior to treatment stop:	_____
Bilirubin VALUE - most recent prior to treatment stop:	_____
Albumin	
Albumin DATE - most recent prior to treatment:	_____
Albumin UNIT - most recent prior to treatment:	◯ g/L ◯ g/dl ◯ µmol/L ◯ Other
If other, please specify:	_____
Albumin VALUE - most recent prior to treatment:	_____
Albumin VALUE - most recent prior to treatment:	_____
Albumin VALUE - most recent prior to treatment:	_____
Albumin VALUE - most recent prior to treatment:	_____
International Normalized Ratio (INR)	
INR DATE - most recent prior to treatment:	_____
INR VALUE - most recent prior to treatment:	_____
INR DATE - highest during treatment:	_____
INR VALUE - highest during treatment:	_____
INR DATE - most recent prior to treatment stop:	_____
INR VALUE - most recent prior to treatment stop:	_____
Serum triglycerides	

Serum triglycerides DATE - most recent prior to treatment:	_____
Serum triglycerides UNIT - most recent prior to treatment:	◯ mmol/L ◯ mg/dL ◯ mg/L ◯ Other
If other, please specify:	_____
Serum triglycerides VALUE - most recent prior to treatment:	_____
Serum triglycerides VALUE - most recent prior to treatment:	_____
Serum triglycerides VALUE - most recent prior to treatment:	_____
Serum triglycerides VALUE - most recent prior to treatment:	_____
Low-density lipoprotein (LDL)	
LDL DATE - most recent prior to treatment:	_____
LDL UNIT - most recent prior to treatment:	◯ mg/dL ◯ mmol/L ◯ Other
If other, please specify:	_____
LDL VALUE - most recent prior to treatment:	_____
LDL VALUE - most recent prior to treatment:	_____
LDL VALUE - most recent prior to treatment:	_____
Laboratory - HCV-RNA **(List most recent measurement prior to treatment initiation and all measurements during treatment)**	
Date (1):	_____

Result (1):	◯ Positive ◯ Negative ◯ Unknown
Type of test (1):	◯ Quantitative ◯ Qualitative
Unit (1):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (1):	_____ (Values below level of detection should be registered as detection limit minus 1 e.g. below 200 would be registered as 199.)
Detection limit (1):	_____
Assay (1):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (1):	_____
Date (2):	_____
Result (2):	◯ Positive ◯ Negative ◯ Unknown
Type of test (2):	◯ Quantitative ◯ Qualitative
Unit (2):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (2):	_____
Detection limit (2):	_____

Assay (2):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (2):	_____
Date (3):	_____
Result (3):	◯ Positive ◯ Negative ◯ Unknown
Type of test (3):	◯ Quantitative ◯ Qualitative
Unit (3):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (3):	_____
Detection limit (3):	_____
Assay (3):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (3):	_____
Date (4):	_____
Result (4):	◯ Positive ◯ Negative ◯ Unknown
Type of test (4):	◯ Quantitative ◯ Qualitative

Unit (4):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (4):	_____
Detection limit (4):	_____
Assay (4):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (4):	_____
Date (5):	_____
Result (5):	◯ Positive ◯ Negative ◯ Unknown
Type of test (5):	◯ Quantitative ◯ Qualitative
Unit (5):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (5):	_____
Detection limit (5):	_____
Assay (5):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (5):	_____

Date (6):	_____
Result (6):	◯ Positive ◯ Negative ◯ Unknown
Type of test (6):	◯ Quantitative ◯ Qualitative
Unit (6):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (6):	_____
Detection limit (6):	_____
Assay (6):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (6):	_____
Date (7):	_____
Result (7):	◯ Positive ◯ Negative ◯ Unknown
Type of test (7):	◯ Quantitative ◯ Qualitative
Unit (7):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (7):	_____
Detection limit (7):	_____

Assay (7):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (7):	_____
Date (8):	_____
Result (8):	◯ Positive ◯ Negative ◯ Unknown
Type of test (8):	◯ Quantitative ◯ Qualitative
Unit (8):	◯ Copies/mL ◯ IU/mL ◯ Other
If other, please specify:	_____
Value (8):	_____
Detection limit (8):	_____
Assay (8):	◯ Abbott Real Time HCV ◯ Roche COBAS Amplicor HCV Monitor ◯ Roche COBAS AmpliPrep/TaqMan HCV Test ◯ Siemens VERSANT HCV DNA (bDNA) ◯ Qiagen artus HCV PCR kit ◯ Other
If other, please specify (8):	_____

Appendix IV: HepHIV Conference 2017 - poster presentation

Poster No. PO1/16

HepHIV 2017 Conference

Regional differences across Europe in advanced fibrosis and cirrhosis among HIV/HCV co-infected persons between 2010-2015

Sarah Amele[1], Lars Peters[2], Jens D. Lundgren[2,3], Jürgen K. Rockstroh[4], Helen Sambatakou[5], Therese Staub[6], Fernando Maltez[7], Clifford Leen[8], Court Pedersen[9], Jose M. Gatell Artigas[10], Santiago Moreno[11], Raimonda Matulionyte[12], Galina Kyselyova[13], Igor Karpov[14], David Jilich[15], Milosz Parczewski[16], Kai Zilmer[17], Hila Elinav[18], Karine Lacombe[19], Matthias Cavassini[20], Janez Tomazic[21] and Amanda Mocroft[1] on behalf of the EuroSIDA study group

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BACKGROUND

The increasing availability of directly acting antivirals (DAAs) for the treatment of hepatitis C coinfected persons has in some countries led to targeting DAAs to those most at need (fibrosis ≥F3) because of their cost. The prevalence of fibrosis ≥F3 across Europe is largely unknown, nor is the extent to which it is changing in different regions of Europe.

AIMS:

- To investigate regional differences in the prevalence of fibrosis ≥F3 or liver events in persons co-infected with HIV/HCV.
- To investigate factors associated with developing fibrosis ≥F3 and how this changes over time across different regions.

METHODS:

- Individuals co-infected with chronic HCV (defined as being HCV-AB positive and HCV-RNA positive) with a liver fibrosis biomarker (liver biopsy, APRI, hyaluronic acid or FibroScan) result whilst under follow-up in EuroSIDA on January 1st each year from 2010 to 2015 were included in this study.
- The proportion of HCV-RNA positive patients with fibrosis METAVIR ≥F3 or liver events (hepatic decompensation, hepatocellular carcinoma) was compared between regions over time. Fibrosis ≥F3 was defined by:

Liver fibrosis biomarker	Result
Liver biopsy	≥F3
APRI	score ≥1.75
Hyaluronic acid	>250ng/mL
FibroScan	≥9kPa

- Adjusted odds ratio of an individual having fibrosis ≥F3 was assessed using logistic regression. Generalised estimating equations were used to allow the inclusion of individuals under follow-up in multiple years. This method was also used to investigate the effect of time within each region on the odds of developing fibrosis ≥F3 .

RESULTS:

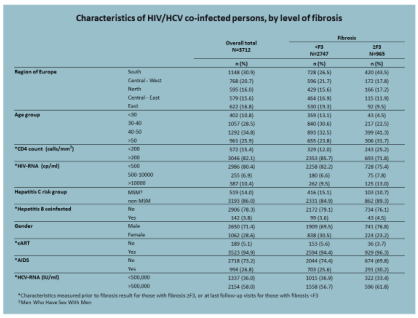
- There were 3712 individuals with chronic HCV and a liver fibrosis biomarker in the study, 965 of which had fibrosis ≥F3 at some point during follow-up (characteristics of patients shown in **Table 1).** 1411, 1367, 1317, 1382, 1371 and 2121 persons were under follow-up on 1/1/2010-2015 respectively.
- The proportion of individuals with fibrosis ≥F3 under follow-up on 1/1/2010-2015 was 20.3%, 22.9% 21.3% 20.4% 20.4% and 23.0% respectively (**Figure 1**); with significant differences between regions each year (p<0.0001).
- The greatest increase over time was in Northern and Southern Europe (17.0% to 23.5% and 26.5% to 34.5%).
- 4.8%, 4.6%, 4.5%, 4.2%, 3.3% and 2.8% of persons under follow-up on 1/1/2010-2015 (respectively) experience a liver-related event.
- The proportion reporting testing HCV positive recently (<5 years) was low, and significantly differed between regions (p<0.0001), as did the median duration of HCV infection, 14 and 7 years in Southern/Eastern Europe respectively (p<0.0001); 15% of those testing positive recently had fibrosis ≥F3 .
- After adjustment, non-MSM individuals had higher odds of fibrosis ≥F3 compared to MSM, as did individuals aged >50 compared to those aged 30-40. Compared to Southern Europe, all regions had lower odds of fibrosis ≥F3, as did those with CD4 count >200/mm^3 **(Figure 2)**.
- The change over time in fibrosis ≥F3 differed between regions (p=0.025). After adjustment, the odds of fibrosis ≥F3 was increasing in Southern Europe over time and showed an early increase before 2014-2015 in Northern Europe, with few changes over time in other regions **(Figure 3).**

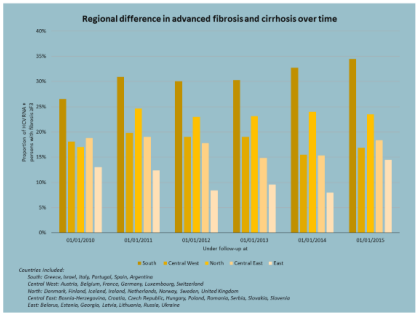
LIMITATIONS:

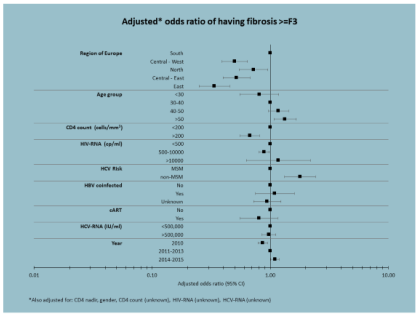
- Not every individual had information on the date they were diagnosed, therefore detailed analysis of late presenters was not feasible.
- The proportion of patients with a liver-related event was also small, which precluded regional comparisons.

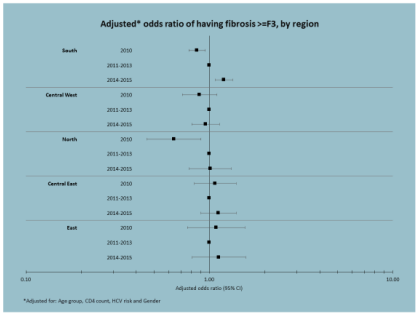
CONCLUSIONS:

26% of individuals with HIV/HCV had fibrosis ≥F3, with significant differences between regions likely attributable to duration of HCV infection. The odds of developing fibrosis ≥F3 was increasing by a small amount each year, with the most marked increases in Southern Europe. Although recent HCV diagnoses were uncommon, there was still a considerable proportion of recently diagnosed individuals with fibrosis ≥F3. The prevalence of fibrosis ≥F3 and the relationship between CD4 and fibrosis ≥F3 highlights the need to prioritise HIV and HCV screening, linkage to care and treatment across Europe. If for any reason HCV cannot be treated, the relationship between CD4 count and fibrosis ≥F3 also highlights the importance of encouraging patients to start ART while waiting for HCV treatment, to maintain HIV suppressions and increase their CD4 cell count.









EuroSIDA study group: http://www.chip.dk/Studies/EuroSIDA/Study-group
Download poster at: www.chip.dk

EuroSIDA

UCL

16th European AIDS Conference
October 25-27, 2017
Milan, Italy

The hepatitis C continuum of care among HIV infected individuals in EuroSIDA

Sarah Amele, Lars Peters, Jens D. Lundgren, Jürgen K. Rockstroh, Maryana Sluzhynska, Alexei Yakovlev, Alexandra Scherrer, Pere Domingo, Jan Gerstoft, Jean-Paul Viard, Robert Zangerle, Robert Flisiak, Sanjay Bagaim, Matti Ristola, Clifford Leen, Elzbieta Jablonowska, Gilles Wandeler, Hans-Jürgen Stellbrink, Karolin Falconer, Antonella d'Arminio Monforte, Andrzej Horban and Amanda Mocroft

on behalf of the EuroSIDA study group

Presenter Disclosure Information

Sarah Amele

disclosed no conflict of interest.

Background

- Globally 2.3 million HIV/HCV co-infected, majority are injecting drug users (IDU) [1]
- WHO goal of eliminating viral hepatitis as a public health threat by 2030[1] - HCV continuum of care (CoC) is an essential framework to monitor and evaluate progress in achieving these targets
- Also useful to identify leaks/breaks in the continuum that need to be addressed to ensure individuals transition through all stages and achieve sustained virologic response (SVR)
- More work is required to develop a standardised continuum for HCV infected people living with HIV (PLWH) to allow cross country or population comparisons

[1]World Health Organization. Global hepatitis report, 2017. 2017. 62 p.

Aims

- To develop and evaluate a HCV continuum of care in HIV co-infected individuals across Europe at 1/1/2015
- Look at regional differences in the continuum
- Examine the proportion of individuals genotyped and with a fibrosis marker
- Describe factors associated with being HCV-RNA tested once already anti-HCV positive

EuroSIDA study

- Large prospective observational cohort study with over 22,000 HIV-positive individuals
- Inclusion criteria
  - HIV positive
  - Under follow-up at 1/1/2015
  - Anti-HCV positive before 1/1/2015
  - >16 years of age

Regions

- **South:** Greece, Israel, Italy, Portugal, Spain, Argentina
- **Central West:** Austria, Belgium, France, Germany, Luxembourg, Switzerland
- **North:** Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom
- **Central East:** Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia
- **East:** Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine

Methods - Definitions

Stage	Definition
1: anti-HCV +ve	Anti-HCV positive, HCV-RNA positive, HCV genotyped or received HCV treatment before 1/1/2015
2: Ever HCV-RNA tested	Ever HCV-RNA tested, HCV genotyped or received HCV treatment before 1/1/2015
3: Currently HCV-RNA +ve	Most recent HCV-RNA test before 1/1/2015 was positive, HCV genotyped but not treated before 1/1/2015, started treatment for the first time after 1/1/2015 or first HCVRNA test result after 1/1/2015 is positive and never treated.
4: Ever HCV-RNA +ve	Ever had a positive HCV-RNA test, received HCV treatment or HCV genotyped before 1/1/2015
5: Ever received treatment	Started HCV treatment on or before 1/1/2015
6: Treatment completed	Completed HCV treatment on or before 1/1/2015
7: FU HCV-RNA available	HCV-RNA test after completing treatment (HCV-RNA test data included for duration of FU to allow for assessment of SVR)
8: SVR	HCV-RNA negative test at least 12 or 24 weeks post treatment (for IFN-free and IFN-based therapy, respectively)

Methods - Statistics

- Tested for regional differences within each stage of continuum
- Identify predictors of being HCV-RNA tested:

Logistic regression

Model adjusted for: age, sex, ethnicity, region in Europe, CD4 count, HIV-RNA, previous use of cART, mode of HIV transmission, mode of HCV transmission, stage of liver fibrosis, hepatitis B co-infected and prior AIDS diagnosis

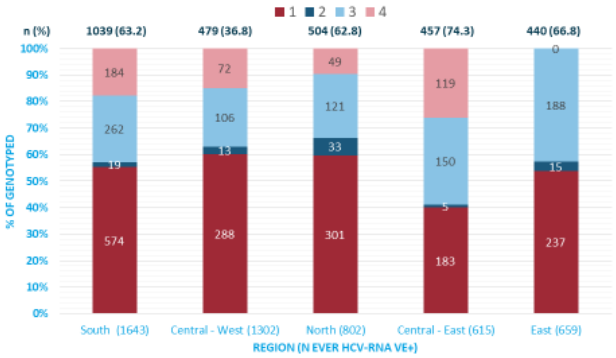
Characteristics at 1/1/2015

Region n (%)		Overall 6985 (100.0)	South 1910 (27.3)	Central - West 1614 (23.1)	North 966 (13.8)	Central - East 925 (13.2)	East 1570 (22.5)
Variables				%			
Gender	Male	71.6	72.5	75.1	78.4	72.0	62.7
Ethnicity	White	88.3	94.3	68.2	82.3	98.6	99.4
Fibrosis	<F3	74.7	73.9	80.9	69.5	69.4	75.7
	≥F3*	12.9	15.4	11.6	12.8	9.8	13.1
HIV risk group	MSM	21.0	16.5	32.2	42.0	21.2	2.0
	IDU	54.2	60.1	40.0	37.9	59.1	68.9
cART	Yes	88.8	95.3	80.4	95.9	95.0	81.7
				Median			
Age		47	50	51	51	41	37
CD4 count (cells/mm^3)		278	297	332	234	244	267

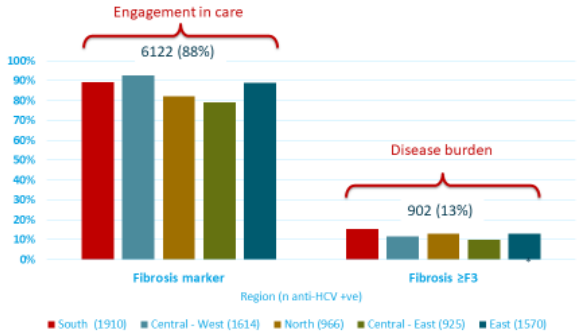
**Either a biopsy (≥METAVIR stage F3), APRI (score >1.5), hyaluronic acid (>160ng/mL) or FibroScan (>9.5kPa) test during follow-up*

Evidence of difference between regions for all variables (p<0.001)

HCV genotype



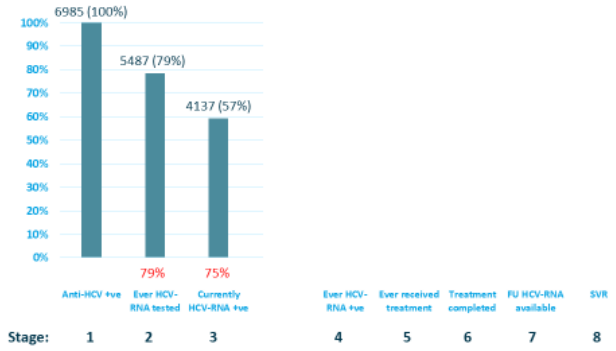
Fibrosis



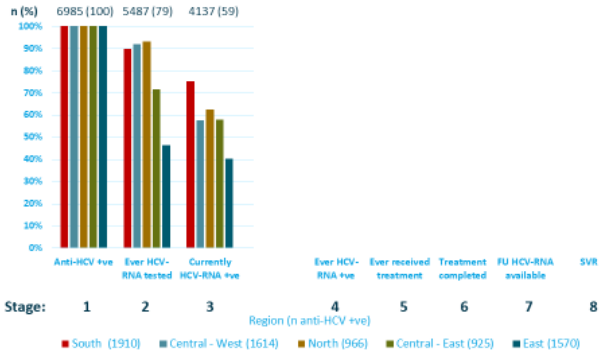
**Either a biopsy (≥METAVIR stage F3), APRI (score >1.5), hyaluronic acid (>160ng/mL) or FibroScan (>9.5kPa) test during follow-up*

Evidence of difference between regions for all variables (p<0.001)

Overall CoC at 1/1/2015

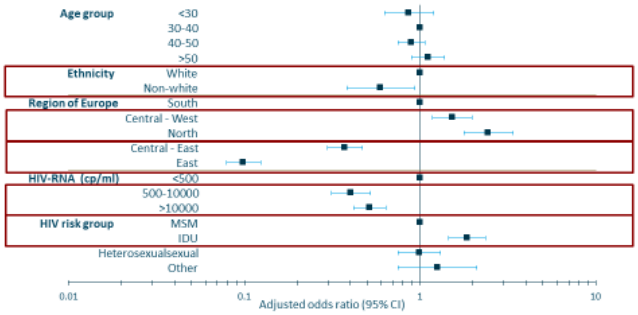


CoC by region at 1/1/2015



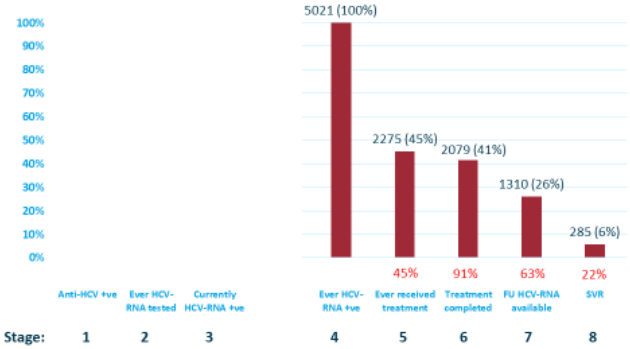
Evidence of difference between regions for all stage (p<0.001)

Odds of being HCV-RNA tested

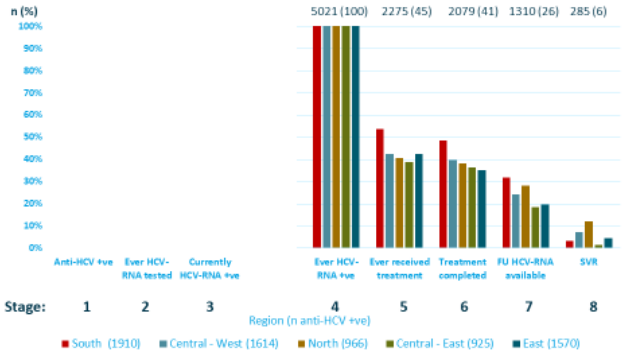


Model also included: gender, CD4 count, previous use of cART, mode of HCV transmission, stage of liver fibrosis, hepatitis B co-infection and prior AIDS diagnosis

Overall CoC at 1/1/2015

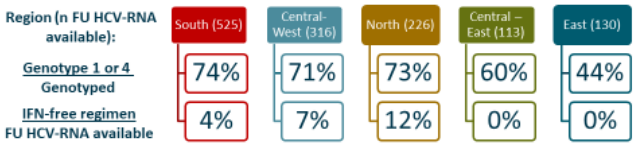


CoC by region at 1/1/2015



Evidence of difference between regions for all stage (p<0.001)

Low SVR?



- High proportion of individuals with genotype 1 or 4 that are hard to treat with IFN based regimens.
- Very low number of individuals received IFN-free treatments

Limitations

- Cohort individuals not necessarily representative of all HCV infected individuals (vulnerable groups, incarcerated population etc. not included in cohort)
- Not everyone has a HCV-RNA measurement at 12/24 weeks after completing treatment
- CoC was examined at a fixed point in time and therefore may be different if repeated now
- Differences in treatment guidelines, access to care and patient management approaches within countries and regions
- Did not look at the whole continuum, undiagnosed population not estimated

Summary

- Significant proportion of individuals lost at all stages of our proposed HCV continuum, with large variations between regions of Europe
- Region, ethnicity, and HIV viral load found to affect the odds of being HCV-RNA tested after anti-HCV +ve test
- Large gap between testing and starting treatment likely due to multifactorial reasons, including access to treatment, lack of DAAs and patient characteristics

Conclusions

- The proportion of individual achieving SVR was low, in part due to our definitions but improvements in HCV treatment cannot be realised unless barriers to care are addressed
- Our proposed definitions would allow repeated analyses over time to monitor changes in the break points
- Further work on defining the HCV CoC is urgently needed

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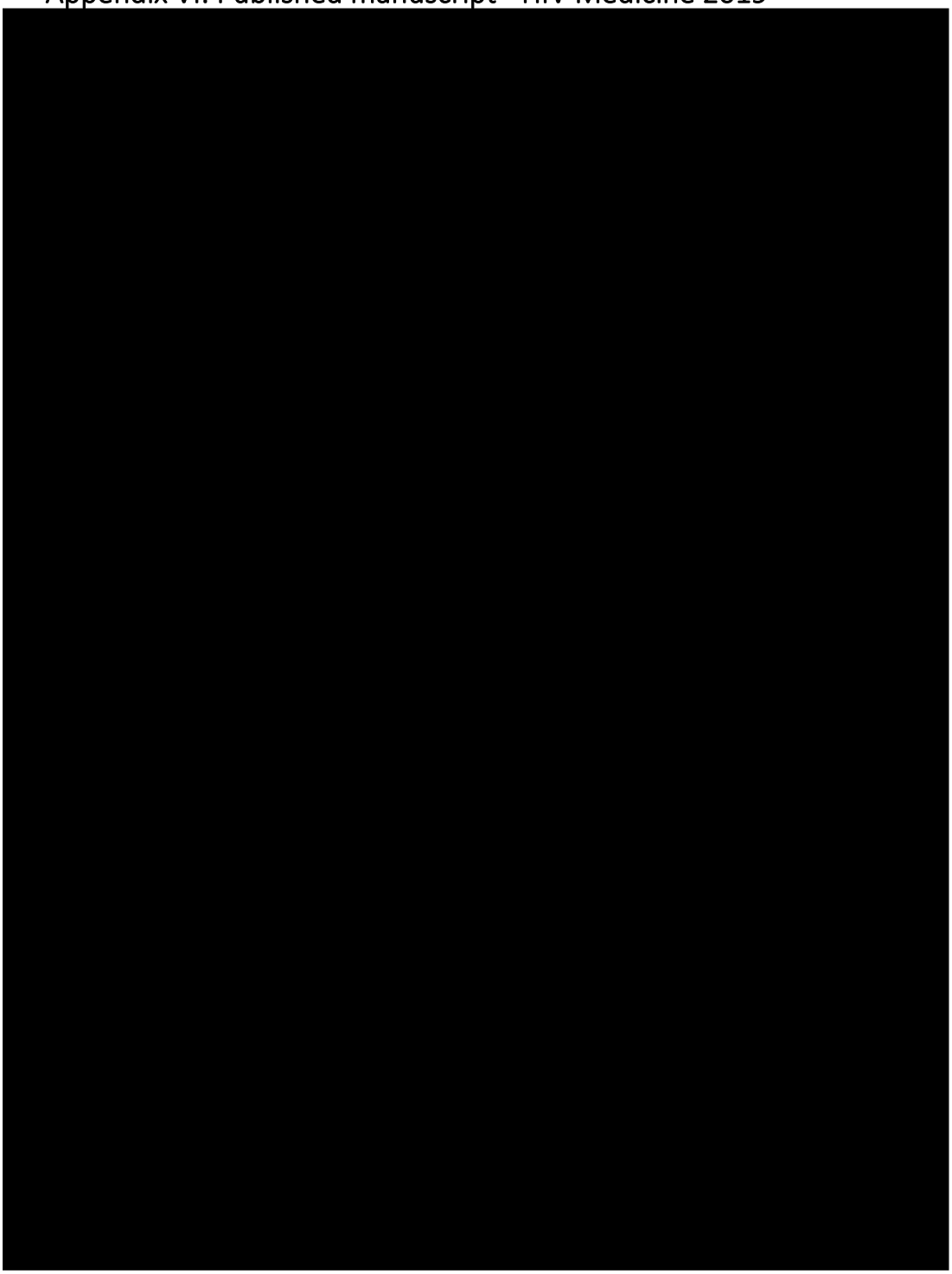
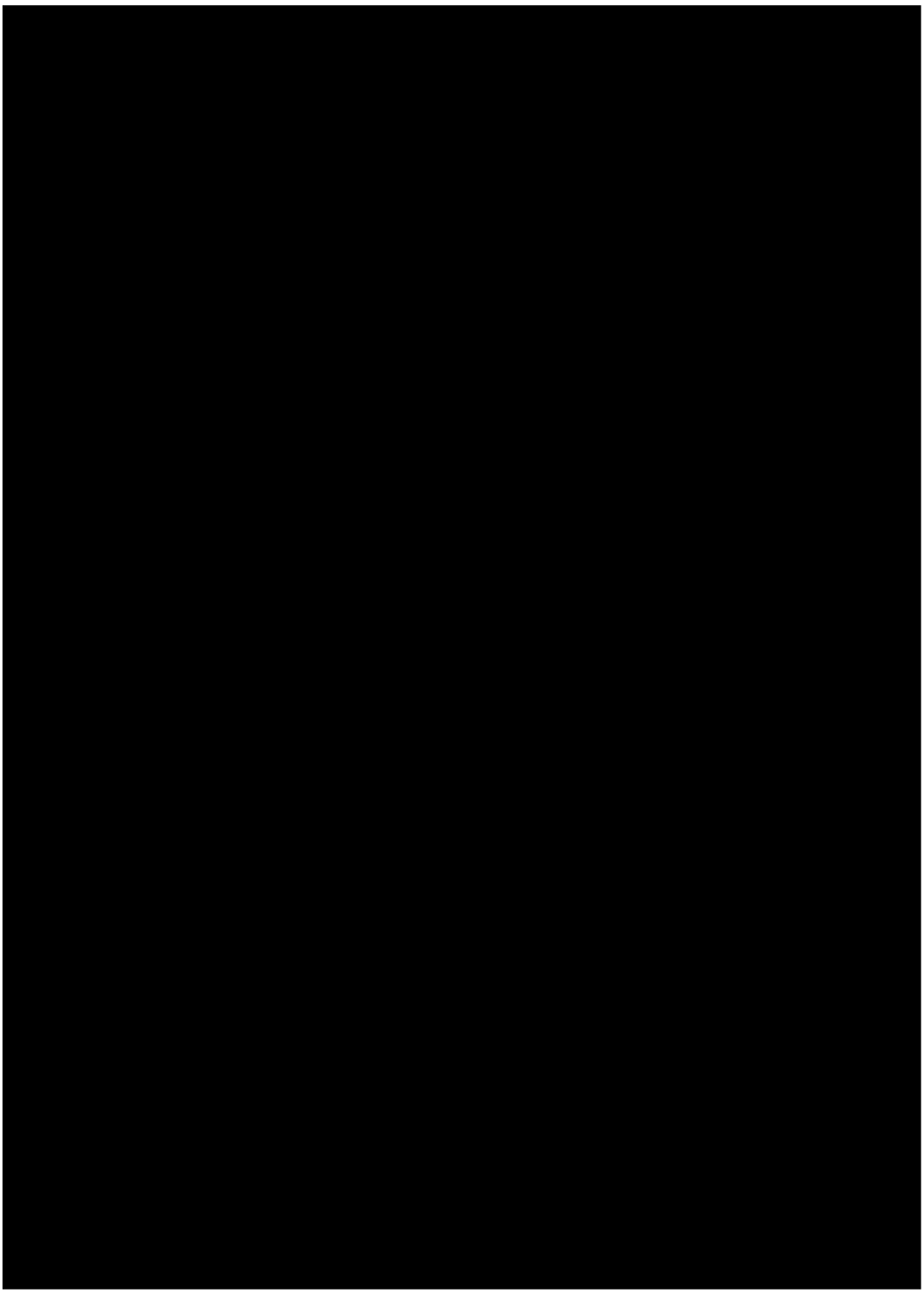
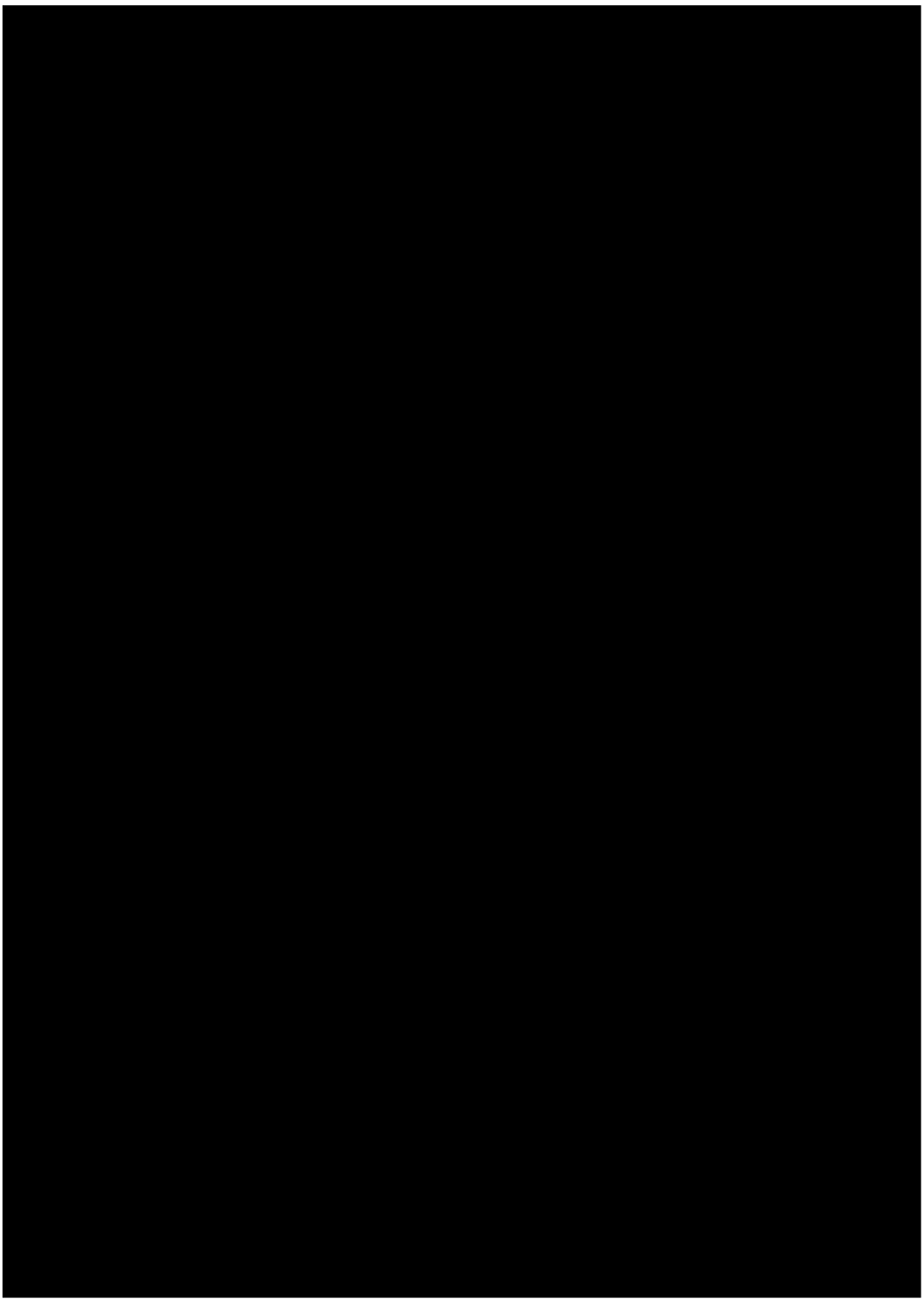
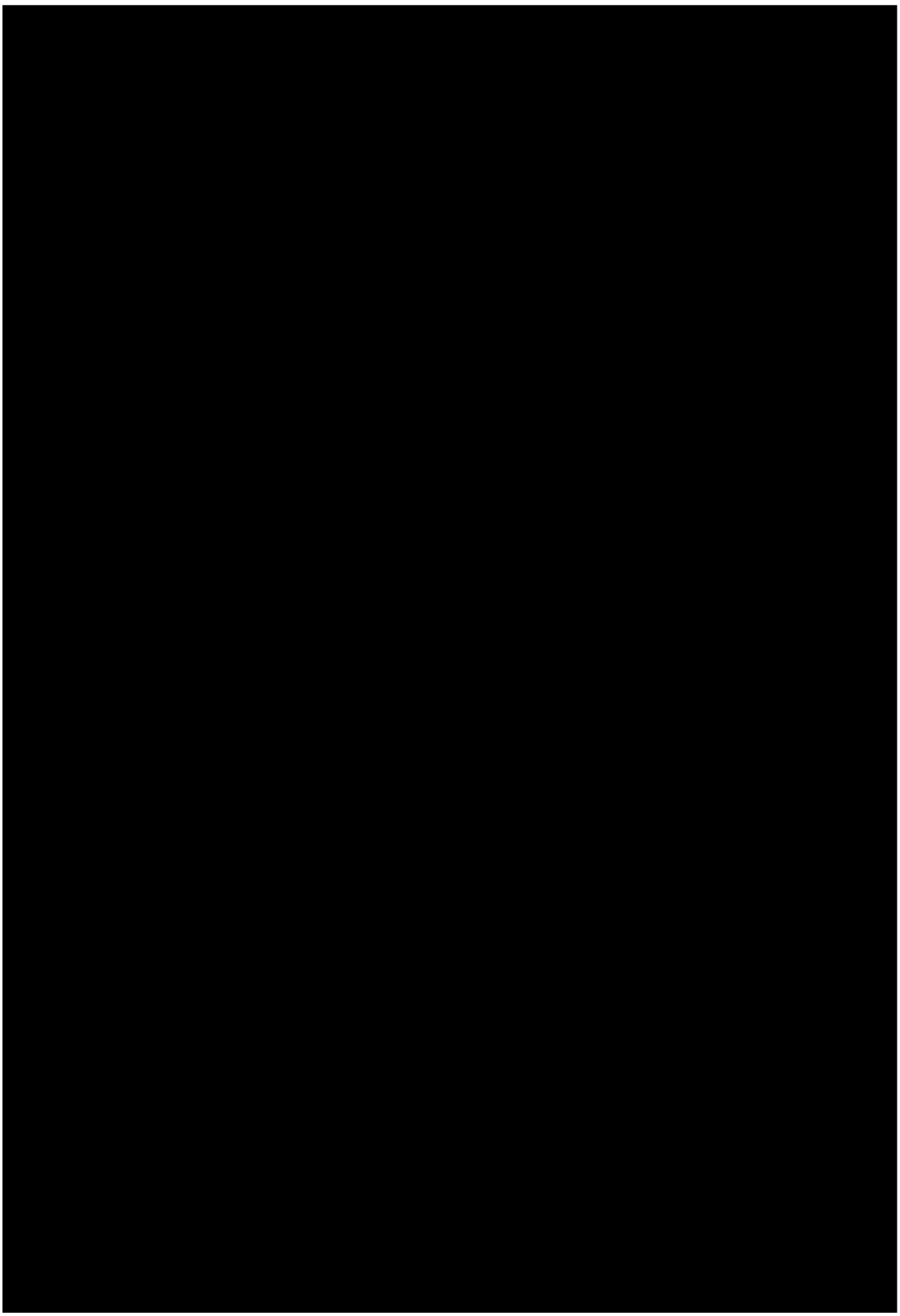
We thank the patients who participated in the study and the staff involved at the participating hospitals

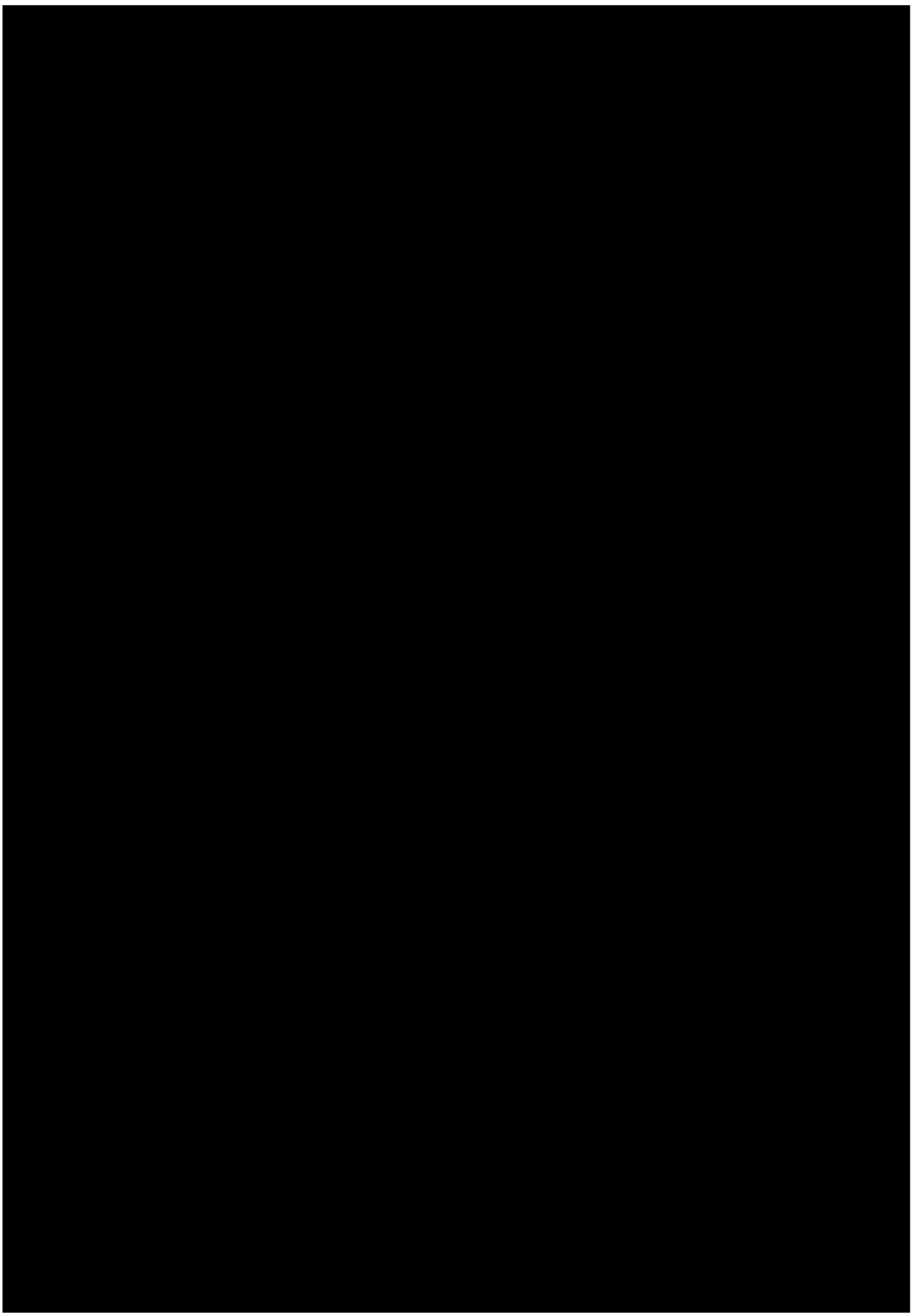
Appendix VI: Published manuscript - HIV Medicine 2019

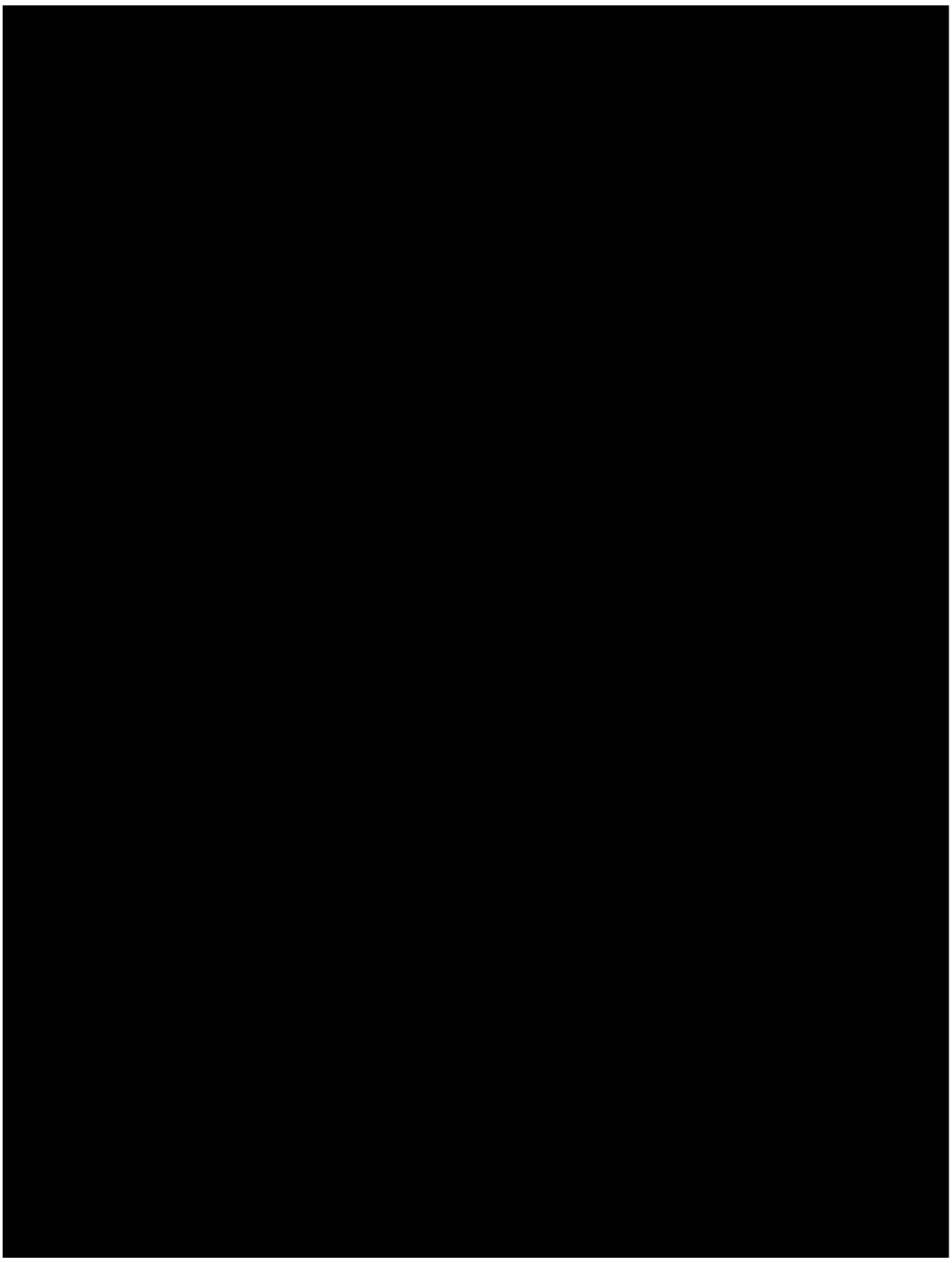


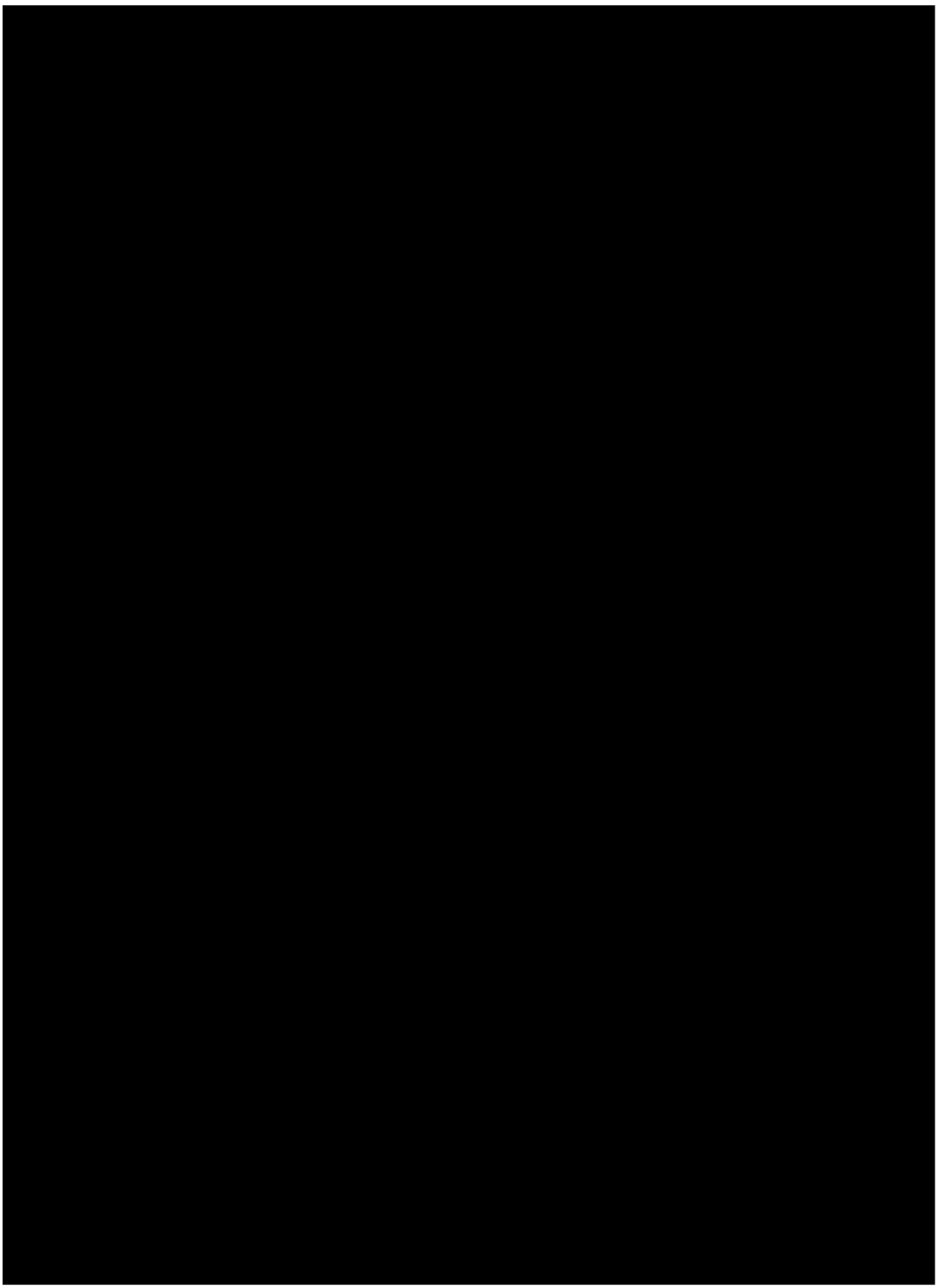


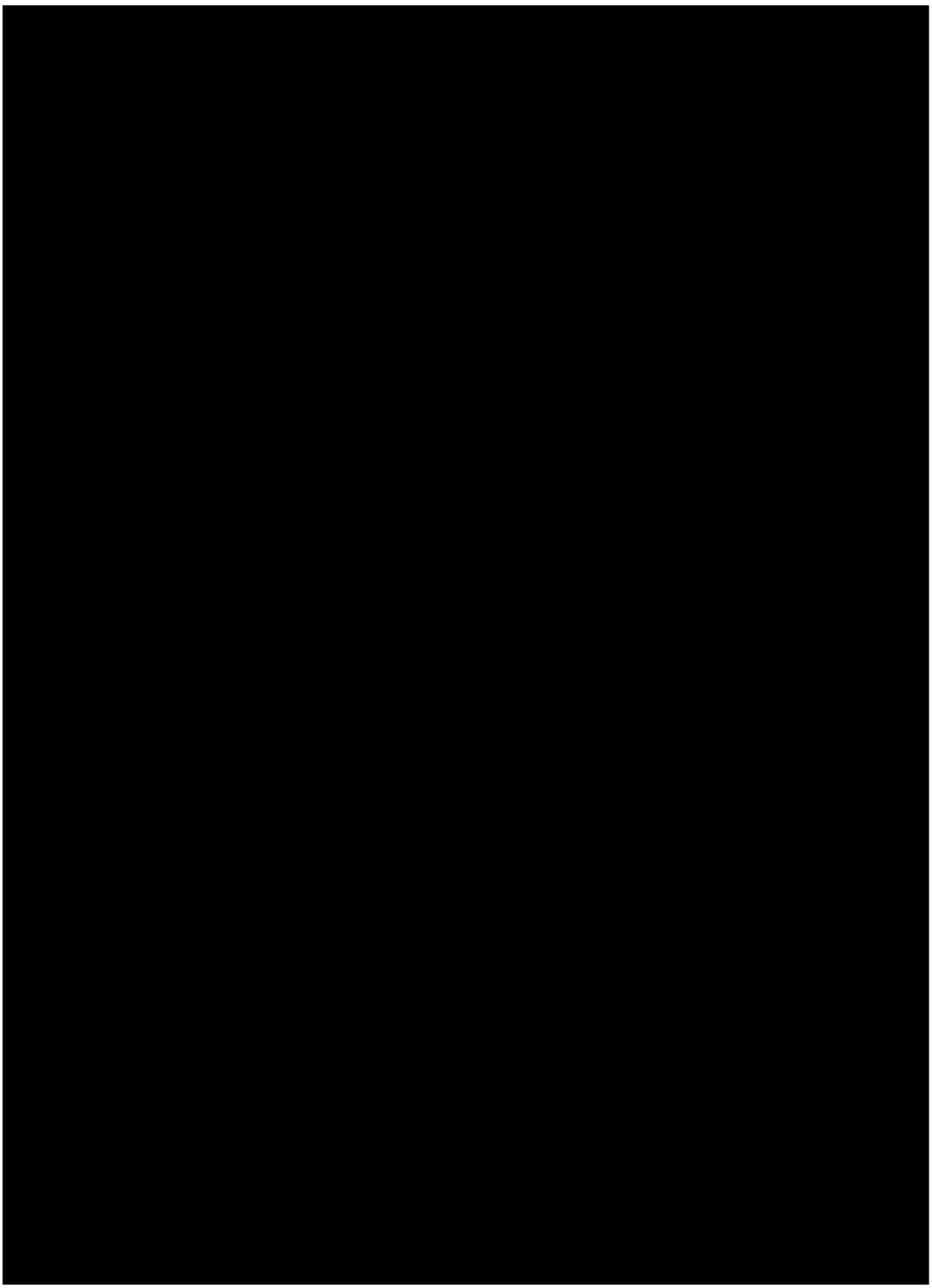


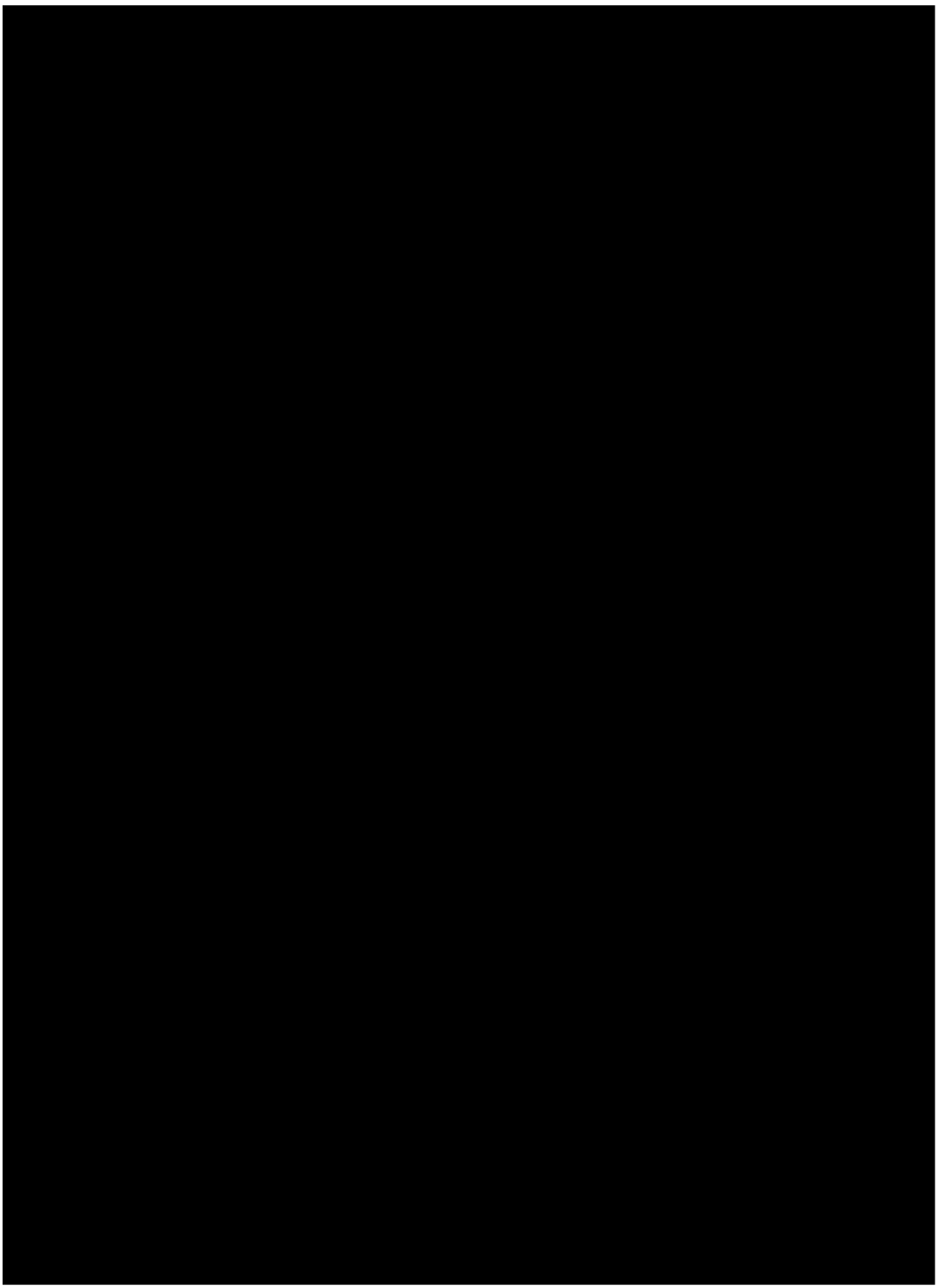


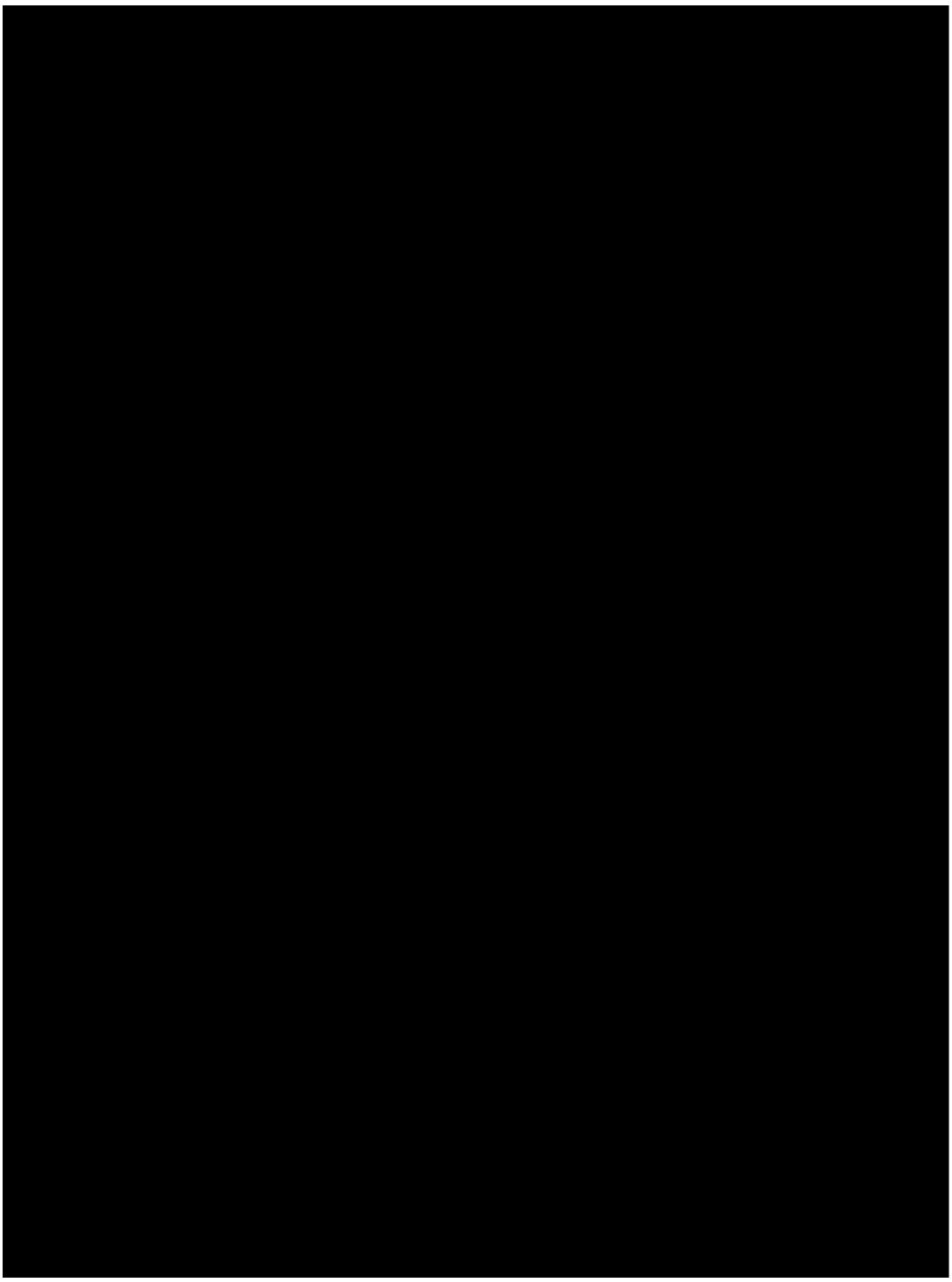












Appendix VII: The International Liver Congress 2018 - poster presentation

Efficacy and safety of IFN-free DAA HCV therapy in HIV/HCV co-infected persons: Results from a pan-European study

L PETERS[1], J. LUNDGREN[1], J. ROCKSTROH[2], R MATULIONYTE[3], C LEEN[4], E JABLONOWSKA[5], L ØSTERGAARD[6], A YAKOLEV[7], S BHAGANI[8], M SARCLETT[9], A CLARKE[10], K FALCONER[11], G WANDELER[12], P DOMINGO[13], F MALTEZ[14], M ZACCARELLI[15], N CHKHARTISVILI[16], J SZLAVIK[17], C STEPHAN[18], L FONQUERNIE[19], I AHO[20], and A. MOCROFT[21]

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INTRODUCTION

Real-life data on efficacy and safety of direct-acting antiviral (DAA) therapy in HIV/HCV co-infected patients from Europe, especially Eastern Europe, are still scarce[1-3].

The EuroSIDA study is a pan-European prospective observational cohort study that follows more than 3000 HIV positive individuals with chronic HCV co-infection in 35 countries in all geographical regions of Europe[4].

AIM

We aimed to investigate the efficacy of DAAs and the prevalence and reasons for premature discontinuation of DAAs in HIV/HCV co-infected individuals in the EuroSIDA study.

METHODS

Patients

Individuals starting a DAA therapy without interferon after 1 June 2014, during prospective follow-up in EuroSIDA. Persons were required to have a CD4 count and a viral load measured before baseline, defined as the date of starting the DAA regimen and be aged >16 at baseline. Persons without 12 weeks follow-up after stopping treatment were excluded from analyses.

Definitions of HCV treatment outcome

1. SVR – undetectable HCV-RNA at 12 weeks or later after stopping treatment
2. Treatment failure – detectable HCV-RNA at end of treatment or later
3. End-of-treatment (EOT) response – undetectable HCV-RNA after treatment stopped but prior to 12 weeks after stopping treatment, and no further HCV-RNA at or after 12 weeks
4. Unknown treatment response – persons with no HCV-RNA data at or after 12 weeks after stopping treatment excluding group 3.

Statistical methods

Logistic regression was used to calculate the odds of having a known response to DAAs, factors significant in univariate analyses (p<0.1) were included in multivariate models. Logistic regression was also used to examine factors associated with SVR.

RESULTS

Patients

Among 632 persons starting DAA, the median age was 51 years and 79% were males. 58% had a history of injecting drug use and 19% were men who have sex with men; 98.6% had HIV-RNA<500 copies/ml and median CD4 cell count was 600/mm^3; 32.4% had cirrhosis.

HCV treatment regimens

The most commonly used regimen was sofosbuvir + ledipasvir +/- ribavirin (n=289, 45.7%), followed by sofosbuvir + daclatasvir +/- ribavirin (n=126, 19.9%) and paritaprevir/ombitasvir + dasabuvir +/- ribavirin (n=84, 13.3%). Ribavirin was used in 272/632 (43%) DAA regimens.

HCV treatment outcome

Among persons with known SVR status, 433/468 (92.5%; 95% CI 90.1 – 94.9%) achieved SVR. The characteristics at time of starting treatment according to treatment outcome among those with known SVR status is shown in the table. 164 persons had unknown SVR status, 82 (50%) of whom were HCV-RNA negative at end of treatment and 82 (50%) with unknown treatment response. Patients with unknown SVR status were generally similar to those with known SVR status, but more likely to be from Central East and Eastern Europe, p=0.059). In an intention to treat analysis, 433/632 (68.5%; 95% CI 64.9-72.1) achieved SVR.

Factors associated with achieving SVR

In adjusted analysis, only white ethnicity vs. non-white ethnicity, fibrosis stage 0-1 vs. 2-4 and treatment duration per one week longer were associated with higher odds of SVR (figure).

Reasons for stopping HCV treatment earlier than scheduled

Thirty-one (4.9%; 95% CI 3.2-6.6%) out of 632 patients stopped one or more HCV drugs earlier than scheduled. The reasons were toxicity (N=11), viral failure (N=1), physician choice (N=3), drug out of stock (N=1), substance abuse (N=1), other (N=7) and unknown (N=7).

The median duration of treatment was 12 weeks for the 20 persons who interrupted treatment for non-toxicity reasons (IQR 8 – 18), 9 weeks for the 11 persons who interrupted treatment for toxicities (IQR 4 – 16) and was 12 weeks for the 601 persons who did not report any interruption (IQR 12-18 weeks), p=0.0011.

Adverse effects of DAA treatment

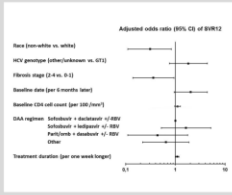
In nine out of 11 treatment stops due to toxicity, ribavirin was the only drug in the regimen that was stopped due to well-known adverse effects (anemia, rash, neuropathy, gastrointestinal symptoms). In only two cases were all drugs stopped early due to toxicity: 1) localized rash (sofosbuvir/ledipasvir) and 2) fatigue, dizziness and anorexia (simeprevir, sofosbuvir/velpatasvir, ribavirin).

Table
Characteristics at time of starting treatment in 468 persons with known SVR status

		SVR	Failure	P*
All (%)		433 (92.5)	35 (7.5)	
Age (median years)		52	51	0.52
Gender (%)	Male	340 (92.9)	26 (7.1)	0.56
	Female	93 (91.2%)	9 (8.8)	
Race (%)	White	401 (93.7)	27 (6.3)	0.0016
	Other	32 (80)	8 (20)	
Region (%)	South/Argentina	196 (92)	17 (8)	0.27
	West.	136 (95.8)	6 (4.2)	
	North	69 (89.6)	8 (10.4)	
	East/Central East	32 (88.9)	4 (11.1)	
HIV transmission risk (%)	IDU	256 (93.1)	19 (6.9)	0.58
	Non-IDU	177 (91.7)	16 (8.3	
HCV genotype (%)	1	234 (94.7)	13 (5.3)	0.26
	2	9 (90.0)	1 (10.0)	
	3	57 (91.9)	5 (8.1)	
	4	59 (86.8)	9 (13.2)	
	Unknown	74 (91.4)	7 (8.6)	
Fibrosis stage (%)	METAVIR 0/1	171 (96.1)	7 (3.9)	0.14
	METAVIR 2	64 (88.9)	8 (11.1)	
	METAVIR 3	72 (93.5)	5 (6.5)	
	METAVIR 4	125 (89.3)	15 (10.7)	
CD4 (median cells/µl)		632	516	0.063
HIV-RNA (% <500 cp/ml)		428 (92.6)	34 (7.4)	0.39

Among 632 persons completing DAA therapy, 164 had unknown SVR status and are excluded from this table.
*The p-value compares the characteristics of persons with SVR vs. failure

Figure
Factors associated with achieving SVR



Model adjusted for factors shown. Gender, age, region of Europe, HIV risk, HCV viral load, prior HCV treatment, HBsAg, nadir CD4 cell count and treatment duration ≤ 12 vs. >12 weeks all had p>0.1 in univariate analysis

CONCLUSIONS

- In a diverse population of HIV/HCV co-infected patients from all regions of Europe, DAA therapy resulted in an overall SVR rates of 92.5% which is similar to what has been shown for national cohorts in Western Europe[1-3].
- There were no significant differences in response across regions, although with limited power in Central East and Eastern Europe, and further follow-up is warranted to confirm these findings.
- Factors associated with higher odds of SVR were white race, fibrosis stage 0/1 and treatment duration per one week longer.
- A quarter of all persons who had completed treatment did not have a follow-up HCV-RNA to determine SVR12.This could either reflect other follow-up schedules than what is seen in clinical trials; treatment outside the HIV clinic, loss to follow-up or data not reported and requires further data to clarify.
- Only 5% stopped one or more HCV drugs earlier than scheduled, and a third of these were due to toxicity mostly related to well-know adverse effects of ribavirin. We saw no new safety signals for DAAs.

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REFERENCES

[1]**Piroth L et al.** Efficacy and safety of direct-acting antiviral regimens in HIV/HCV-co-infected patients - French ANRS CO13 HEPAVIH cohort. *J Hepatol. 2017 Jul;67(1):23-31*

[2]**Boesecke et al.** Liver Cirrhosis as a Risk Factor for Direct-Acting Antiviral Therapy Failure in Real-Life Hepatitis C Virus/Human Immunodeficiency Virus Coinfection. ***Open Forum Infect Dis. 2017 Jul 27;4(3)***

[3]**Béguelin C et al.** Trends in HCV treatment uptake, efficacy and impact on liver fibrosis in the Swiss HIV Cohort Study. *Liver Int. 2018 Mar;38(3):424-431.*

[4]**Peters L et al.** Uptake of HCV Therapy in HIV/ HCV Coinfected Patients across Europe in the Era of Direct-Acting Antivirals, AASLD, Nov. 11-15, 2016, Abstract 1954

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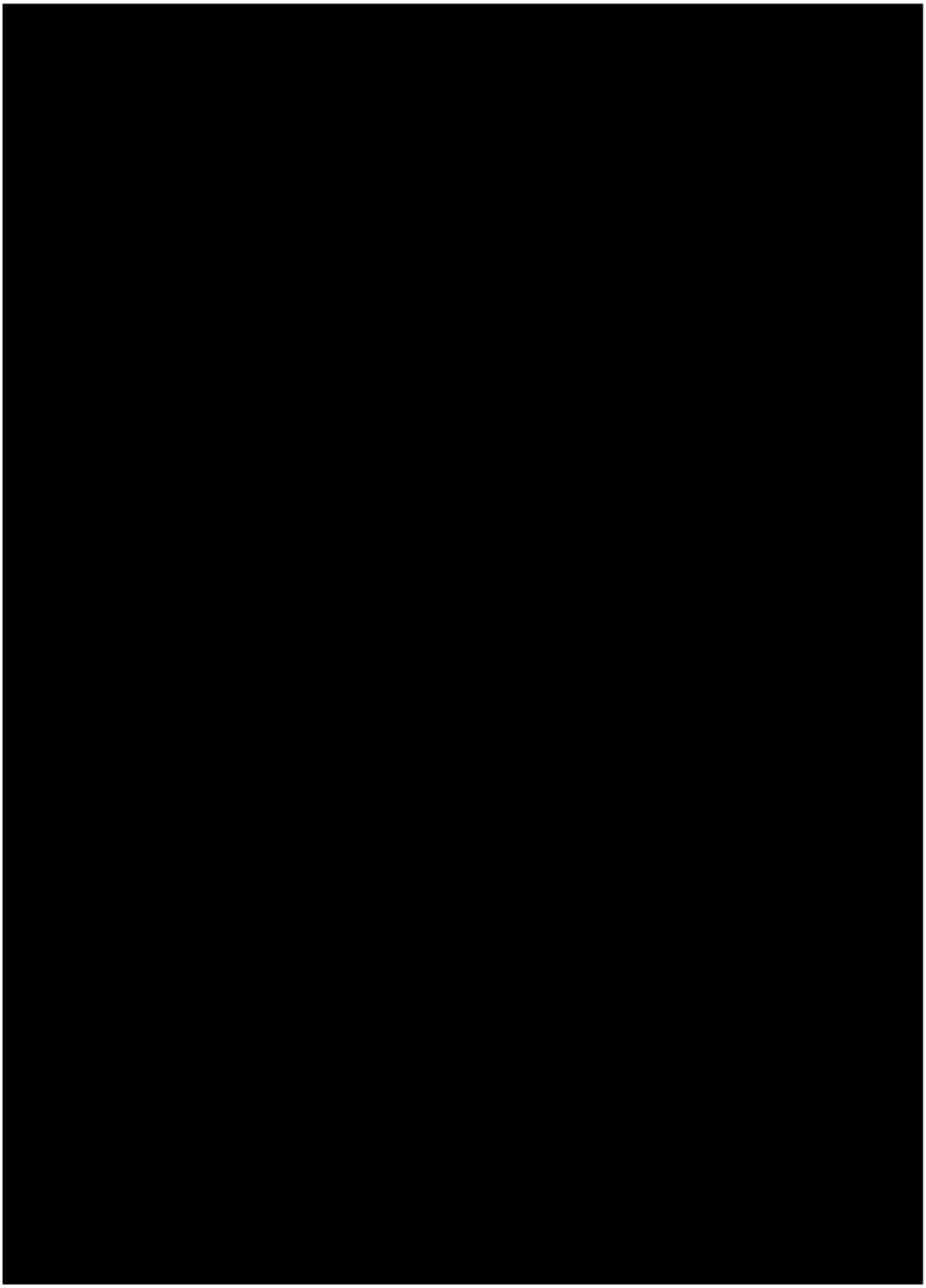
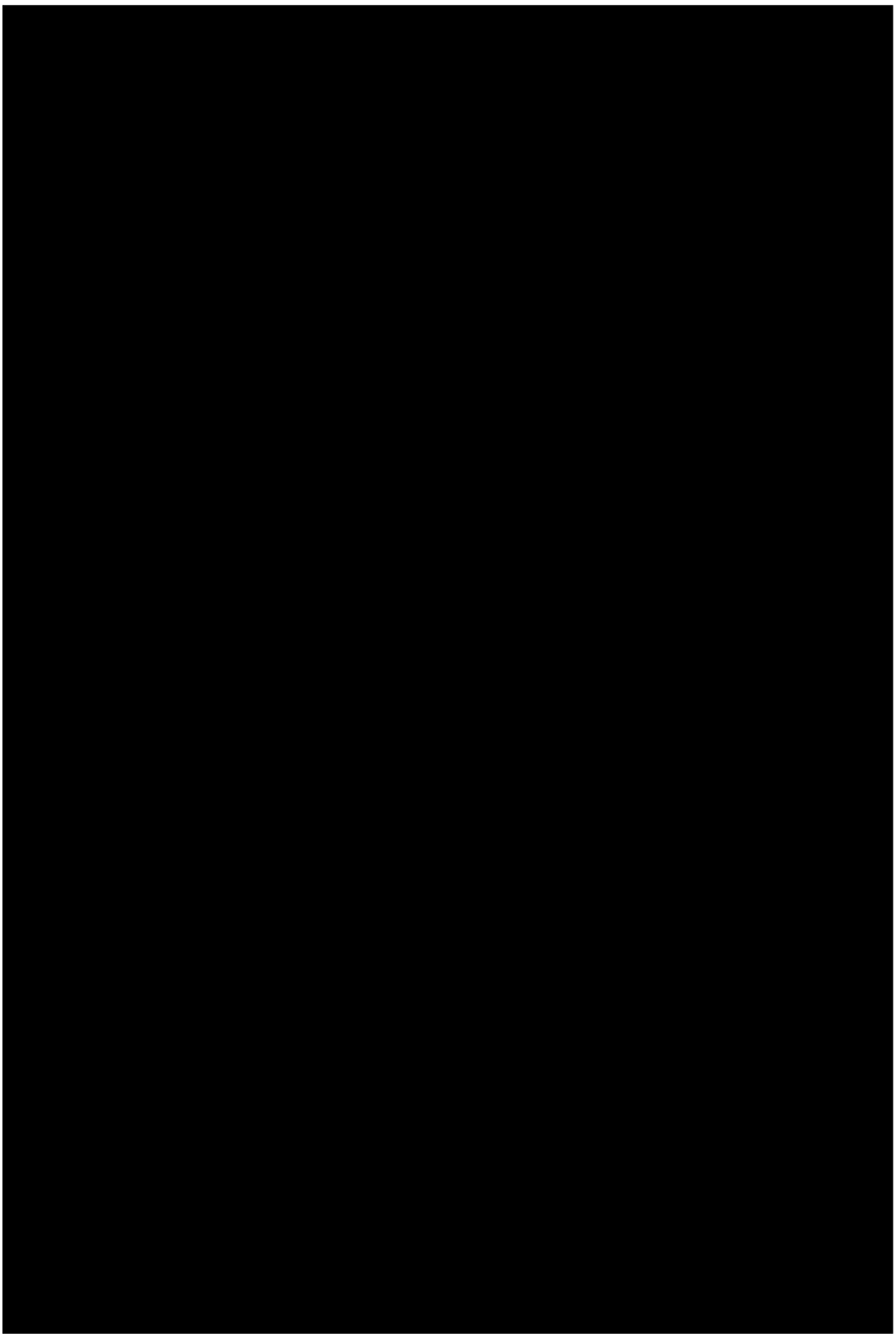
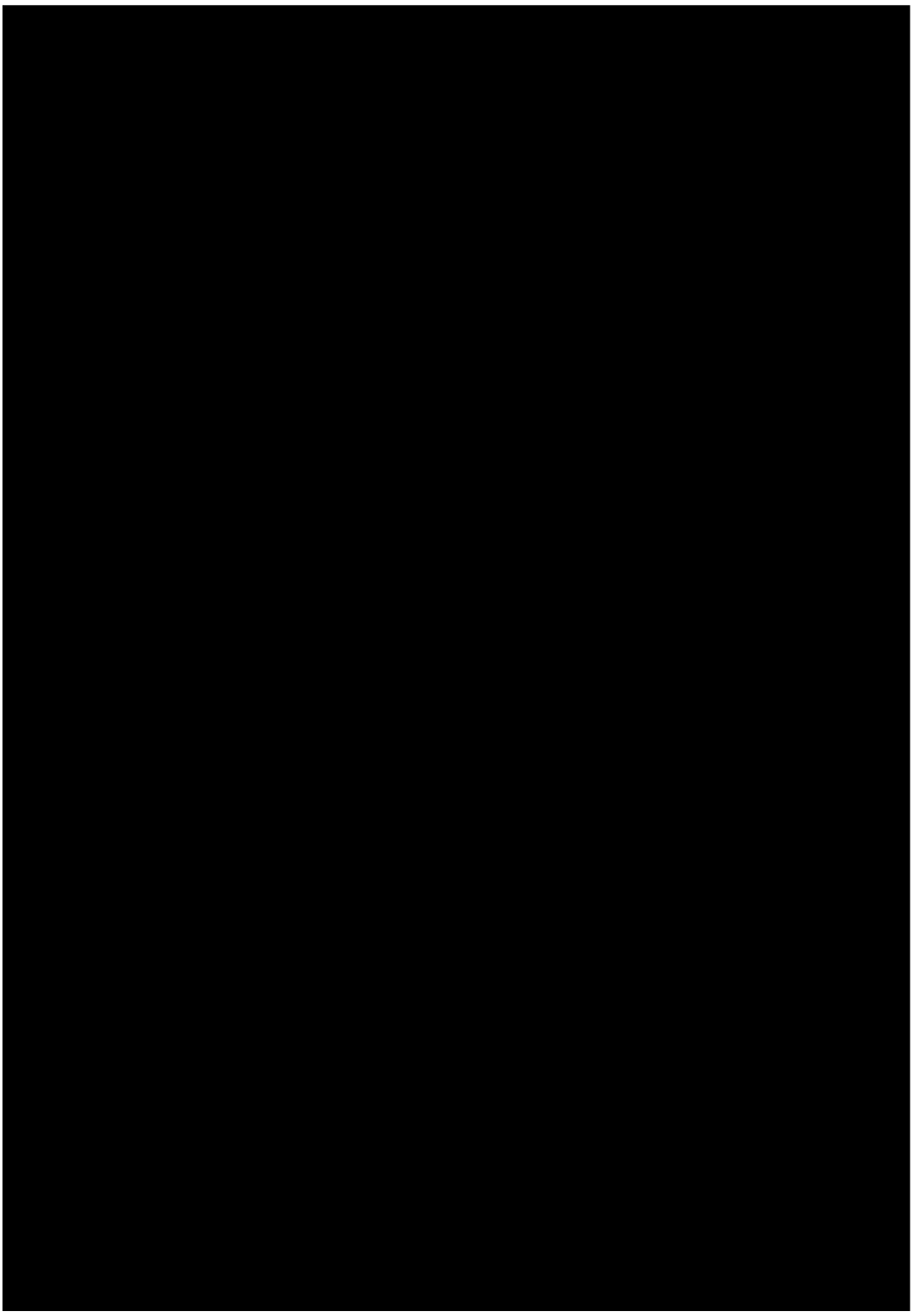
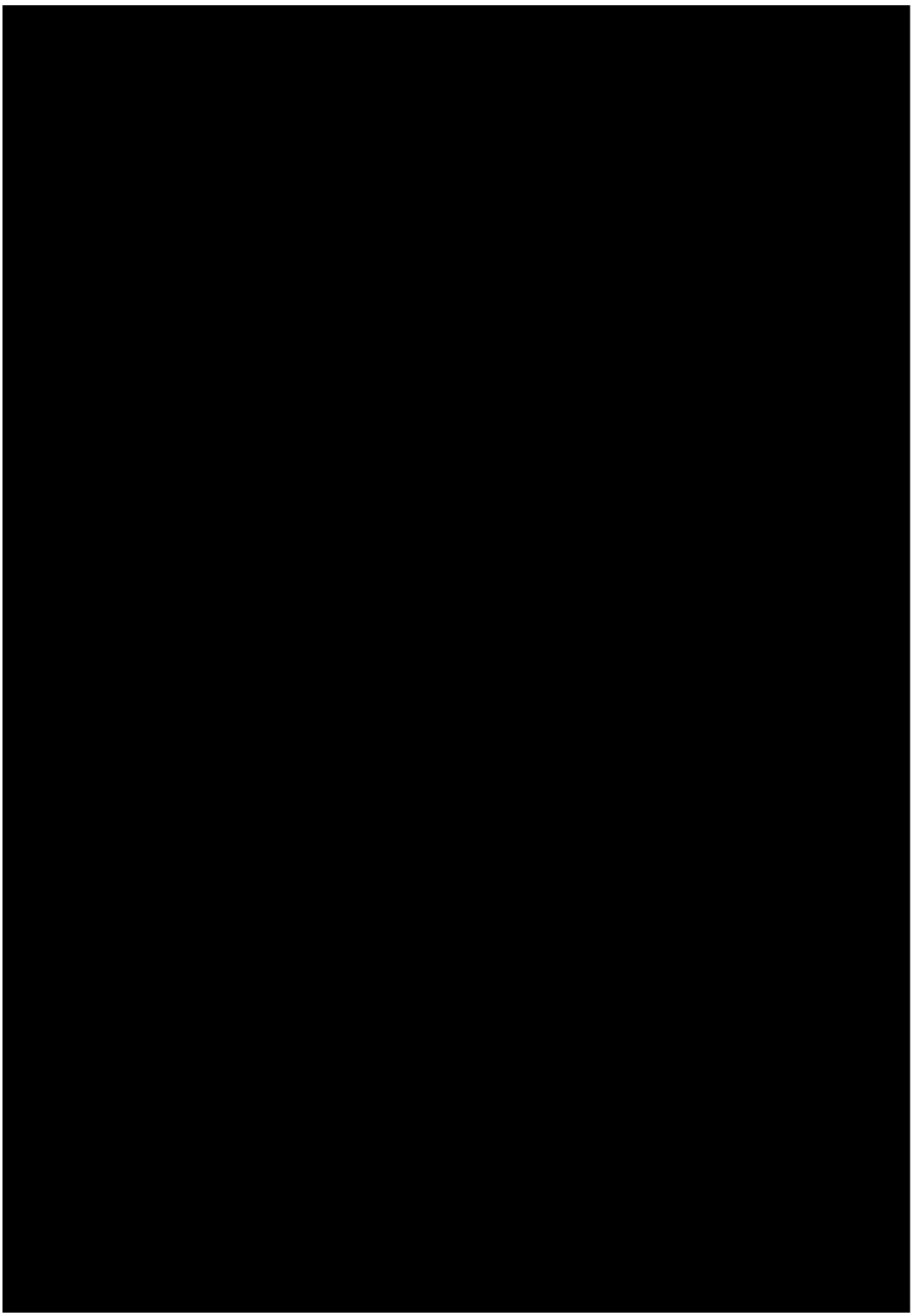
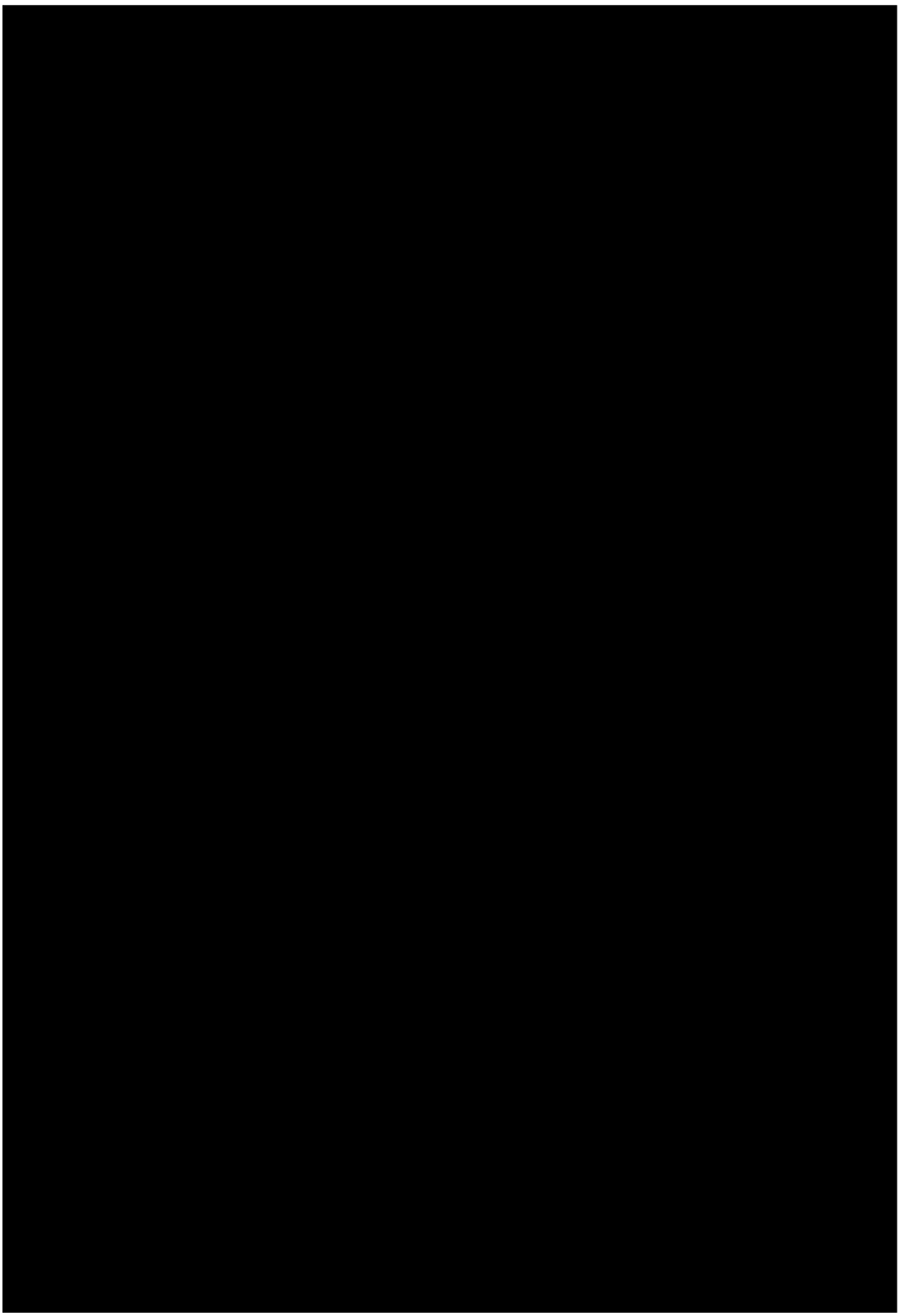
Appendix VIII: Published manuscript - Journal of Acquired Immune Deficiency Syndromes 2021

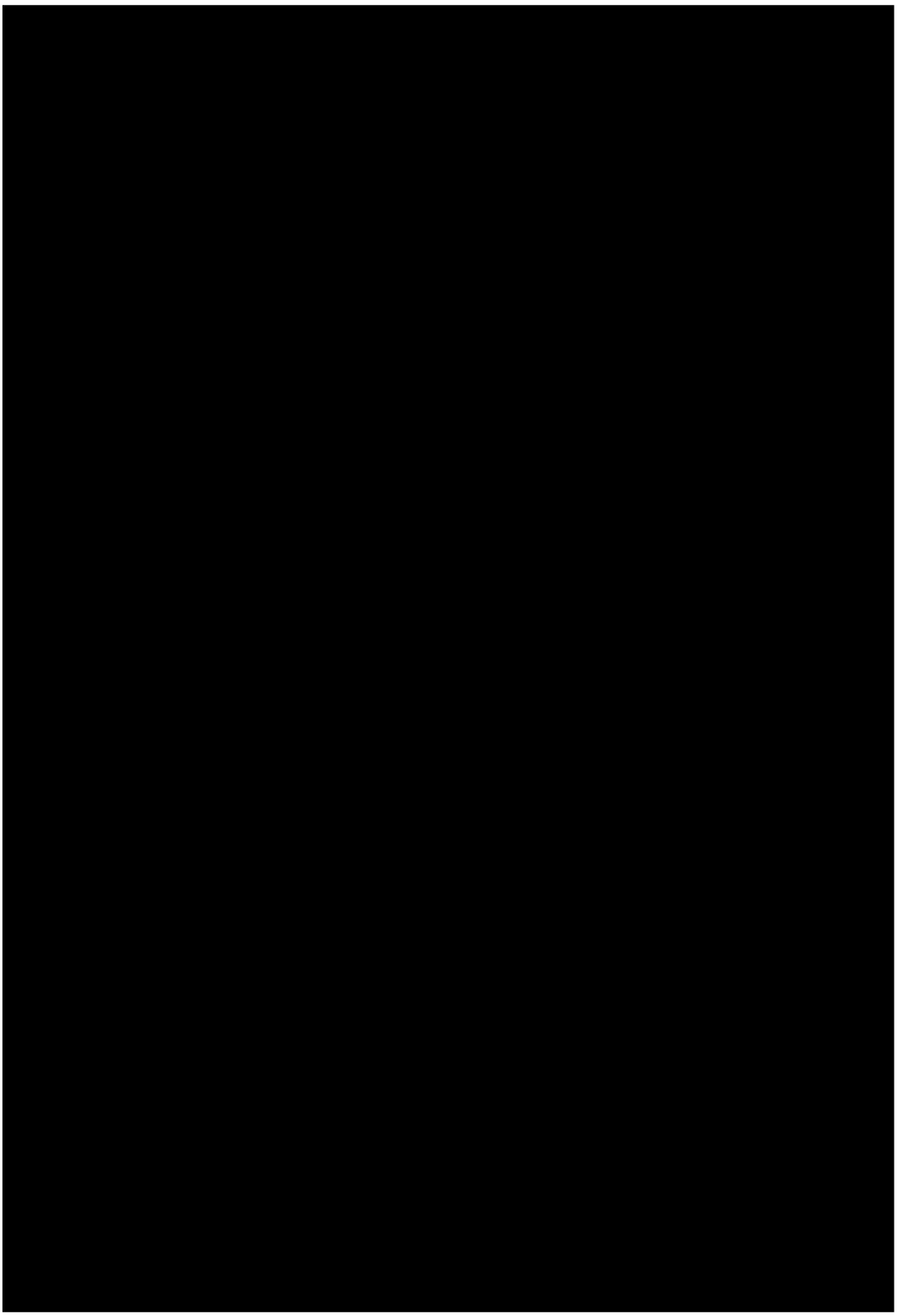


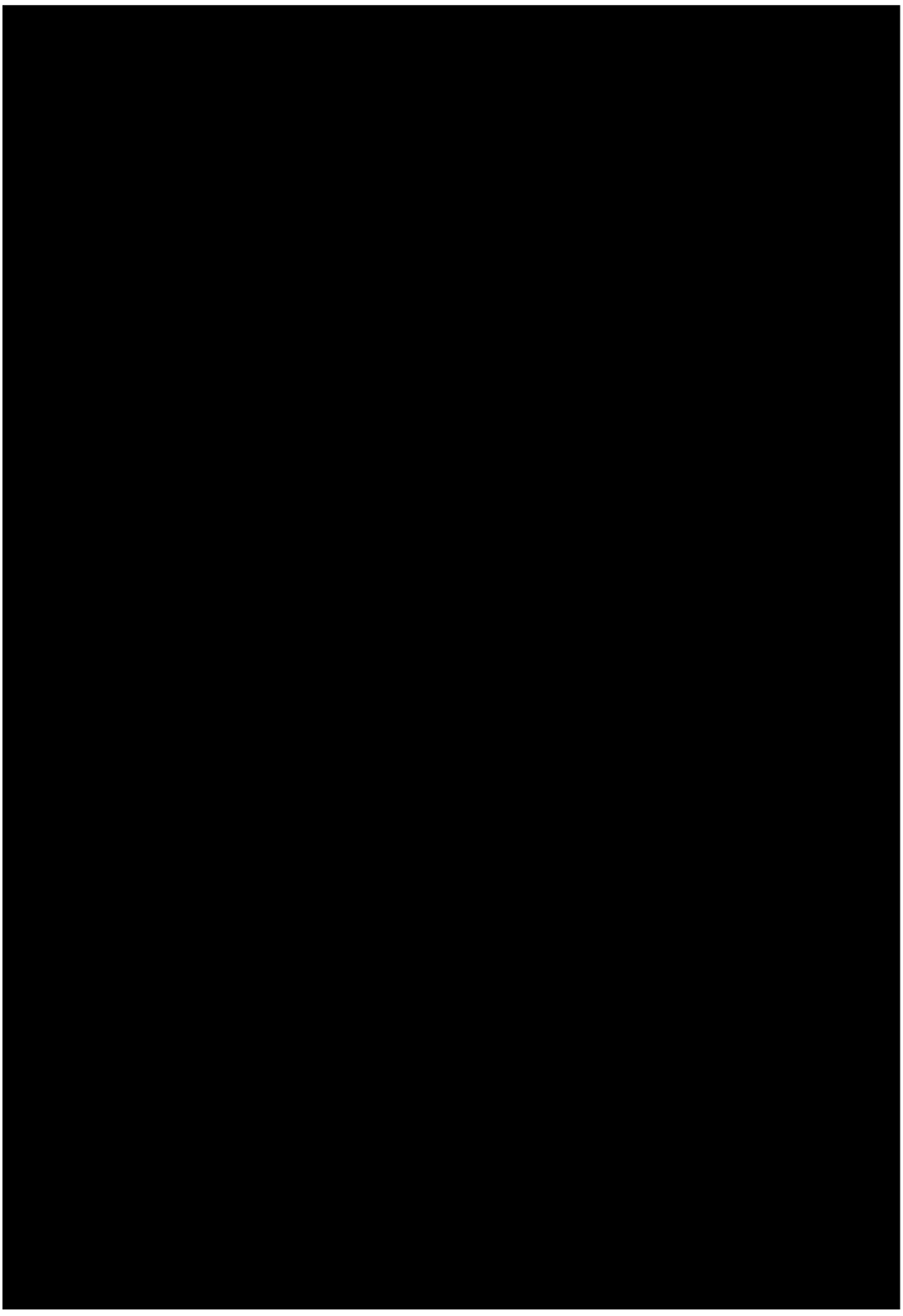


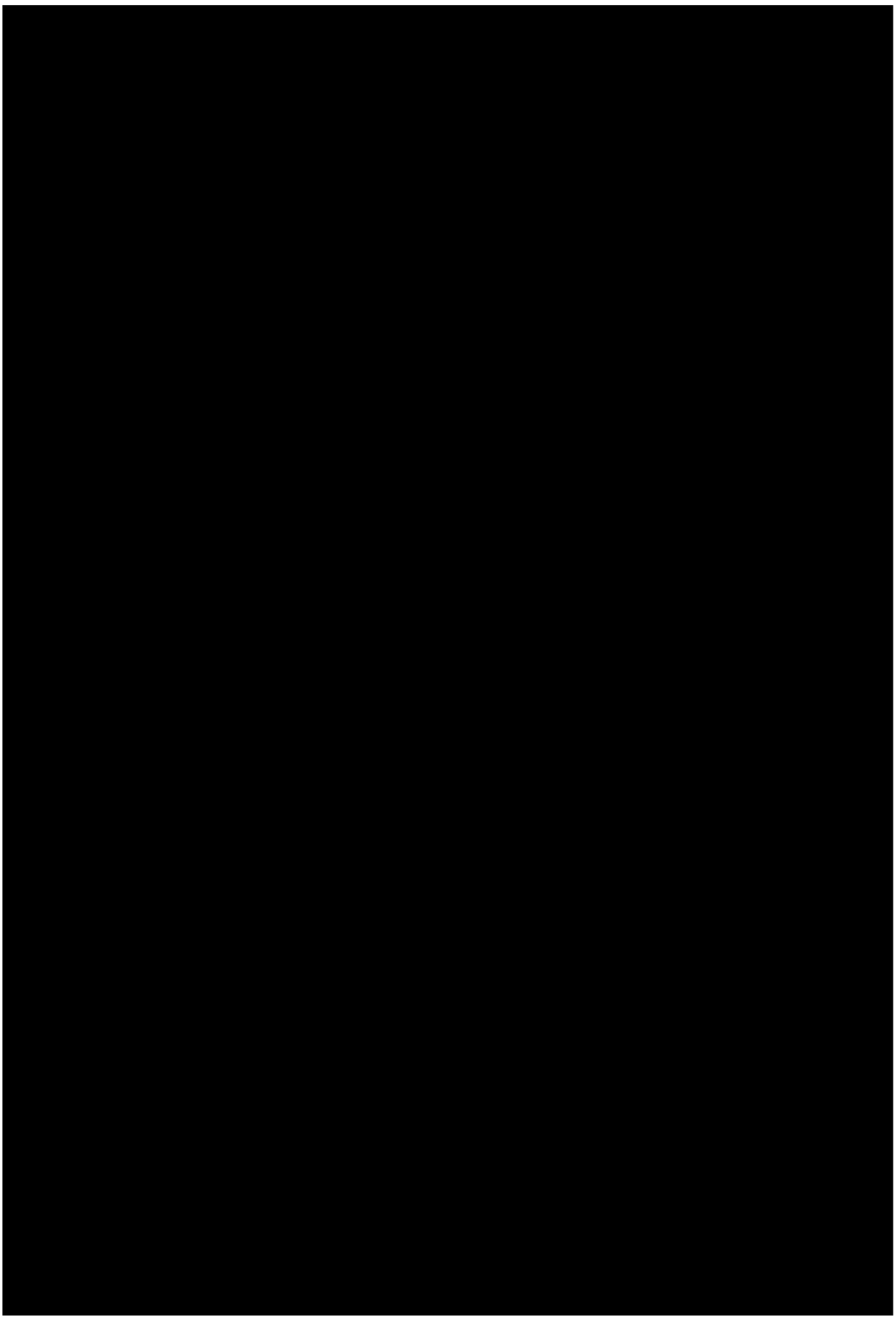


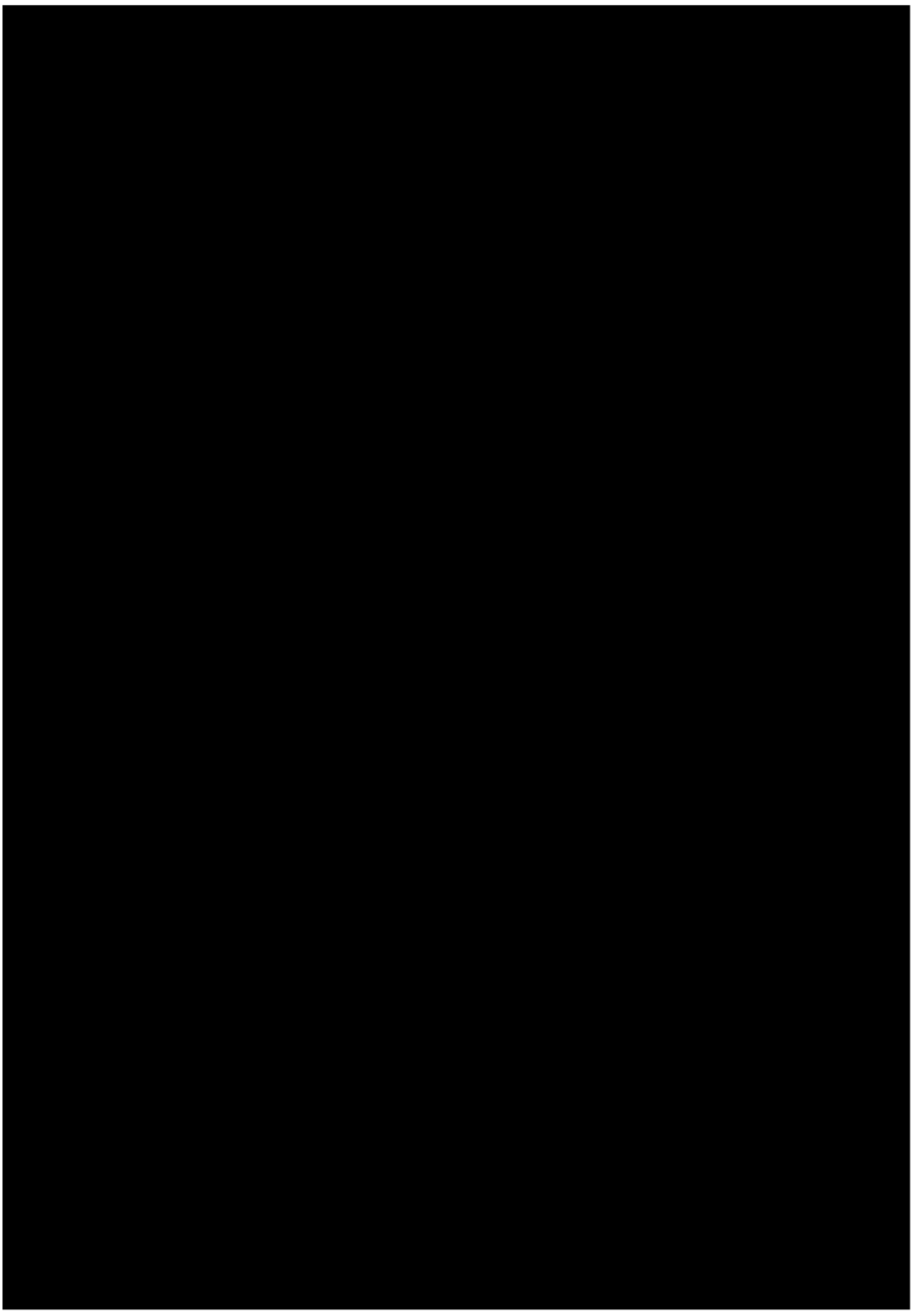


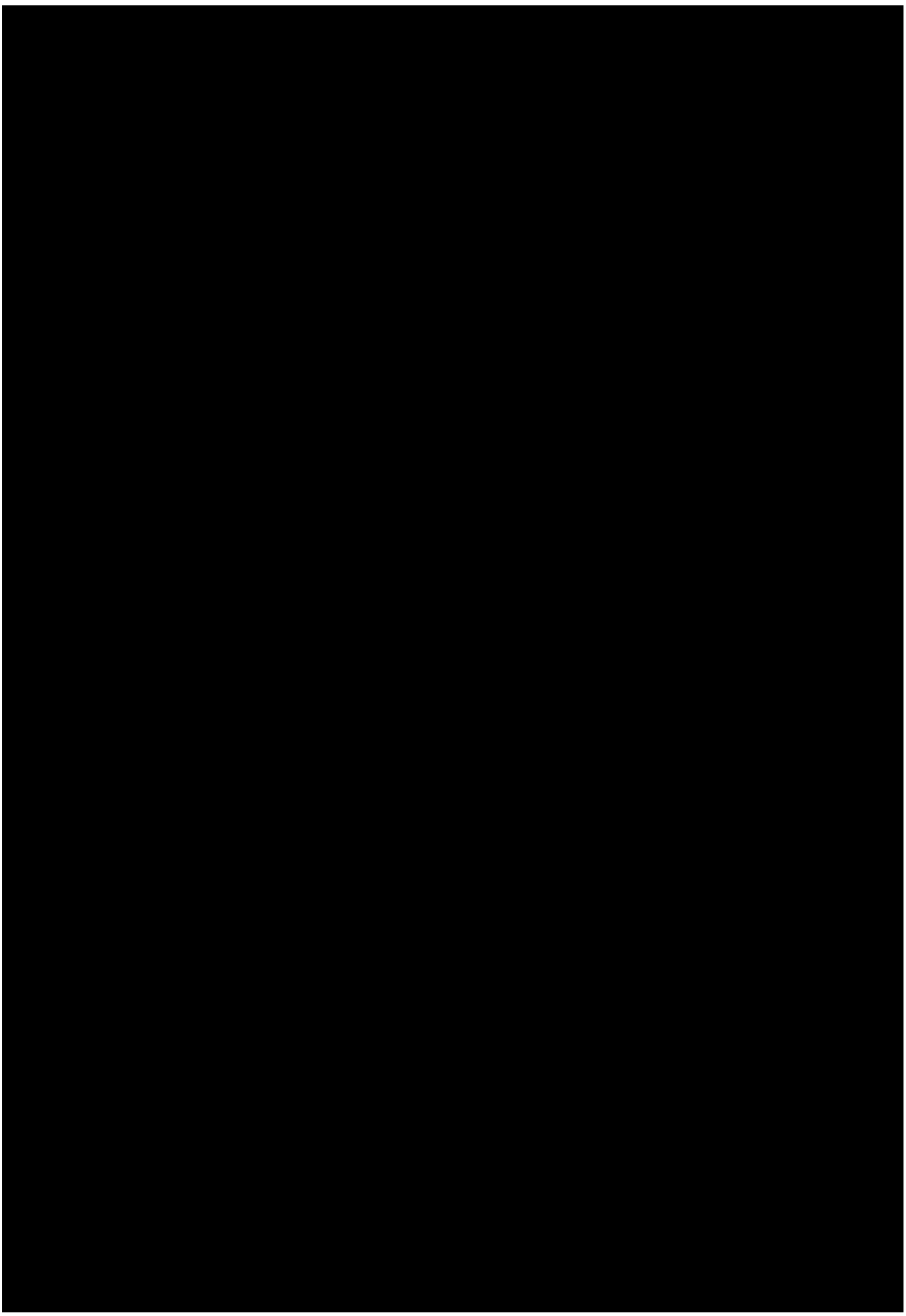












Appendix IX: International HIV/Viral Hepatitis Co-Infection Meeting 2019 - poster presentation

Poster No. 833

IAS 2019

HCV reinfection among HIV/HCV co-infected individuals in Europe

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BACKGROUND

In the absence of a vaccine against HCV, those who have been cured are still at risk of reinfection. The overall risk is generally low, however reinfection is of particular concern among HIV co-infected individuals (injection drug users (IDU), and HIV positive men who have sex with men (MSM)), as well as HIV negative MSM who use PrEP[1,2]. While Directly Acting Antivirals (DAAs) can clear HCV in nearly all HIV/HCV co-infected individuals, high rates of reinfection may hamper efforts to eliminate HCV in this population[3].

AIMS

- To examine the risk of reinfection after achieving sustained virological response (SVR) in HIV/HCV co-infected individuals in Europe
- To assess whether the risk of reinfection varies depending on HIV risk group, treatment regimen (interferon-based regimens vs interferon-free DAAs), regional differences, or sociodemographic variables

METHODS

- Individuals from EuroSIDA that achieved SVR12 or SVR24, with ≥24 months follow-up and ≥1 HCV-RNA test after SVR were included (Figure 1)
- Factors associated with the odds of reinfection were assessed using multivariable logistic regression
- Reinfection was defined as being HCV-RNA positive, HCV genotyped or receiving HCV treatment within 24 months of SVR12/SVR24

RESULTS

- There were 585 individuals included in this analysis
- The median age of the study population was 47 (interquartile range (IQR) 41-52 years), 77.4% were male, 77.8% were white, 48.0% were IDUs, 30.3% were MSM, and the majority received an interferon-based regimen (475, 81.2%) (Table 1)
- 78 (13.3%, 95% confidence interval (CI) 10.6%-16.0%) individuals were re-infected within 24 months
- Central-West Europe had the highest proportion of reinfections (18.0%), while Southern Europe had the lowest (4.9%; p=0.0030) (Figure 2). Reinfections in MSM were 16.4% and 13.5% in IDUs (p=0.1471)
- After adjustment, Central-West and East/Central-East Europe had higher odds of reinfection (compared to Southern Europe; Figure 1), as did those with CD4 count >500 cells/mm^3, or fibrosis ≥F3. Females, and those who achieved SVR after 2014 had a lower odds of reinfection (Figure 3)
- There was no statistically significant association between age, HIV risk group, or the use of interferon-free DAA regimens, with reinfection, although all had wide confidence intervals

LIMITATIONS

- We cannot rule out that some late relapses could have been misclassified as reinfection, though this is unlikely[1]
- Clinics may have targeted HCV-RNA testing to those at highest risk of reinfection or with signs of reinfection

CONCLUSIONS

- The proportion of reinfections among HIV/HCV co-infected individuals within 24 months of achieving SVR was 13%
- Active surveillance to detect early HCV reinfection with an offer of early treatment is essential as is harm reduction in those treated to reduce rates of reinfection, and reach the goal of elimination by 2030[4]

Figure 1. Flowchart for inclusion in analysis

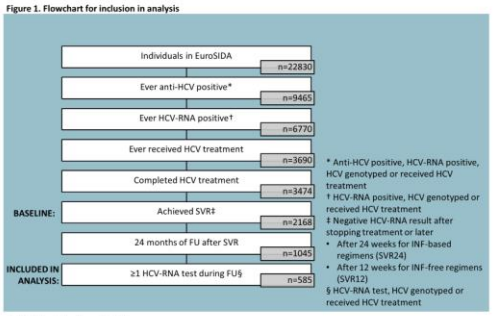


Table 1. Baseline characteristics

		Overall n (%)	Not reinfected n (%)	Reinfected n (%)	P-value
Overall		585 (100.0)	507 (86.7)	78 (13.3)	
Age (years)	Median (IQR)	47 (41-52)	47 (41-52)	47 (42-51)	0.9358
Gender	Male	453 (77.4)	385 (85.0)	68 (15.0)	0.0270
	Female	132 (22.6)	122 (92.4)	10 (7.6)	
Ethnicity	White	455 (77.8)	408 (89.7)	47 (10.3)	0.0002
	Global Majority	7 (1.2)	7 (100.0)	(0.0)	
	Unknown	123 (21.0)	92 (74.8)	31 (25.2)	
HIV risk group	MSM	177 (30.3)	148 (83.6)	29 (16.4)	0.1471
	IDU	281 (48.0)	243 (86.5)	38 (13.5)	
	Other	127 (21.7)	116 (91.3)	11 (8.7)	
CD4 count (cells/mm^3)	Median (IQR)	514 (346-695)	503 (344-695)	546 (384-704)	0.5787
HCV treatment	Interferon	475 (81.2)	412 (86.7)	63 (13.3)	0.9174
	DAA	110 (18.8)	95 (86.4)	15 (13.6)	
Year SVR	<2014	312 (53.3)	261 (83.7)	51 (16.3)	0.0219
	≥2014	273 (46.7)	246 (90.1)	27 (9.9)	
Fibrosis	<F3	415 (70.9)	363 (87.5)	52 (12.5)	0.4080
	≥F3*	46 (7.9)	37 (80.4)	9 (19.6)	
HCV genotype	G1	236 (40.3)	204 (86.4)	32 (13.6)	0.9906
	G2 - G4	183 (31.3)	159 (86.9)	24 (13.1)	
cART	No	46 (7.9)	42 (91.3)	4 (8.7)	0.4963
	Yes	539 (92.1)	465 (86.3)	74 (13.7)	
Prior HCV treatment	No	427 (73.0)	374 (87.6)	53 (12.4)	0.2813
	Yes	158 (27.0)	133 (84.2)	25 (15.8)	

*Either a biopsy (eMETAVIR stage F3), APRI (score >1.5), hyaluronic acid (>160ng/mL) or FibroScan (>9.5kPa) test

Figure 2. Reinfection by region

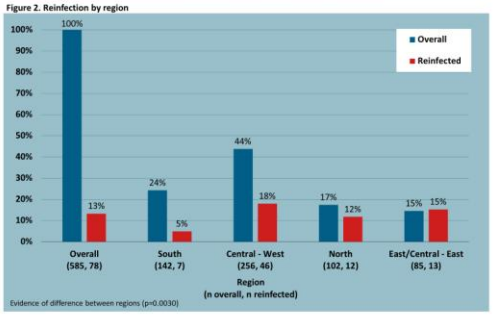
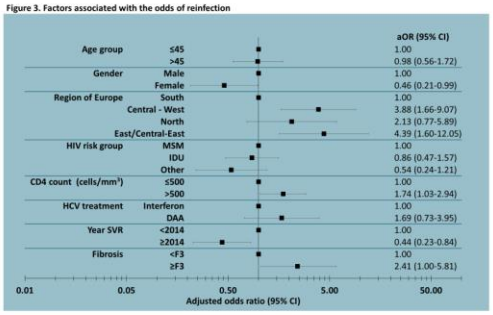


Figure 3. Factors associated with the odds of reinfection



REFERENCES

[1]**Simmons B**. Clin Infect Dis. 2015;62(6):683–94. [2]**Ingiliz P**. J Hepatol. 2017;66(2):282–7. [3]**Virlogeux V**. BMC Med. 2017;15(1):1–11. [4]**WHO**. Global hepatitis report, 2017. 2017

EuroSIDA

UCL INSTITUTE FOR GLOBAL HEALTH

The EuroSIDA Study Group:
https://chip.dk/Studies/EuroSIDA

Download poster at: www.chip.dk

Appendix X: International AIDS Society Conference on HIV Science 2019 - oral presentation

HCV reinfection among HIV/HCV co-infected individuals in Europe

Sarah Amele, Lars Peters, Alison Rodger, Linos Vandekerckhove, Thomas Benfield, Ana Milinkovic, Claudine Duvivier, Hans-Jürgen Stellbrink, Helen Sambatakou, Nikoloz Chkhartishvili, Luis Caldeira, Montse Laguno, Pere Domingo, Gilles Wandeler, Robert Zangerle, Elena Kuzovatova, Gordana Dragovic, Brygida Knysz, Raimonda Matulionyte, Jürgen K. Rockstroh, Jens D. Lundgren, and Amanda Mocroft on behalf of the EuroSIDA study group

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Share your thoughts on this presentation with #IAS2019

Presenter Disclosure Information

Sarah Amele

disclosed no conflict of interest.

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Background

- In the absence of a vaccine against HCV, those who have been cured are still at risk of reinfection
- The overall risk is generally low, however reinfection is of particular concern among HIV co-infected individuals (PWID and HIV positive MSM), and HIV negative MSM on PrEP[1,2]
- While Directly Acting Antivirals (DAAs) can clear HCV in nearly all HIV/HCV co-infected individuals, high rates of reinfection may hamper efforts to eliminate HCV in these populations[3]
- Important to describe the prevalence of reinfection, and how this varies depending on risk group and region

[1]Simmons B. Clin Infect Dis. 2015;62(6):683–94. [2]Ingiliz P. J Hepatol. 2017;66(2):282–7. [3]Virlogeux V. BMC Med. 2017;15(1):1–11.

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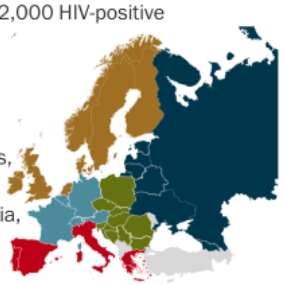
Aims

- To examine the risk of reinfection within 2 years of achieving sustained virological response (SVR) in HIV/HCV co-infected individuals in Europe
- To assess whether the risk of reinfection varies depending on risk group for HIV infection, HCV treatment regimen (interferon-based regimens vs interferon-free DAAs), regional differences, or sociodemographic variables

EuroSIDA study

Large prospective observational cohort study with over 22,000 HIV-positive individuals

- South: Argentina, Greece, Israel, Italy, Portugal, Spain
- Central West: Austria, Belgium, France, Germany, Luxembourg, Switzerland
- North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom
- East/Central East: Belarus, Bosnia-Herzegovina, Croatia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Slovenia



Methods - Definitions

- SVR: defined as a negative HCV-RNA result after treatment end date
  - 24 weeks or later for INF-based regimens (SVR24)
  - 12 weeks or later for INF-free DAA regimens (SVR12)
- Reinfection: defined as being HCV-RNA positive, HCV genotyped or receiving HCV treatment within 24 months of SVR12/SVR24

Methods - Statistics

- Tested for differences in baseline characteristics between those reinfected within 2 years of SVR and not reinfected
- Logistic regression was used to identify risk factors associated with reinfection within 2 years of achieving SVR

Potential risk factors: age, sex, ethnicity, region in Europe, mode of HIV transmission, CD4 count, CD4 nadir, HIV-RNA, AIDS, non-ADI*, HCV treatment type, year of SVR, stage of liver fibrosis†, HCV genotype, previous use of cART, prior HCV treatment, HBV infection

*Non-ADI: non-AIDS defining malignancy, cardiovascular disease, end stage liver disease, end stage renal disease, pancreatitis
†Determined by a biopsy (≥METAVIR stage F3), APRI (score >1.5), hyaluronic acid (>160ng/mL), or FibroScan (>9.5kPa) test

Inclusion criteria

- HIV positive
- HCV-RNA positive
- Completed HCV treatment
- Achieved SVR12 or SVR24
- ≥24 months FU after SVR
- ≥1 HCV-RNA test after SVR during 24 months FU

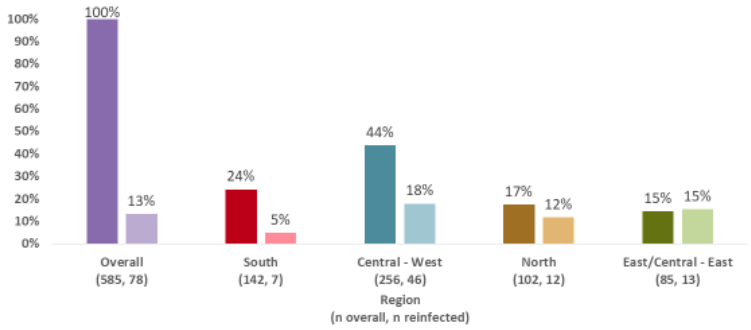
Who was included?

	Ever anti-HCV positive	n = 9465
	Ever HCV-RNA positive	n = 6770
	Completed HCV treatment	n = 3474
Baseline	Achieved SVR	n = 2168
	24 months of FU after SVR	n = 1045
Included	≥1 HCV-RNA test during 24 months of FU	n = 585

Results – Reinfection by treatment

		Interferon	DAA
Study population	585	475	110
Reinfected	78, 13.3% (10.6-16.0%)	63, 13.3% (10.2-16.3%)	15, 13.6% (7.2-20.0%)
Median time to reinfection	312 days IQR: 116-518 days	354 days IQR: 133-524 days	120 days IQR: 73-421 days

Results – Reinfection by region



Results – Characteristics at SVR (1)

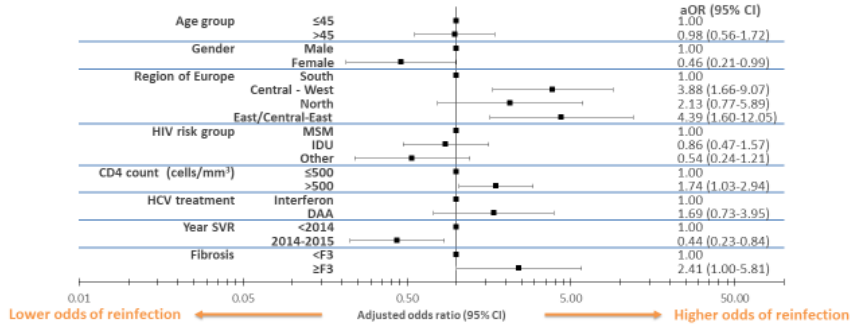
		Overall n (%)	Not reinfected n (%)	Reinfected n (%)	P-value
Overall		**585 (100.0)**	**507 (86.7)**	**78 (13.3)**	
Sex	Male	453 (77.4)	385 (85.0)	68 (15.0)	0.0270
	Female	132 (22.6)	122 (92.4)	10 (7.6)	
Ethnicity	White	455 (77.8)	408 (89.7)	47 (10.3)	0.0002
	Global Majority	7 (1.2)	7 (100.0)	0 (0.0)	
	Unknown	123 (21.0)	92 (74.8)	31 (25.2)	
Region of Europe	South	142 (24.3)	135 (95.1)	7 (4.9)	0.0030
	Central - West	256 (43.8)	210 (82.0)	46 (18.0)	
	North	102 (17.4)	90 (88.2)	12 (11.8)	
	East/Central - East	85 (14.5)	72 (84.7)	13 (15.3)	
Year SVR	<2014	312 (53.3)	261 (83.7)	51 (16.3)	0.0219
	2014-2015	273 (46.7)	246 (90.1)	27 (9.9)	
HIV risk group	MSM	177 (30.3)	148 (83.6)	29 (16.4)	0.1471
	IDU	281 (48.0)	243 (86.5)	38 (13.5)	

Results – Characteristics at SVR (2)

		Overall n (%)	Not reinfected n (%)	Reinfected n (%)	P-value
Overall		**585 (100.0)**	**507 (86.7)**	**78 (13.3)**	
HCV treatment	Interferon	475 (81.2)	412 (86.7)	63 (13.3)	0.9174
	DAA	110 (18.8)	95 (86.4)	15 (13.6)	
Fibrosis	<F3	415 (70.9)	363 (87.5)	52 (12.5)	0.4080
	≥F3*	46 (7.9)	37 (80.4)	9 (19.6)	
HCV genotype	G1	236 (40.3)	204 (86.4)	32 (13.6)	0.9906
	G2 - G4	183 (31.3)	159 (86.9)	24 (13.1)	
cART	No	46 (7.9)	42 (91.3)	4 (8.7)	0.4963
	Yes	539 (92.1)	465 (86.3)	74 (13.7)	
Prior HCV treatment	No	427 (73.0)	374 (87.6)	53 (12.4)	0.2813
	Yes	158 (27.0)	133 (84.2)	25 (15.8)	
			Median (IQR)		
Age		47 (41-52)	47 (41-52)	47 (42-51)	0.9358
CD4 count (cells/mm^3)		514 (346-695)	503 (344-695)	546 (384-704)	0.5787

*Either a biopsy (≥METAVIR stage F3), APRI (score >1.5), hyaluronic acid (>160ng/mL) or FibroScan (>9.5kPa) test

Results – Odds of reinfection



Limitations

- FU HCV-RNA data not available for all
- No data on HCV risk behaviours
- The number of individuals on DAAs is limited
- Cohort individuals not necessarily representative of all HIV/HCV co-infected individuals
  - Majority of study are of white ethnicity– unable to explore differences in reinfection based on ethnicity
- Differences in access to care, and patient management approaches within countries and regions
- Clinics may have targeted HCV-RNA testing to those at highest risk of reinfection, or with signs of reinfection

Summary

- The proportion of reinfections among HIV/HCV co-infected individuals within 24 months of achieving SVR was 13%
- Individuals from Central-West and East/Central-Eastern Europe, with a CD4 count >500 cells/mm^3, and those with fibrosis ≥F3 were found to have increased odds of reinfection
- Females, and those who achieved SVR ≥2014 were found to have a decreased odds of reinfection
- No evidence of a difference in the proportion of individuals that were reinfected based on treatment (interferon vs interferon-free DAA).

Discussion

- Active surveillance to detect early HCV reinfection (with an offer of early treatment) is essential
- Harm reduction services for PWID are crucial to reduce rates of reinfection
- Reducing the rate of HCV reinfection is urgently needed to reach the goal of elimination by 2030, especially among marginalised groups[1]

[1]World Health Organization (WHO). Global hepatitis report, 2017. 2017.

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The EuroSIDA Study Group

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References

1. Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1260–344.

2. Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, Aboyans V, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151–210.

3. UNAIDS. Fact sheet - World AIDS Day 2017 [Internet]. 2017. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

4. UNAIDS. UNAIDS data 2017 [Internet]. 2017. Available from: http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf

5. Wang H, Wolock TM, Carter A, Nguyen G, Kyu HH, Gakidou E, et al. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. Lancet HIV. 2016;3(8):e361–87.

6. Nations U. United Nations Millenium Declaration. Gen Assem. 2000;(September):9.

7. List of Millennium Development Goals , and Goal 8 Targets and Indicators Goals 1 to 7 Goal 8 : Develop a global partnership for development Targets Indicators *. :100.

8. United Nations. The Millennium Development Goals Report. United Nations.

2015;72.

9. World Trade Organization. Declaration on the TRIPS agreement and public health. 2001;

10. United Nations Joint Programme on HIV/AIDS (UNAIDS). 15 by 15 - A Global Target Achieved. Geneva: UNAIDS [Internet]. 2015;1–52. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_15by15_en.pdf

11. United Nations. Transforming our world: the 2030 Agenda for Sustainable Development. Gen Assem 70 Sess. 2015;16301(October):1–35.

12. UNAIDS. 90-90-90 - An ambitious target to help end the AIDS epidemic. United Nations [Internet]. 2014; Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf

13. UNAIDS. Ending Aids: Progress Towards the 90-90-90 Targets. Glob Aids Updat [Internet]. 2017;198. Available from: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

14. UNAIDS. Women and girls and HIV. 2018.

15. Cohen MS, Hellmann N, Levy JA, Decock K, Lange J. The spread, treatment, and prevention of HIV-1: Evolution of a global pandemic. J Clin Invest. 2008;118(4):1244–54.

16. AVERT. GLOBAL HIV AND AIDS STATISTICS [Internet]. [cited 2018 Mar 19]. Available from: https://www.avert.org/global-hiv-and-aids-statistics

17. European Centre for Disease Prevention and Control (ECDC). HIV/AIDS surveillance in Europe 2017 [Internet]. 2017. 2016–2017 p. Available from: https://ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2007

18. DeHovitz J, Uuskula A, El-Bassel N. The HIV epidemic in Eastern Europe and Central Asia. Curr HIV/AIDS Rep. 2014;11(2):168–76.

19. Hamers FF, Downs AM. HIV in central and eastern Europe. Lancet [Internet]. 2003;361(9362):1035–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12660072

20. Sullivan LE, Metzger DS, Fudala PJ, Fiellin DA. Decreasing international HIV transmission: The role of expanding access to opioid agonist therapies for injection drug users. Addiction. 2005;100(2):150–8.

21. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010;375(9719):1014–28.

22. Harm Reduction International. Global State of Harm Reduction 2018: 6th Edition [Internet]. 2018. Available from: www.hri.global

23. UNAIDS. Do No Harm, Health, Human Rights and Peolple Who Use Drugs. United Nations [Internet]. 2016;1–144. Available from: http://www.unaids.org/sites/default/files/media_asset/donoharm_en.pdf

24. Zhu T, Korber BT, Nahmias AJ, Hooper E, Sharp PM, Ho DD. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. Nature. 1998;391(6667):594–7.

25. Worobey M, Gemmel M, Teuwen DE, Haselkorn T, Kunstman K, Bunce M, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature [Internet]. 2008;455(7213):661–4. Available from: http://www.nature.com/doifinder/10.1038/nature07390

26. Hahn BH, Shaw GM, De Cock KM, Sharp PM. AIDS as a zoonosis: scientific and public health implications. Science [Internet]. 2000;287(5453):607–14.

Available from: https://www.researchgate.net/publication/12664725_AIDS_-_AIDS_as_a_zoonosis_scientific_and_public_health_implications

27. Lever AML. HIV: the virus. Medicine (Baltimore). 2009;37(7):313–6.

28. Sharp PM, Hahn BH. The evolution of HIV-1 and the origin of AIDS. Philos Trans R Soc B Biol Sci [Internet]. 2010;365(1552):2487–94. Available from: http://rstb.royalsocietypublishing.org/cgi/doi/10.1098/rstb.2010.0031

29. Kalish ML, Wolfe ND, Ndongmo CB, McNicholl J, Robbins KE, Aidoo M, et al. Central African hunters exposed to simian immunodeficiency virus. Emerg Infect Dis. 2005;11(12):1928–30.

30. Chitnis A, Rawls D, Moore J. Origin of HIV type 1 in colonial French Equatorial Africa? AIDS Res Hum Retroviruses. 2000;16(1):5–8.

31. Gilbert MTP, Rambaut A, Wlasiuk G, Spira TJ, Pitchenik AE, Worobey M. The emergence of HIV/AIDS in the Americas and beyond. Proc Natl Acad Sci [Internet]. 2007;104(47):18566–70. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0705329104

32. Pneumocystis Pneumonia — Los Angeles. MMWR Morb Mortal Wkly Rep. 1981;30(21):250–2.

33. Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homosexual Men — New York City and California. MMWR Morb Mortal Wkly Rep. 1981;30(25):305–8.

34. Brennan RO, Durack DT. Gay compromise syndrome. Lancet. 1981;318(8259):1338–9.

35. Friedman-Kien AE. Disseminated Kaposi's sarcoma syndrome in young homosexual men. J Am Acad Dermatol. 1981;5(4):468–71.

36. Masur H, Michelis MA, Greene JB, Onorato I, Vande Stouwe RA, Holzman RS,

et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med. 1981;305(24):1431–8.

37. Pneumocystis carinii Pneumonia among Persons with Hemophilia A. MMWR Morb Mortal Wkly Rep [Internet]. 1982;31(27):365–7. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001126.htm

38. Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) -- California. MMWR Morb Mortal Wkly Rep [Internet]. 1982;31(48):652–4. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001203.htm

39. Unexplained Immunodeficiency and Opportunistic Infections in Infants -- New York, New Jersey, California. MMWR Morb Mortal Wkly Rep [Internet]. 1982;31(49):665–7. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001208.htm

40. Thomsen H, Jacobsen M, Malchow-Moller A. KAPOSI SARCOMA AMONG HOMOSEXUAL MEN IN EUROPE. 1981;318(8248):688.

41. Bois RMD, Branthwaite MA, Mikhail JR, Batten JC. Primary Pneumocystis carinii and cytomegalovirus infections. Lancet. 1981;318(8259):1339.

42. Vilaseca J, Arnau JM, Bacardi R, Mieras C, Serrano A, Navarro C. Kaposi'S Sarcoma and Toxoplasma Gondii Brain Abscess in a Spanish Homosexual. Lancet. 1982;319(8271):572.

43. Rozenbaum W, Coulaud JP, Saimot AG, Klatzmann D, Mayaud C, Carettec MF. Multiple opportunistic infection in a male homosexual in France. 1982;572–3.

44. Marquart K-H, Müller HAG, Sailer J, Moser R. Slim disease (AIDS). 1985;326(8465):1186–7.

45. Serwadda D, Sewankambo NK, Carswell JW, Bayley AC, Tedder RS, Weiss RA,

et al. Slim Disease: a New Disease in Uganda and Its Association With Htlv-Iii Infection. Lancet. 1985;326(8460):849–52.

46. Update on acquired immune deficiency syndrome (AIDS)--United States. MMWR Morb Mortal Wkly Rep [Internet]. 1982;31(32):507–8, 513–4. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001163.htm

47. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. N Engl J Med. 1982;306(4):248–52.

48. Barre-Sunoussi F, Chermann JC, Rey F, Nugeyre T, Chamaret S, Gruest J, et al. Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS). Science (80-). 1983;220(4599):868–71.

49. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Haynes BF, Palker TJ, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science (80-). 1984;224(4648):500–3.

50. Marx JL. Strong New Candidate for AIDS Agent. Science (80-) [Internet]. 1984;224(4648):475–7. Available from: http://www.jstor.org/stable/1692493%5Cnhttp://about.jstor.org/terms

51. Vahlne A. A historical reflection on the discovery of human retroviruses. Retrovirology. 2009;6(40):1–9.

52. Gallo RC. and his response. Nature. 1991;351(6325):358.

53. Case K. Nomenclature: Human Immunodeficiency Virus. Ann Intern Med. 1986;105(1):133.

54. Coffin J, Haase A, Levy J a., Montagnier L, Oroszlan S, Teich N, et al. What to call the AIDS virus? Nature [Internet]. 1986;321(6065):10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3010128

55. Sainski AM, Cummins NW, Badley AD. HIV: Cell binding and entry [Internet]. [cited 2017 Aug 18]. Available from: http://www.antimicrobe.org/hiv02.asp

56. Clavel F, Guetard D, Brun-Vezinet F, Chamaret S, Rey M, Santos-Ferreira M, et al. Isolation of a new human retrovirus from West African patients with AIDS. Science (80-) [Internet]. 1986;233(4761):343–6. Available from: http://www.sciencemag.org/cgi/doi/10.1126/science.2425430

57. Holmes EC. On the origin and evolution of the human immunodeficiency virus (HIV). Biol Rev Camb Philos Soc [Internet]. 2001;76(2):239–54. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11396848%5Cnhttp://onlinelibrary.wiley.com/store/10.1017/S1464793101005668/asset/S1464793101005668.pdf?v=1&t=gv66wijl&s=6273716399b356d51485448611378fa9517c4678

58. Lewthwaite P, Wilkins E. Natural history of HIV/AIDS. Medicine (Baltimore) [Internet]. 2009;37(7):333–7. Available from: http://dx.doi.org/10.1016/j.mpmed.2009.04.015

59. Chiu IM, Yaniv A, Dahlberg JE, Gazit A, Skuntz SF, Tronick SR, et al. Nucleotide sequence evidence for relationship of AIDS retrovirus to lentiviruses. Nature. 1985;317(6035):366–8.

60. Goto T, Nakai M, Ikuta K. The life-cycle of human immunodeficiency virus type 1. Micron. 1998;29(2–3):123–38.

61. Meštrović T. What is Lentivirus? [Internet]. News Medical Life Science. 2014 [cited 2017 Apr 4]. p. 1–3. Available from: http://www.news-medical.net/life-sciences/What-is-Lentivirus.aspx

62. International Committee on Taxonomy of Viruses (ICTV). Taxonomy [Internet]. [cited 2017 Apr 4]. Available from: https://talk.ictvonline.org/taxonomy/

63. Smith JA, Daniel R. Following the path of the virus: the exploitation of host DNA

repair mechanisms by retroviruses. ACS Chem Biol. 2006;1(4):217–26.

64. Pornillos O, Ganser-Pornillos BK. HIV-1 Virion Structure. In: Hope T., Stevenson M., Richman D. (eds) Encyclopedia of AIDS. Springer, New York, NY. 2013. In: Hope TJ, Richman D, Stevenson M, editors. Encyclopedia of AIDS. New York, NY: Springer; 2013.

65. Campbell EM, Hope TJ. Live cell imaging of the HIV-1 life cycle. Trends Microbiol. 2008;16(12):580–7.

66. Engelman A, Cherepanov P. The structural biology of HIV-1: mechanistic and therapeutic insights. Nat Rev Microbiol [Internet]. 2012;10(4):279–90. Available from: http://www.nature.com/doifinder/10.1038/nrmicro2747

67. Weiss RA. Gulliver's travels in HIVland. Nature. 2001;410(6831):963–7.

68. Parham P. The Immune System. Garl Sci Taylor Fr Group, LLC. 2015;313(16):1686.

69. McCune JM. The dynamics of CD4+ T-cell depletion in HIV disease. Nature. 2001;410:974–9.

70. Weiss RA. Getting to know HIV. Trop Med Int Heal. 2000;5(7):A10–5.

71. Berger EA, Murphy PM, Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annu Rev Immunol [Internet]. 1999;17(1):657–700. Available from: http://www.annualreviews.org/doi/10.1146/annurev.immunol.17.1.657

72. Davis CW, Doms RW. HIV Transmission: Closing All the Doors. J Exp Med. 2004;199(8):1037–40.

73. Giese S, Pelchen-Matthews A, Marsh M. HIV – The Cell Biology of Virus Infection and Replication. In: Bradshaw RA, Stahl PD, editors. Encyclopedia of Cell Biology. Waltham, MA: Academic Press; 2016. p. 828–38.

74. Walker BD, Korber BT. Immune control of HIV: The obstacles of HLA and viral diversity. Nat Immunol. 2001;2(6):473–5.

75. Perreau M, Levy Y, Pantaleo G. Immune response to HIV. Curr Opin HIV AIDS. 2013;8(4):333–40.

76. Adler MW, Edwards SG, Miller RF, Sethi G, Williams I. ABC Of HIV And AIDS [Internet]. 6th Editio. Wiley-Blackwell; 2012. Available from: https://www.dawsonera.com/readonline/9781118425800

77. Van der Graaf M, Diepersloot RJA. Transmission of Human Immunodeficiency Virus (HIV/HTLV-III/LAV): A Review. Infection. 1986;14(5):203–11.

78. MMWR Morbidity and Mortality Weekly Report. Current Trends Update: Acquired Immunodeficiency Syndrome (AIDS) -- United States. 1983;32(35):465–7. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00000137.htm

79. Chun TW, Fauci AS. HIV reservoirs: Pathogenesis and obstacles to viral eradication and cure. Aids. 2012;26(10):1261–8.

80. Chun TW, Finzi D, Margolick J, Chadwick K, Schwartz D, Siliciano RF. In vivo fate of HIV-1-infected T cells: Quantitative analysis of the transition to stable latency. Nat Med. 1995;1(12):1284–90.

81. Centers for Disease Control and Prevention. HIV Risk and Prevention [Internet]. [cited 2018 Jun 1]. Available from: https://www.cdc.gov/hiv/risk/index.html

82. Park LS, Tate JP, Sigel K, Brown ST, Crothers K, Gibert C, et al. Association of Viral Suppression With Lower AIDS-Defining and Non-AIDS-Defining Cancer Incidence in HIV-Infected Veterans: A Prospective Cohort Study. Ann Intern Med Med [Internet]. 2018; Available from: http://annals.org/article.aspx?doi=10.7326/M16-

2094%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/29893768

83. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Van Lunzen J, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA - J Am Med Assoc. 2016;316(2):171–81.

84. Centers for Disease Control and Prevention. HIV transmission [Internet]. [cited 2018 Jun 1]. Available from: https://www.cdc.gov/hiv/basics/transmission.html

85. Quinn TC, Wawer MJ, Sewankambo H, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med. 2000;342(13):921–9.

86. Royce RA, Sena A, Cates W, Cohen MS. Sexual Transmission Of HIV. N Engl J Med. 1997;336(15):1072–8.

87. Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. 2011;365(6):493–505.

88. World Health Organization (WHO). Antiretroviral treatment as prevention (TASP) of HIV and TB. 2012;

89. Lundgren J, Phillips A. Prevention of HIV transmission by antiretroviral therapy. Lancet HIV [Internet]. 2018;5(3):e108–9. Available from: http://dx.doi.org/10.1016/S2352-3018(17)30204-7

90. U.S. Food and Drug Administration. Truvada for PrEP Fact Sheet: Ensuring Safe and Proper Use. 2012.

91. Molina JM, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV.

2017;4(9):e402–10.

92. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): Effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet [Internet]. 2016;387(10013):53–60. Available from: http://dx.doi.org/10.1016/S0140-6736(15)00056-2

93. CDC Centers for Disease Control and Prevention. HIV Among Gay and Bisexual Men [Internet]. [cited 2018 Jun 1]. Available from: https://www.cdc.gov/hiv/group/msm/index.html

94. Koblin BA, Husnik MJ, Colfax G, Huang Y, Madison M, Mayer K, et al. Risk factors for HIV infection among men who have sex with men. AIDS. 2006;(January).

95. Altman D, Aggleton P, Williams M, Kong T, Reddy V, Harrad D, et al. Men who have sex with men: Stigma and discrimination. Lancet [Internet]. 2012;380(9839):439–45. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60920-9

96. Tebit DM, Ndembi N, Weinberg A, Quiñones-Mateu ME. Mucosal transmission of human immunodeficiency virus. Curr HIV Res [Internet]. 2012;10(1):3–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22264040%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3744389

97. World Health Organization (WHO). Consolidated guideline on sexual and reproductive health and rights of women living with HIV [Internet]. 2017. Available from: http://www.who.int/reproductivehealth/publications/gender_rights/Ex-Summ-srhr-women-hiv/en/

98. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A.

Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLoS Med. 2005;2(11):1112–22.

99. World Health Organization (WHO). Male circumcision for HIV prevention [Internet]. World Helath Organization. 2015 [cited 2018 Feb 1]. Available from: http://www.who.int/hiv/topics/malecircumcision/en/

100. Rezza G., Titti F., Tempesta E., di Giannantonio M., Welsert A., Rossi GB, et al. Needle sharing and other behaviours related to HIV spread among intravenous drug users. Vol. 3, Aids. 1989. p. 247–8.

101. Leparc GF. Safety of the Blood Supply. Cancer Control. 2015;22(1):7–15.

102. Busch MP, Operskalski EA, Mosley JW, Lee TH, Henrard D, Herman S, et al. Factors influencing human immunodeficiency virus type 1 transmission by blood transfusion. Transfusion Safety Study Group. J Infect Dis [Internet]. 1996;174(1):26–33. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8656010

103. Roberts BD. HIV Antibody Testing Methods, 1985-1988. J Insur Med. 1994;26(1):13–4.

104. MMWR Morbidity and Mortality Weekly Report. Acquired Immunodeficiency Syndrome (AIDS): Precautions for Health-Care Workers and Allied Professionals. 1983;32(34):450–1. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00000133.htm

105. UNAIDS. The Gap Report [Internet]. 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf

106. Harm Reduction International. The Case for a Harm Reduction Decade: Progress, potential and paradigm shifts [Internet]. 2016. Available from:

https://www.hri.global/files/2016/03/10/Report_The_Case_for_a_Harm_Reduction_Decade.pdf

107. United Nations General Assembly. Political Declaration on HIV/AIDS: Intensifying our Efforts to Eliminate HIV/AIDS [Internet]. 2011. Available from: http://www.unaids.org/sites/default/files/sub_landing/files/20110610_UN_A-RES-65-277_en.pdf%5Cnhttp://www.unaids.org/sites/default/files/sub_landing/files/20110610_UN_A-RES-65-277_en.pdf%5Cnwww.unaids.org/en/.../unaids/.../20110610_un_a-res-65-277_en.pdf

108. Forbes JC, Alimenti AM, Singer J, Brophy JC, Bitnun A, Samson LM, et al. A national review of vertical HIV transmission. Aids. 2012;26(September 2011):757–63.

109. MMWR Morbidity and Mortality Weekly Report. Current Trends Recommendations for Assisting in the Prevention of Perinatal Transmission of Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus and Acquired Immunodeficiency Syndrome. 1985;34(48):721-6,731-2. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00033122.htm

110. MMWR Morbidity and Mortality Weekly Report. Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus. 1994;43(RR11):1–20. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00032271.htm

111. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. N Engl J Med. 1994;331(18):1173–80.

112. Lurie P, Wolfe SM. Unethical Trials of Interventions to Reduce Perinatal

Transmission of the Human Immunodeficiency Virus in Developing Countries. N Engl J Med. 1997;337:853–6.

113. CDC Centers for Disease Control and Prevention. HIV Among Pregnant Women, Infants, and Children [Internet]. [cited 2018 Jun 1]. Available from: https://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html

114. World Health Organization (WHO). Mother-to-child transmission of HIV [Internet]. [cited 2018 Jun 1]. Available from: http://www.who.int/hiv/topics/mtct/about/en/

115. Dao H, Mofenson LM, Ekpini R, Gilks CF, Barnhart M, Bolu O, et al. International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update. Am J Obstet Gynecol. 2007;197(3):S42-55.

116. World Health Organization (WHO). Guideline on When To Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. World Heal Organ [Internet]. 2015;(September):78. Available from: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/

117. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV. N Engl J Med. 2015;373(9):795–807.

118. The TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015;373(9):808–22.

119. UNAIDS. 2015 Progress report on the Global Plan towards the eliminations of new HIV infections among children and keeping their mothers alive [Internet]. 2015. Available from: http://www.unaids.org/sites/default/files/media_asset/JC2774_2015ProgressReport_GlobalPlan_en.pdf%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/27355509%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3161890&tool=pmcentrez&rendertype=abstract

120. Revised Surveillance Case Definition for HIV Infection — United States , 2014. MMWR Morb Mortal Wkly Rep. 2014;63(3):1–10.

121. WHO HIV/AIDS Programme. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2006; Available from: http://womenchildrenhiv.org

122. Pantaleo G, Graziosi C, Fauci AS. The immunopathogenesis of human immunodeficiency virus infection. N Engl J Med. 1993;328(5):327–35.

123. Mindel A, Tenant-flowers M. Natural history and management of early HIV infection. Br Med J. 2001;322(7297):1290–3.

124. O'Cofaigh E, Lewthwaite P. Natural history of HIV and AIDS. Med (United Kingdom). 2013;41(8):411–6.

125. DeGruttola V, Lange N, Dafni U. Modeling the progression of HIV infection. J Am Stat Assoc [Internet]. 1991;86(415):569–77. Available from: http://www.jstor.org/stable/2290384%5Cnhttp://about.jstor.org/terms

126. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient High Levels of Viremia in Patients with Primary Human Immunodeficiency Virus Type 1 Infection. N Engl J Med [Internet]. 1991;324(4):961–4. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJM199007193230303

127. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. Aids. 2003;17(13):1871–9.

128. Schacker TW, Hughes JP, Shea T, Coombs RW, Corey L. Biological and virologic characteristics of primary HIV infection. Ann Intern Med [Internet]. 1998;128(8):613–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9537934

129. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med. 1996;125(4):257–64.

130. Pantaleo G, Graziosi C, Demarest JF, Butini L, Montroni M, Fox CH, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature. 1993;362(6418):355–8.

131. O'Connell KA, Bailey JR, Blankson JN. Elucidating the elite: mechanisms of control in HIV-1 infection. Trends Pharmacol Sci. 2009;30(12):631–7.

132. Boritz EA, Darko S, Swaszek L, Wolf G, Wells D, Wu X, et al. Multiple Origins of Virus Persistence during Natural Control of HIV Infection. Cell [Internet]. 2016;166(4):1004–15. Available from: http://dx.doi.org/10.1016/j.cell.2016.06.039

133. Poropatich K, Sullivan DJ. Human immunodeficiency virus type 1 long-term non-progressors: The viral, genetic and immunological basis for disease non-progression. J Gen Virol. 2011;92(2):247–68.

134. McMichael A, Rowland-Jones S. Cellular immune responses to HIV. Nature [Internet]. 2001;410(6831):980–7. Available from: http://www.nature.com/nature/journal/v410/n6831/abs/410980a0.html

135. Rodríguez B, Sethi AK, Cheruvu VK, Mackay W, Bosch RJ, Kitahata M, et al. Predictive Value of Plasma HIV RNA Level on Rate of CD4 T-Cell Decline in Untreated HIV Infection. JAMA - J Am Med Assoc. 2006;296(12):1498–506.

136. Schellekens PT, Tersmette M, Roos MT, Keet RP, de Wolf F, Coutinho RA, et al. Biphasic rate of CD4+ cell count decline during progression to AIDS correlates with HIV-1 phenotype [Internet]. Vol. 6, Aids. 1992. p. 665–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1354447

137. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Time from HIV-1 seroconversion to AIDS and

death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Lancet. 2000;355(9210):1131–7.

138. Jacobson LP, Kirby AJ, Polk S, Phair JP, Besley DR, Saah AJ, et al. Changes in survival after acquired immunodeficiency syndrome (AIDS): 1984- 1991. Am J Epidemiol [Internet]. 1993;138(11):952–64. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L24002361%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=00029262&id=doi:&atitle=Changes+in+survival+after+acquired+immunodeficiency+syndrome+%28AIDS%29%3A+1984-+1991&stitle=AM.

139. Poorolajal J, Hooshmand E, Mahjub H, Esmailnasab N, Jenabi E. Survival rate of AIDS disease and mortality in HIV-infected patients: a meta-analysis. Public Health [Internet]. 2016;139:3–12. Available from: http://dx.doi.org/10.1016/j.puhe.2016.05.004

140. Gail MH, Tan W-Y, Pee D, Goedert JJ. Survival After AIDS Diagnosis in a Cohort of Hemophilia Patients. JAIDS J Acquir Immune Defic Syndr [Internet]. 1997;15(5):363–9. Available from: http://ovidsp.tx.ovid.com.libproxy.ucl.ac.uk/sp-3.30.0b/ovidweb.cgi?QS2=434f4e1a73d37e8cf2a910ebf0ab2f073d7235aa939b833e4e46fcbc57665fbc445b6b5896df7d7c38fd34dc6361f3d770c25602eddbc58209f569eee15db281e666680c6a29b9e55364bae73b45006991802183b1c48def12bfdd8

141. Cheng DM, Nunes D, Libman H, Vidaver J, Alperen JK, Saitz R, et al. Impact of hepatitis C on HIV progression in adults with alcohol problems. Alcohol Clin Exp Res. 2007;31(5):829–36.

142. Carlos Martín J, Castilla J, López M, Arranz R, González-Lahoz J, Soriano V. Impact of Chronic Hepatitis C on HIV-1 Disease Progression. HIV Clin Trials [Internet]. 2004;5(3):125–31. Available from: http://www.tandfonline.com/doi/full/10.1310/YFV8-FE5K-5LN9-DQ4C

143. Ullum H, Cozzi Lepri A, Aladdin H, Katzenstein T, Victor J, Phillips AN, et al. Natural immunity and HIV disease progression. Aids [Internet]. 1999;13(5):557–63. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10203380

144. Fletcher M a, Mosley JW, Hassett J, Gjerset GF, Kaplan J, Parker JW, et al. Effect of age on human immunodeficiency virus type 1-induced changes in lymphocyte populations among persons with congenital clotting disorders. Transfusion Safety Study Group. Blood [Internet]. 1992;80(3):831–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1638032

145. Solomon GF, Benton D, Harker JO, Bonavida B, Fletcher MA. Prolonged asymptomatic states in HIV-seropositive persons with fewer than 50 CD4+ T cells per MM3. Ann N Y Acad Sci [Internet]. 1994;741(1):185–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8105075

146. Smith C, Sabin C a, Lundgren JD, Thiebaut R, Weber R, Law M, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS [Internet]. 2010;24(10):1537–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20453631

147. Langford SE, Ananworanich J, Cooper DA. Predictors of disease progression in HIV infection: A review. AIDS Res Ther. 2007;4(11):1–14.

148. Marlink R, Kanki P, Thior I, Travers K, Eisen G, Siby T, et al. Reduced Rate of Disease Development After HIV-2 Infection as Compared to HIV-1 Mboup and Max Essex Published by : American Association for the Advancement of Science Stable URL : http://www.jstor.org/stable/2884570 JSTOR is a not-for-profit service that h. Scand J Infect Dis. 2018;265(5178):1587–90.

149. Garcia De La Hera M, Ferreros I, Del Amo J, Garcia De Olalla P, Perez Hoyos S, Mugo R, et al. Gender differences in progression to AIDS and death from HIV

seroconversion in a cohort of injecting dug users from 1986 to 2001. J Epidemiol Community Health. 2004;58(11):944–50.

150. The HIV-CAUSAL Collaboration. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. Aids [Internet]. 2010;24(1):123–37. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201001020-00017

151. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Heal Organ. 2016;

152. Palmisano L, Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Ann Ist Super Sanità. 2011;47(1):44–8.

153. Hirsch MS, Kaplan JC. Treatment of human immunodeficiency virus infections. Antimicrob Agents Chemother. 1987;31(6):839–43.

154. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. Antivir Res. 2010;85(1):1–38.

155. Approval of AZT [Internet]. [cited 2018 Feb 12]. Available from: https://aidsinfo.nih.gov/news/274/approval-of-azt

156. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. [Internet]. Vol. 317, The New England journal of medicine. 1987. p. 185–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3299089

157. Wright K. First tentative signs of therapeutic promise. Nature. 1986;323(6086):283.

158. Richman DD, Fischl MA, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et

al. The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. N Engl J Med. 1987;317(4):192–7.

159. Béthune M De. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), their discovery , development , and use in the treatment of HIV-1 infection: A review of the last 20 years (1989 – 2009). Antiviral Res. 2010;85(1):75–90.

160. Lundgren J, Phillips A, Pedersen C, Clumeck N, Gatell J, Johnson A, et al. Comparison of long-term prognosis of patients with AIDS treated and not treated with zidovudine. JAMA [Internet]. 1994;271(14):1088–92. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8151850

161. Larder BA, Darby G, Richman DD. HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy. Science (80-). 1989;243(4899):1731–4.

162. Larder BA, Kemp SD. Multiple Mutations in HIV-1 Reverse Transcriptase Confer High-Level Resistance to Zidovudine (AZT). Science (80-). 1989;246(4934):1155–8.

163. Connolly KJ, Allan JD, Fitch H, Jackson-Pope L, McLaren C, Canetta R, et al. Phase I study of 2′-3′-dideoxyinosine administered orally twice daily to patients with AIDS or AIDS-related complex and hematologic intolerance to zidovudine. Am J Med. 1991;91(5):471–8.

164. Gatell JM, González-Lahoz J, Clotet B, Antunes F, Kasparova L, Gil-Aguado A, et al. Switching from Zidovudine to Didanosine in Patients with Symptomatic HIV Infection and Disease Progression. J Acquir Immune Defic Syndr Hum Retrovirology [Internet]. 1996;12(3):249–58. Available from: http://ovidsp.tx.ovid.com/sp-3.28.0a/ovidweb.cgi?QS2=434f4e1a73d37e8cfbbbce9d866d3c88b44974794328cdaff332603311beefa22139faf68816302dd02035b3a352586d329d8c200ee78d6fbb9db517d02bd809b35dfd56ad6db7a2d437681e5e117df267292aec1

2d2da1d80eb4f4bf08de450a8d64ecb9e

165. Darbyshire J, Foulkes M, Peto R, Duncan W, Babiker A, Collins R, et al. Zidovudine (AZT) versus AZT plus didanosine (ddI) versus AZT plus zalcitabine (ddC) in HIV infected adults. Cochrane database Syst Rev [Internet]. 2000; Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=10796851

166. Herbert S, Chung E, Waters L. HIV Treatment. Curr Treat Options Infect Dis. 2014;6(3):271–93.

167. Wensing AMJ, van Maarseveen NM, Nijhuis M. Fifteen years of HIV Protease Inhibitors: raising the barrier to resistance. Antiviral Res. 2010;85(1):59–74.

168. Williams IG, De Cock KM. The XI international conference on AIDS. Vancouver 7-12 July 1996. A review of Clinical Science Track B. Genitourin Med. 1996;72(5):365–9.

169. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. Vol. 33, International Journal of Antimicrobial Agents. 2009. p. 307–20.

170. James J. Saquinavir (Invirase): first protease inhibitor approved--reimbursement, information hotline numbers. AIDS Treat News [Internet]. 1995;22(237):1–2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Saquinavir+(Invirase)%3A+first+protease+inhibitor+approved--reimbursement%2C+information+hotline+numbers

171. Luber AD. Genetic barriers to resistance and impact on clinical response. J Int AIDS Soc [Internet]. 2005;7(3):1–10. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2804709&tool=pmcentrez&rendertype=abstract

172. World Health Organization (WHO). HIV Drug resistance report 2017 [Internet]. Hiv Drug Resistance Report 2017 Trends Quality Action. 2017. Available from: http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf%0Ahttp://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf?ua=1

173. Krentz HB, Cosman I, Lee K, Ming JM, Gill MJ. Pill burden in HIV infection : 20 years of experience. Antivir Ther. 2012;17(5):833–40.

174. Hütter G, Nowak D, Mossner M, Ganepola S, Müßig A, Kristina Allers PD, et al. Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell TransplantationBrief Report: N Engl J Med [Internet]. 2009;360(7):692–8. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0802905

175. Cocchetto DM, Jones DR. Faster Access to Drugs for Serious or Life-Threatening Illnesses through use of the Accelerated Approval Regulation in the United States. Drug Inf J. 1998;32(1):27–35.

176. Treatment use of an investigational new drug [Internet]. [cited 2018 Feb 12]. Available from: https://www.gpo.gov/fdsys/pkg/CFR-1999-title21-vol5/xml/CFR-1999-title21-vol5-sec312-34.xml

177. Katz R. Biomarkers and surrogate markers: an FDA perspective. NeuroRx [Internet]. 2004;1(2):189–95. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=534924&tool=pmcentrez&rendertype=abstract%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/15717019%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC534924

178. Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in Asymptomatic Human Immunodeficiency Virus Infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med [Internet]. 1990;322(14):941–9. Available from:

http://www.nejm.org/doi/pdf/10.1056/NEJM199007193230303

179. Fleming TR, Demets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Ann Intern Med. 1996;125(7):605–13.

180. Moore DAJ, Goodall RL, Ives NJ, Hooker M, Gazzard BG, Easterbrook PJ. How generalizable are the results of large randomized controlled trials of antiretroviral therapy ? HIV Med. 2000;1(3):149–54.

181. Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL. Recruitment for Controlled Clinical Trials : Literature Summary and Annotated Bibliography. Control Clin Trials. 1997;18(4):328–52.

182. Madge S, Mocroft A, Wilson D, Youle M, Lipman MCI, Phillips A, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. HIV Med. 2000;1(4):212–8.

183. Sabin CA, Phillips AN. Treatment comparisons in HIV infection: the benefits and limitations of observational cohort studies. J Antimicrob Chemother. 2001;47(4):371–5.

184. HIV iBASE. Introduction to Art Therapy. HIV iBASE. 2016;368.

185. Cihlar T, Ray AS. Nucleoside and nucleotide HIV reverse transcriptase inhibitors : 25 years after zidovudine. Antiviral Res. 2010;85(1):39–58.

186. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012;2(4):1–23.

187. Association BH. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. HIV Med. 2016;17(Suppl4):s2–104.

188. EACS. European AIDS Clinical Society Guidelines Version 9.0 October 2017 [Internet]. European AIDS Clinical Society (EACS). 2017. Available from:

http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

189. Koczor CA, Lewis W. Nucleoside reverse transcriptase inhibitor toxicity and mitochondrial DNA. Expert Opin Drug Metab Toxicol [Internet]. 2010;6(12):1493–504. Available from: http://www.tandfonline.com/doi/full/10.1517/17425255.2010.526602

190. POZ. An HIV Drug Says Goodbye [Internet]. 2006 [cited 2018 Mar 19]. Available from: https://www.poz.com/article/An-HIV-Drug-Says-Goodbye-7749-6766

191. Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration. Lancet. 2008;371(9622):1417–26.

192. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of Myocardial Infarction in Patients with HIV Infection Exposed to Specific Individual Antiretroviral Drugs from the 3 Major Drug Classes: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. J Infect Dis [Internet]. 2010;201(3):318–30. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1086/649897

193. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. Aids. 2010;24(11):1667–78.

194. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir Effect on the Kidneys of HIV-Infected Patients: A Double-Edged Sword? J Am Soc Nephrol [Internet]. 2013;24(10):1519–27. Available from: http://www.jasn.org/cgi/doi/10.1681/ASN.2012080857

195. Ding X, Andraca-carrera E, Cooper C, Miele P, Kornegay C, Soukup M, et al. No Association of Myocardial Infarction with Abacavir Use : Findings of an FDA Meta-analysis. J Acquir Immune Defic Syndr [Internet]. 2012;61(4):441–7.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/22932321

196. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic Review and Meta-analysis: Renal Safety of Tenofovir Disoproxil Fumarate in HIV-Infected Patients. Clin Infect Dis [Internet]. 2010;51(5):496–505. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/655681

197. Laskey SB, Siliciano RF. A mechanistic theory to explain the efficacy of antiretroviral therapy. Nat Rev Microbiol [Internet]. 2014;12(11):772–80. Available from: http://dx.doi.org/10.1038/nrmicro3351

198. Flexner C. HIV-protease inhibitors. N Engl J Med. 1998;338(18):1281–92.

199. Gallant JE, Koenig E, Andrade-Villanueva JF, Chetchotisakd P, DeJesus E, Antunes F, et al. Cobicistat Compared With Ritonavir as a Pharmacoenhancer for Atazanavir in Combination With Emtricitabine/Tenofovir Disoproxil Fumarate: Week 144 Results. J Acquir Immune Defic Syndr. 2015;69(3):338–40.

200. Bierman WFW, Van Agtmael MA, Nijhuis M, Danner SA, Boucher CAB. HIV monotherapy with ritonavir-boosted protease inhibitors: A systematic review. Aids. 2009;23(3):279–91.

201. Virlogeux V, Zoulim F, Pugliese P, Poizot-Martin I, Valantin M-A, Cuzin L, et al. Modeling HIV-HCV coinfection epidemiology in the direct-acting antiviral era: The road to elimination. BMC Med. 2017;15(1):1–11.

202. Arribas J, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: Week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load <50 HIV-1 RNA copies/mL at baseline. HIV Med. 2012;13(7):398–405.

203. Gazzard B, Moecklinghoff C, Hill A. New strategies for lowering the costs of

antiretroviral treatment and care for people with HIV/AIDS in the United Kingdom. Clin Outcomes Res. 2012;4(1):193–200.

204. Paton NI, Stöhr W, Arenas-Pinto A, Fisher M, Williams I, Johnson M, et al. Protease inhibitor monotherapy for long-term management of HIV infection: A randomised, controlled, open-label, non-inferiority trial. Lancet HIV. 2015;2(10):e417–26.

205. Carr A. HIV Protease Inhibitor-Related Lipodystrophy Syndrome. Clin Infect Dis. 2000;30(Suppl 2):S135–42.

206. Sluis-Cremer N, Tachedjian G. Mechanisms of inhibition of HIV replication by non-nucleoside reverse transcriptase inhibitors. Virus Res. 2008;134(1–2):147–56.

207. Raffi F, Pozniak AL, Wainberg MA. Has the time come to abandon efavirenz for first-line antiretroviral therapy? J Antimicrob Chemother. 2014;69(7):1742–7.

208. Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet. 2007;370(9581):39–48.

209. Hughes A, Barber T, Nelson M. New treatment options for HIV salvage patients: An overview of second generation PIs, NNRTIs, integrase inhibitors and CCR5 antagonists. J Infect. 2008;57(1):1–10.

210. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. N Engl J Med [Internet]. 2013;369(19):1807–18. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1215541

211. Haqqani AA, Tilton JC. Entry inhibitors and their use in the treatment of HIV-1 infection. Antiviral Res [Internet]. 2013;98(2):158–70. Available from:

http://dx.doi.org/10.1016/j.antiviral.2013.03.017

212. Lazzarin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M, et al. Efficacy of Enfuvirtide in Patients Infected with Drug-Resistant HIV-1 in Europe and Australia. N Engl J Med [Internet]. 2003;348(22):2186–95. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa035211

213. Esté JA, Telenti A. HIV entry inhibitors. Lancet. 2007;370(9581):81–8.

214. Henrich TJ, Kuritzkes DR. HIV-1 entry inhibitors: Recent development and clinical use. Curr Opin Virol [Internet]. 2013;3(1):51–7. Available from: http://dx.doi.org/10.1016/j.coviro.2012.12.002

215. Trepo C. A brief history of hepatitis milestones. Liver Int. 2014;34(s1):29–37.

216. Bayer ME, Blumberg BS, Werner B. Particles associated with Australia antigen in the sera of patients with leukaemia, down's syndrome and hepatitis. Nature. 1968;218(5146):1057–9.

217. Feinstone S, Kapikian A, Purcell R. Hepatitis A : detection by immune electron microscopy of a virus like antigen associated with acute illness. Science (80-). 1973;182(4116):1026–8.

218. Feinstone SM, Kapikian AZ, Purcell RH, Alter HJ, Holland P V. Transfusion-Associated Hepatitis Not Due to Viral Hepatitis Type A or B. N Engl J Med. 1975;292:767–70.

219. Choo Q, Kuo G, Weiner A, Overby L, Bradley D, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science (80-) [Internet]. 1989;244(4902):359–62. Available from: http://www.sciencemag.org/cgi/doi/10.1126/science.2523562

220. Houghton M. The long and winding road leading to the identification of the hepatitis C virus. J Hepatol [Internet]. 2009;51(5):939–48. Available from: http://dx.doi.org/10.1016/j.jhep.2009.08.004

221. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis [Internet]. 2005;5(9):558–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16122679

222. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34–41.

223. Bertino G, Ardiri A, Proiti M, Rigano G, Frazzetto E, Demma S, et al. Chronic hepatitis C: This and the new era of treatment. World J Hepatol. 2016;8(2):92–106.

224. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology [Internet]. 2002 Nov;36(S1):S21–9. Available from: http://doi.wiley.com/10.1002/9781444327298.ch7

225. Mauss S, Pol S, Buti M, Duffell E, Gore C, Lazarus J V., et al. Late presentation of chronic viral hepatitis for medical care: a consensus definition. BMC Med [Internet]. 2017;15(1):1–5. Available from: http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0856-y

226. Blach S, Zeuzem S, Manns M, Altraif I, Duberg A-S, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol [Internet]. 2017;2(3):161–76. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2468125316301819

227. World Health Organization (WHO). Global hepatitis report, 2017 [Internet]. 2017 [cited 2017 Dec 1]. Available from: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

228. World Health Organization (WHO). Progress report on access to hepatitis C treatment: Focus on overcoming barriers in low- and middle-income countries

[Internet]. 2018. Available from: http://apps.who.int/iris/bitstream/10665/260445/1/WHO-CDS-HIV-18.4-eng.pdf?ua=1

229. World Health Organization (WHO). Resolution WHA63.18. Viral hepatitis. In: Sixty-third World Health Assembly, Geneva, 17–21 May 2010 Resolutions and decisions, annexes [Internet]. Geneva; 2010. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-en.pdf

230. World Health Organization (WHO). Resolution WHA67.6. Hepatitis. In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014 Resolutions and decisions, annexes [Internet]. Geneva; 2014. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=1

231. World Health Organization (WHO). Global health sector strategy on viral hepatitis 2016-2021. In Geneva; 2016.

232. Taherkhani R, Farshadpour F. Global elimination of hepatitis C virus infection: Progresses and the remaining challenges. World J Hepatol. 2017;9(33):1239–52.

233. Lazarus J V., Wiktor S, Colombo M, Thursz M. Micro-elimination – A path to global elimination of hepatitis C. J Hepatol [Internet]. 2017;67(4):665–6. Available from: http://dx.doi.org/10.1016/j.jhep.2017.06.033

234. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. 2008;33:126–33.

235. Iversen J, Grebely J, Topp L, Wand H, Dore G, Maher L. Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999-2011. J Viral Hepat. 2014;21:198–207.

236. World Health Organization (WHO). Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection [Internet]. Geneva; 2016. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27227200

237. European Centre for Disease Prevention and Control (ECDC). Systematic review on hepatitis B and C prevalence in the EU/EEA [Internet]. Stockholm; 2016. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/systematic-review-hepatitis-B-C-prevalence.pdf%0Ahttp://ecdc.europa.eu/en/publications/Publications/systematic-review-hepatitis-B-C-prevalence.pdf

238. European Centre for Disease Prevention and Control (ECDC). Annual Epidemiological Report for 2016: Hepatitis C. Stockholm; 2018.

239. Razavi H, Robbins S, Zeuzem S, Negro F, Buti M, Duberg AS, et al. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(5):314–5.

240. Dusheiko G. Hepatitis C in the EU: setting the terms for elimination. Lancet Gastroenterol Hepatol [Internet]. 2017;2(5):314–5. Available from: http://dx.doi.org/10.1016/S2468-1253(17)30073-0

241. Sharma P, Balan V, Hernandez J, Rosati M, Williams J, Rodriguez-Luna H, et al. Hepatic Steatosis in Hepatitis C Virus Genotype 3 Infection: Does It Correlate with Body Mass Index, Fibrosis, and HCV Risk Factors? Dig Dis Sci. 2004;49(1):25–9.

242. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87.

243. Webster DP, Klenerman P, Dusheiko GM. Lancet Seminar – Hepatitis C. Lancet

(London, England) [Internet]. 2015;385(9973):1124–35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4878852/

244. Peters L, Klein MB. Epidemiology of hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS [Internet]. 2015;10:297–302. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L606418788%5Cnhttp://dx.doi.org/10.3748/wjg.v21.i38.10790

245. Grint D, Peters L, Rockstroh JK, Rakmanova A, Trofimova T, Lacombe K, et al. Liver-related death among HIV/hepatitis C virus-co-infected individuals. Aids [Internet]. 2015;29(10):1205–15. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201506190-00012

246. European Centre for Disease Prevention and Control (ECDC). HIV/AIDS surveillance in Europe 2015 [Internet]. 2015 [cited 2017 Dec 1]. Available from: http://ecdc.europa.eu/en/publications/Publications/HIV-AIDS-surveillance-Europe-2015.pdf

247. Hernandez MD, Sherman KE. HIV/hepatitis C coinfection natural history and disease progression. Curr Opin HIV AIDS. 2011;6(6):478–82.

248. Arends JE, Lieveld FI, Boeijen LL, De Kanter CTMM, Van Erpecum KJ, Salmon D, et al. Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms? J Hepatol [Internet]. 2015;63(5):1254–62. Available from: http://dx.doi.org/10.1016/j.jhep.2015.06.034

249. Kitahata MM, Gange SJ, Abraham AG, Merriman B. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. N Engl J Med. 2009;360(18):1815–26.

250. Saeed S, Strumpf EC, Walmsley SL, Rollet-Kurhajec K, Pick N, Martel-Laferrière V, et al. How generalizable are the results from trials of direct antiviral agents to people coinfected with HIV/HCV in the real world? Clin Infect Dis.

2016;62(7):919–26.

251. van der Helm JJ, Prins M, del Amo J, Bucher HC, Chêne G, Dorrucci M, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. Aids [Internet]. 2011;25(8):1083–91. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201105150-00008

252. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H, editors. Hepatology. A clinical textbook. 8th ed. 2017. 703 p.

253. Wakita T, Pietschmann T, Kato T, Date T, Miyamoto M, Zhao Z, et al. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. Nat Med. 2005;11(7):791–6.

254. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. Nat Rev Microbiol. 2007;5(6):453–63.

255. Sabahi A. Hepatitis C Virus entry: The early steps in the viral replication cycle. Virol J. 2009;6(117):1–11.

256. Bartosch B, Cosset FL. Cell entry of hepatitis C virus. Virology. 2006;348(1):1–12.

257. Evans MJ, Von Hahn T, Tscherne DM, Syder AJ, Panis M, Wölk B, et al. Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. Nature. 2007;446(7137):801–5.

258. Liu S, Yang W, Shen L, Turner JR, Coyne CB, Wang T. Tight Junction Proteins Claudin-1 and Occludin Control Hepatitis C Virus Entry and Are Downregulated during Infection To Prevent Superinfection. J Virol [Internet]. 2009;83(4):2011–4. Available from: http://jvi.asm.org/cgi/doi/10.1128/JVI.01888-08

259. Li HC, Lo SY. Hepatitis C virus: Virology, diagnosis and treatment. World J

Hepatol. 2015;7(10):1377–89.

260. Paul D, Madan V, Bartenschlager R. Hepatitis C virus RNA replication and assembly: Living on the fat of the land. Cell Host Microbe [Internet]. 2014;16(5):569–79. Available from: http://dx.doi.org/10.1016/j.chom.2014.10.008

261. Dubuisson J, Cosset FL. Virology and cell biology of the hepatitis C virus life cycle - An update. J Hepatol [Internet]. 2014;61(1):S3–13. Available from: http://dx.doi.org/10.1016/j.jhep.2014.06.031

262. The C. Everett Koop Institute. Geisel School of Medicine. Dartmouth-Hitchcock Medical Center. Dartmouth College. The life cycle of hepatitis C [Internet]. [cited 2018 Jul 20]. Available from: http://www.epidemic.org/thefacts/hepatitisc/lifeCycle/

263. CDC Centers for Disease Control and Prevention. Viral Hepatitis: Hepatitis C [Internet]. [cited 2018 Jul 20]. Available from: https://https//www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section2

264. Logez S, Soyolgerel G, Fields R, Luby S, Hutin Y. Rapid assessment of injection practices in Mongolia. Am J Infect Control. 2004;32(1):31–7.

265. Luby SP, Qamruddin K, Shah AA, Omair A, Pahsa O, Khan AJ, et al. The Relationship between Therapeutic Injections and High Prevalence of Hepatitis C Infection in Hafizabad, Pakistan. Epidemiol Infect [Internet]. 1997;119(3):349–56. Available from: https://dictionary.cambridge.org/dictionary/english

266. World Health Organization (WHO). Blood safety and availability [Internet]. 2017 [cited 2018 Aug 1]. Available from: http://www.who.int/en/news-room/fact-sheets/detail/blood-safety-and-availability

267. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV

infection. Nat Rev Gastroenterol Hepatol [Internet]. 2013;10(9):553–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23817321

268. Ahmed Kiani R, Anwar M, Waheed U, Asad MJ, Abbasi S, Abbas Zaheer H. Epidemiology of Transfusion Transmitted Infection among Patients with β-Thalassaemia Major in Pakistan. J Blood Transfus [Internet]. 2016;2016:1–5. Available from: http://www.hindawi.com/journals/jbt/2016/8135649/

269. Tagny CT, Owusu-Ofori S, Mbanya D, Deneys V. The blood donor in sub-Saharan Africa: A review. Vol. 20, Transfusion Medicine. 2010. p. 1–10.

270. Heintges T, Wands J. Hepatitis C virus: epidemiology and transmission. Hepatology [Internet]. 1997;1–6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/hep.510260338/abstract

271. Clarke a, Kulasegaram R. Hepatitis C transmission -- where are we now? Int J STD AIDS. 2006;17(2):74–80; quiz 80.

272. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The Risk of Transfusion-Transmitted Viral Infections. N Engl J Med. 1996;334(26):1685–90.

273. Takano S, Omata M, Oht M, Satomura Y. Prospective Assessment of Donor Blood Screening for Antibody to Hepatitis C Virus and High-titer Antibody to HBcAg as a Means of Preventing Posttransfusion Hepatitis. Hepatology. 1993;18(3):235–9.

274. Busch MP, Glynn SA, Wright DJ, Hirschkorn D, Laycock ME, McAuley J, et al. Relative sensitivities of licensed nucleic acid amplification tests for detection of viremia in early human immunodeficiency virus and hepatitis C virus infection. Transfusion. 2005;45(12):1853–63.

275. Goldberg D, Anderson E. Hepatitis C: who is at risk and how do we identify them? J Viral Hepat. 2004;11(Suppl. 1):12–8.

276. Goldberg D, Abt P, Blumberg E, Van Deerlin V, Levine M, Reddy K, et al. Trial of

Transplantation of HCV-Infected Kidneys into Uninfected Recipients. 2017;376(24):2394–5.

277. Sulkowski MS, Ray SC, Thomas DL. Needlestick transmission of hepatitis C. Jama [Internet]. 2002;287(18):2406–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11988061

278. Midgard H, Weir A, Palmateer N, Lo Re V, Pineda JA, Macías J, et al. HCV epidemiology in high-risk groups and the risk of reinfection. J Hepatol [Internet]. 2016;65(1):S33–45. Available from: http://dx.doi.org/10.1016/j.jhep.2016.07.012

279. Sutton AJ, Hope VD, Mathei C, Mravcik V, Sebakova H, Vallejo F, et al. A comparison between the force of infection estimates for blood-borne viruses in injecting drug user populations across the European Union: A modelling study. J Viral Hepat. 2008;15(11):809–16.

280. Cottrell EB, Chou R, Wasson N, Rahman B, Guise J-M. Review Reducing Risk for Mother-to-Infant Transmission of Hepatitis C Virus : A Systematic Review for the U S Preventive Services Task Force. Ann Intern Med. 2013;158(2):109–13.

281. Prasad MR, Honegger JR. Hepatitis C virus in pregnancy. Am J Perinatol. 2013;30(2):149–59.

282. Papaevangelou V, Pollack H, Rochford G, Kokka R, Hou Z, Chernoff D, et al. Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV)-infected infants of HIV- and HCV-coinfected women. J Infect Dis [Internet]. 1998;178(4):1047–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9806033%5Cnhttp://jid.oxfordjournals.org/content/178/4/1047.full.pdf

283. England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. Lancet Infect Dis. 2006;6(2):83–90.

284. Hershow RC, Riester KA, Lew J, Quinn TC, Mofenson M, Davenny K, et al. Increased Vertical Transmission of Human Immunodeficiency Virus from Hepatitis C Virus-Coinfected Mothers. J Infect Dis. 1997;176(2):414–20.

285. NHS. Hepatitis C [Internet]. [cited 2018 Jul 27]. Available from: https://www.nhs.uk/conditions/hepatitis-c/

286. Vandelli C, Renzo F, Romano L, Tisminetzky S, De Palma M, Stroffolini T, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: Results of a 10-year prospective follow-up study. Am J Gastroenterol. 2004;99(5):855–9.

287. Danta M, Rodger AJ. Transmission of HCV in HIV-positive populations. Curr Opin HIV AIDS. 2011;6(6):451–8.

288. Matthews G V., Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: Response to Danta et al. [2]. AIDS. 2007;21(15):2112–3.

289. Wandeler G, Gsponer T, Bregenzer A, Günthard HF, Clerc O, Calmy A, et al. Hepatitis C virus infections in the swiss HIV cohort study: A rapidly evolving epidemic. Clin Infect Dis. 2012;55(10):1408–16.

290. van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of a Large, International Network of HCV Transmission in HIV-Positive Men Who Have Sex With Men. Gastroenterology. 2009;136(5):1609–17.

291. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol [Internet]. 2014;61(1):S58–68. Available from: http://dx.doi.org/10.1016/j.jhep.2014.07.012

292. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47–52.

293. Butt AA, Yan P, Lo Re V, Rimland D, Goetz MB, Leaf D, et al. Liver Fibrosis

Progression in Hepatitis C Virus Infection After Seroconversion. JAMA Intern Med [Internet]. 2015 Feb 1;175(2):178. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2014.6502

294. Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. Aids. 2009;23(1):89–93.

295. Thomson EC, Smith JA, Klenerman P. The natural history of early hepatitis C virus evolution; lessons from a global outbreak in human immunodeficiency virus-1-infected individuals. J Gen Virol [Internet]. 2011 Oct 1;92(10):2227–36. Available from: https://insights.ovid.com/crossref?an=00002030-200901020-00012

296. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24(2):289–93.

297. El-Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. Gastroenterology. 2007;132(7):2557–76.

298. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. Arthritis Rheum. 1999;42(10):2204–12.

299. Cacoub P, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, et al. Extrahepatic manifestations associated with hepatitis C virus infection: A prospective multicenter study of 321 patients. Medicine (Baltimore). 2000;79(1):47–56.

300. Soriano V, Berenguer J. Extrahepatic comorbidities associated with hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS. 2015;10(5):309–15.

301. Mahale P, Engels EA, Li R, Torres HA, Hwang LY, Brown EL, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018;67(3):553–61.

302. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. Hepatology. 2008;48(2):418–31.

303. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol. 2001;34(5):730–9.

304. Rayhill SC, Wu YM, Katz DA, Voigt MD, LaBrecque DR, Kirby PA, et al. Older donor livers show early severe histological activity, fibrosis, and graft failure after liver transplantation for hepatitis C. Transplantation. 2007;84(3):331–9.

305. Sinn DH, Paik SW, Kang P, Kil JS, Park SU, Lee SY, et al. Disease progression and the risk factor analysis for chronic hepatitis C. Liver Int. 2008;28(10):1363–9.

306. Féray C, Caccamo L, Alexander GJM, Ducot B, Gugenheim J, Casanovas T, et al. European Collaborative Study on Factors Influencing Outcome after liver transplantation for hepatitis C. Gastroenterology. 1999;117(3):619–25.

307. Missiha SB, Ostrowski M, Heathcote EJ. Disease Progression in Chronic Hepatitis C: Modifiable and Nonmodifiable Factors. Gastroenterology. 2008;134(6):1699–714.

308. Nguyen GC, Segev DL, Thuluvath PJ. Racial Disparities in the Management of Hospitalized Patients with Cirrhosis and Complications of Portal Hypertension: A National Study. Hepatology. 2007;45(5):1282–9.

309. Matsuura K, Tanaka Y. Host genetic variants influencing the clinical course of hepatitis C virus infection. J Med Virol [Internet]. 2016 Feb;88(2):185–95. Available from: http://doi.wiley.com/10.1002/jmv.24334

310. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, Ohuigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature [Internet]. 2009;461(7265):798–801. Available from: http://dx.doi.org/10.1038/nature08463

311. Graham C. Hepatitis C and HIV Co-infection: Closing the Gaps. JAMA [Internet]. 2015;313(12):1217–8. Available from: http://dx.doi.org/10.1001/jama.2015.1111

312. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-Lymphocyte Recovery in Individuals With Advanced HIV-1 Infection Receiving Potent Antiretroviral Therapy for 4 Years. Arch Intern Med [Internet]. 2003 Oct 13;163(18):2187–95. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.163.18.2187

313. Rockstroh JK, Mocroft a, Soriano V, Tural C, Losso MH, Horban a, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis [Internet]. 2005;192(6):992–1002. Available from: http://jid.oxfordjournals.org/content/192/6/992.full.pdf

314. Bataller R, Brenner D. Liver fibrosis. J Clin Invest. 2005;115(2):209–18.

315. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371(9615):835–51.

316. Sebastiani G, Gkouvatsos K, Pantopoulos K. Chronic hepatitis C and liver fibrosis. World J Gastroenterol. 2014;20(32):11033–53.

317. EACS. European AIDS Clinical Society Guidelines Version 10.1 October 2020. European AIDS Clinical Society (EACS). 2020.

318. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. Hepatology. 2000;32(3):477–81.

319. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology [Internet]. 2010;139(4):1230–7. Available from: http://dx.doi.org/10.1053/j.gastro.2010.06.015

320. Papastergiou V, Tsochatzis E, Burroughs AK. Non-invasive assessment of liver fibrosis. Ann Gastroenterol. 2012;25(3):218–31.

321. Bedossa P, Dargère D, Paradis V. Sampling Variability of Liver Fibrosis in Chronic Hepatitis C. Hepatology. 2003;38(6):1449–57.

322. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002;97(10):2614–8.

323. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis. Hepatology. 2011;53(3):726–36.

324. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. Clin Infect Dis. 2011;52(7):889–900.

325. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis c virus receiving pegylated interferon and ribavirin. Hepatology. 2010;51(4):1122–6.

326. Manns MP. Treating viral hepatitis C: efficacy, side effects, and complications. Gut [Internet]. 2006;55(9):1350–9. Available from: http://gut.bmj.com/cgi/doi/10.1136/gut.2005.076646

327. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. Hepatology. 2018;68(3):827–38.

328. Labarga P, Fernández-Montero J V., De Mendoza C, Barreiro P, Soriano V. Long-term survival and liver-related events after pegylated interferon/ribavirin therapy in HIV-infected patients with chronic hepatitis C. Antivir Ther. 2015;20(1):65–72.

329. Reichard O, Norkrans G, Glaumann H, Frydén A, Weiland O, Wejstål R. Long-term follow-up of chronic hepatitis C patients with sustained virological response to alpha-interferon. 1999;30(5):783–7.

330. Maylin S, Martinot-Peignoux M, Moucari R, Boyer N, Ripault MP, Cazals-Hatem D, et al. Eradication of Hepatitis C Virus in Patients Successfully Treated for Chronic Hepatitis C. Gastroenterology. 2008;135(3):821–9.

331. Hoofnagle J, Mullen K, Jones D, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of Chronic Non-A, Non-B Hepatitis with Recombinant Human Alpha Interferon. N Engl J Med [Internet]. 1986;315(25):1575–8. Available from: http://doi.wiley.com/10.1002/cld.1

332. Di Bisceglie A, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med. 1989;321(22):1506–10.

333. Davis G, Balart L, Schiff E, Lindsay K, Bodenheimer HJ, Perrillo R, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. Hepatitis Intervention Therapy Group. N Engl J Med. 1989;321(22):1501–6.

334. Strader DB, Seeff LB. A brief history of the treatment of viral hepatitis C. Clin Liver Dis [Internet]. 2012;1(1):6–11. Available from: http://doi.wiley.com/10.1002/cld.1

335. Dusheiko G, Main J, Thomas H, Reichard O, Lee C, Dhillon A, et al. Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled

study. J Hepatol. 1996;25:591–8.

336. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon Alfa-2b Alone or in Combination with Ribavirin as Initial Treatment for Chronic Hepatitis C. N Engl J Med [Internet]. 1998;339(21):1485–92. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199811193392101

337. Zeuzem SVF. Peginterferon Alfa-2a in Patients with Chronic Hepatitis C. N Engl J Med. 2000;343(23):1666–72.

338. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet [Internet]. 2001;358(9286):958–65. Available from: http://www.sciencedirect.com/science/article/pii/S0140673601061025

339. Hauser G, Awad T, Brok J, Thorlund K, Štimac D, Mabrouk M, et al. Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C (Review). 2014.

340. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004;351(5):451–9.

341. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial Trial. JAMA [Internet]. 2004;292(23):2839–48. Available from: http://dx.doi.org/10.1001/jama.292.23.2839

342. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-García J, Lazzarin A, et al. Peginterferon Alfa-2a plus Ribavirin for Chronic Hepatitis C

Virus Infection in HIV-Infected Patients. N Engl J Med [Internet]. 2004;351(5):438–50. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa040842

343. Laguno M, Murillas J, Blanco JL, Martínez E, Miquel R, Sánchez-Tapias JM, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS. 2004;18(13):27–36.

344. Berenguer J, González-García J, López-Aldeguer J, Von-Wichmann MA, Quereda C, Hernando A, et al. Pegylated interferon α2a plus ribavirin versus pegylated interferon α2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. J Antimicrob Chemother. 2009;63(6):1256–63.

345. Coppola N. Treatment of chronic hepatitis C in patients with HIV/HCV coinfection. World J Virol [Internet]. 2015;4(1):1. Available from: http://www.wjgnet.com/2220-3249/full/v4/i1/1.htm

346. Berenguer M, García-Eliz M, Baiguera C, Puoti M. Beyond cure: preventing and managing the complications of end-stage liver disease. Curr Opin HIV AIDS [Internet]. 2015;10(5):355–60. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01222929-201509000-00010

347. Wyles DL, Sulkowski MS, Dieterich D. Management of Hepatitis C/HIV Coinfection in the Era of Highly Effective Hepatitis C Virus Direct-Acting Antiviral Therapy: Table 1. Clin Infect Dis [Internet]. 2016;63(Suppl 1):S3–11. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw219

348. Walker CM. Designing an HCV vaccine: a unique convergence of prevention and therapy? Curr Opin Virol [Internet]. 2017;23:113–9. Available from: http://dx.doi.org/10.1016/j.coviro.2017.03.014

349. Stone J, Martin NK, Hickman M, Hellard M, Scott N, McBryde E, et al. The potential impact of a hepatitis C vaccine for people who inject drugs: Is a vaccine needed in the age of direct-acting antivirals? PLoS One. 2016;11(5):1–19.

350. Pawlotsky JM, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. J Hepatol [Internet]. 2015;62(1):S87–99. Available from: http://dx.doi.org/10.1016/j.jhep.2015.02.006

351. Schlabe S, Rockstroh JK. Advances in the treatment of HIV/HCV coinfection in adults. Expert Opin Pharmacother [Internet]. 2018;19(1):49–64. Available from: https://doi.org/10.1080/14656566.2017.1419185

352. Chopra S, Arora S. Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection [Internet]. UpToDate. 2018 [cited 2018 Jul 1]. Available from: https://www.uptodate.com/contents/patient-evaluation-and-selection-for-antiviral-therapy-for-chronic-hepatitis-c-virus-infection#H620696786

353. McGivern DR, Masaki T, Lovell W, Hamlett C, Saalau-Bethell S, Graham B. Protease Inhibitors Block Multiple Functions of the NS3/4A Protease-Helicase during the Hepatitis C Virus Life Cycle. J Virol [Internet]. 2015;89(10):5362–70. Available from: http://jvi.asm.org/lookup/doi/10.1128/JVI.03188-14

354. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. N Engl J Med. 2011;364:1195–206.

355. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. N Engl J Med [Internet]. 2011;364(25):2405–16. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1012912

356. Spengler U. Direct antiviral agents (DAAs) - A new age in the treatment of

hepatitis C virus infection. Pharmacol Ther [Internet]. 2018;183:118–26. Available from: https://doi.org/10.1016/j.pharmthera.2017.10.009

357. Li G, De Clercq E. Current therapy for chronic hepatitis C: The role of direct-acting antivirals. Antiviral Res [Internet]. 2017;142:83–122. Available from: http://dx.doi.org/10.1016/j.antiviral.2017.02.014

358. The American Association for the Study of Liver Diseases (AASLD) and the, Infectious Diseases Society of America (IDSA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. 2017.

359. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol [Internet]. 2017;66(1):153–94. Available from: http://dx.doi.org/10.1016/j.jhep.2016.09.001

360. Martin NK, Thornton A, Hickman M, Sabin C, Nelson M, Cooke GS, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic among Men Who Have Sex with Men in the United Kingdom? Epidemiological and Modeling Insights. Clin Infect Dis. 2016;62(9):1072–80.

361. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis [Internet]. 2013 Aug 15;57(Suppl 2):S39-45. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciu093

362. Braun D, et al. for the Swiss HIV Cohort Study. A treatment as prevention trial to eliminate HCV in HIV+ MSM: The Swiss HCVREE trial. 25th Conference on Retroviruses and Opportunistic Infections, March 04-07, 2018, Boston; abstract LB87. Available from:

https://www.croiconference.org/abstract/treatment-prevention-trial-eliminate-hcv-hiv-msm-swiss-hcvree-trial/

363. Boerekamps A, Berk GE Van Den, Lauw FN, Leyten EM, Kasteren ME Van, Eeden A Van, et al. Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex With Men After Unrestricted Access to HCV Therapy. Clin Infect Dis. 2018;66(9):1360–5.

364. World Health Organization (WHO). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. 2018.

365. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol [Internet]. 2018; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0168827818319688

366. Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. Lancet Gastroenterol Hepatol. 2018;3(2):125–33.

367. EACS. European AIDS Clinical Society Guidelines Version 10.0 November 2019 [Internet]. European AIDS Clinical Society (EACS). 2019. Available from: https://www.eacsociety.org/files/guidelines-10.0_final_2_2.pdf

368. Peters L, Laut K, Resnati C, Del Campo S, Leen C, Falconer K, et al. Uptake of HCV treatment in HIV/HCV coinfected patients across europe in the era of direct-acting antivirals. AIDS [Internet]. 2018;32(14):1995–2004. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29912062

369. Asher AK, Portillo CJ, Cooper BA, Dawson-Rose C, Vlahov D, Page KA. Clinicians' Views of Hepatitis C Virus Treatment Candidacy With Direct-Acting Antiviral Regimens for People Who Inject Drugs. Subst Use Misuse [Internet]. 2016;51(9):1218–23. Available from: http://dx.doi.org/10.3109/10826084.2016.1161054

370. Gvinjilia L, Nasrullah M, Sergeenko D, Tsertsvadze T, Kamkamidze G, Butsashvili M, et al. National Progress Toward Hepatitis C Elimination — Georgia, 2015–2016. MMWR Morb Mortal Wkly Rep [Internet]. 2016;65(41):1132–5. Available from: http://www.cdc.gov/mmwr/volumes/65/wr/mm6541a2.htm

371. Cox AL. Global control of hepatitis C virus. Science (80-). 2015;349(6250):790–1.

372. Falade-Nwulia O, Sulkowski M. The HCV care continuum does not end with cure: A call to arms for the prevention of reinfection. J Hepatol [Internet]. 2017;66(2):267–9. Available from: http://dx.doi.org/10.1016/j.jhep.2016.10.027

373. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection with Hepatitis C Virus after Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis. 2015;62(6):683–94.

374. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. Lancet Infect Dis. 2012;12(5):408–14.

375. Weir A, McLeod A, Innes H, Valerio H, Aspinall EJ, Goldberg DJ, et al. Hepatitis C reinfection following treatment induced viral clearance among people who have injected drugs. Drug Alcohol Depend [Internet]. 2016;165:53–60. Available from: http://dx.doi.org/10.1016/j.drugalcdep.2016.05.012

376. Midgard H, Bjøro B, Mæland A, Konopski Z, Kileng H, Damås JK, et al. Hepatitis C reinfection after sustained virological response. J Hepatol. 2016;64(5):1020–6.

377. Ingiliz P, Martin TC, Rodger A, Stellbrink HJ, Mauss S, Boesecke C, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men

who have sex with men in Western Europe. J Hepatol [Internet]. 2017;66(2):282–7. Available from: http://dx.doi.org/10.1016/j.jhep.2016.09.004

378. El-Sherif O, Khoo S, Solas C. Key drug-drug interactions with direct-acting antiviral in HIV-HCV coinfection. Curr Opin HIV AIDS. 2015;10(5):348–54.

379. Martinello M, Dore GJ, Skurowski J, Bopage RI, Finlayson R, Baker D, et al. Antiretroviral use in the CEASE cohort study and implications for direct-acting antiviral therapy in human immunodeficiency virus/hepatitis C virus coinfection. Open Forum Infect Dis. 2016;3(2):1–8.

380. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: A global systematic review and meta-analysis. Lancet Infect Dis [Internet]. 2016;16(7):797–808. Available from: http://dx.doi.org/10.1016/S1473-3099(15)00485-5

381. Sethi A, Sterling RK. HIV-HCV coinfection. Gastroenterol Hepatol. 2006;2(5):357–65.

382. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of Human Immunodeficiency Virus Infection on the Course of Hepatitis C Virus Infection: A Meta-Analysis. Clin Infect Dis [Internet]. 2001;33(4):562–9. Available from: http://cid.oxfordjournals.org/lookup/doi/10.1086/321909

383. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): A multicohort collaboration. Lancet [Internet]. 2014;384(9939):241–8. Available from: http://dx.doi.org/10.1016/S0140-6736(14)60604-8

384. Perlman DC, Jordan AE, Nash D. Conceptualizing Care Continua: Lessons from HIV, Hepatitis C Virus, Tuberculosis and Implications for the Development of Improved Care and Prevention Continua. Front Public Heal [Internet].

2017;4:1–9. Available from: http://journal.frontiersin.org/article/10.3389/fpubh.2016.00296/full

385. Jose S, Delpech V, Howarth A, Burns F, Hill T, Porter K, et al. A continuum of HIV care describing mortality and loss to follow-up: a longitudinal cohort study. Lancet HIV. 2018;5(6):e301–8.

386. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence — What Is It and What Can It Tell Us? N Engl J Med [Internet]. 2016;375(23):2293–7. Available from: http://www.nejm.org/doi/10.1056/NEJMsb1609216

387. World Health Organization (WHO). Hepatitis A fact sheet [Internet]. [cited 2020 Dec 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-a

388. Laut K, Kirk O, Rockstroh J, Phillips A, Ledergerber B, Gatell J, et al. The EuroSIDA study: 25 years of scientific achievements. HIV Med [Internet]. 2019;(September):1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31647187

389. Lundgren JD, Pedersen C, Clumeck N, Gatell JM, Johnson AM, Ledergerber B, et al. Survival differences in European patients with AIDS, 1979–89. BMJ [Internet]. 1994;308(6936):1068–73. Available from: https://www-bmj-com.libproxy.ucl.ac.uk/content/308/6936/1068

390. HIV Cohorts Data Exchange Protocol [Internet]. [cited 2020 Dec 9]. Available from: http://hicdep.org/

391. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–35.

392. Kowalska JD, Friis-møller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV (CoDe) Project: Initial Results and Evaluation of Methodology. 2011;22(4):516–23.

393. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, et al. Loss to follow-up in an international, multicentre observational study. HIV Med. 2008;9(5):261–9.

394. Peters L, Mocroft A, Lundgren J, Grint D, Kirk O, Rockstroh J. HIV and hepatitis C co-infection in Europe, Israel and Argentina: a EuroSIDA perspective. BMC Infect Dis [Internet]. 2014;14(Suppl 6):1–8. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-S6-S13

395. Liang K-Y, Zeger SL. Biometrika Trust Longitudinal Data Analysis Using Generalized Linear Models Author (s): Kung-Yee Liang and Scott L . Zeger Published by : Oxford University Press on behalf of Biometrika Trust Stable URL : http://www.jstor.org/stable/2336267 REFERENCES L. Biometrika. 1986;73(1):13–22.

396. Kirkwood BR, Sterne JAC. Essential Medical Statistics. Second Edi. Science B, editor. 2003.

397. Rabe-Hesketh S, Skrondal A. Multilevel and longitudinal modeling using Stata. Volume, Continuous responses [Internet]. 3rd editio. Texax: Stata Press; 2012. Available from: https://books.google.co.uk/books?hl=en&lr=&id=woi7AheOWSkC&oi=fnd&pg=PR21&dq=multilevel+and+longitudinal+modeling+using+stata&ots=eeFA7b6NOB&sig=S3IfrIXVh4RoRAk_FcJGHMsuSc0#v=onepage&q&f=false

398. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Third edit. Lippincott Williams & Wilkins; 2008. 219 p.

399. Jones MP. Indicator and stratification methods for missing explanatory in

Multiple Linear Regression. J Am Stat Assoc. 1996;91(433):222–30.

400. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research : potential and pitfalls. BMJ. 2009;339(7713):157–60.

401. Vandenbroucke JP, Elm E Von, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. Epidemiology. 2007;18(6):805–35.

402. Macías J, Berenguer J, Japón MA, Girón JA, Rivero A, López-Cortés LF, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. Hepatology. 2009;50(4):1056–63.

403. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. Clin Infect Dis. 2015;61(5):730–40.

404. Mocroft A, Lundgren J, Gerstoft J, Rasmussen LD, Bhagani S, Aho I, et al. Clinical Outcomes in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus: Impact of Hepatitis C Virus Treatment. Clin Infect Dis. 2020;70(10):2131–40.

405. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): A non-randomised, open-label trial. Lancet HIV. 2015;2(8):e319–27.

406. Rockstroh JK, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer AF, et al. Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus-1: the EXPEDITION-2 Study. Clin Infect Dis [Internet]. 2018;1–8. Available from:

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciy220/4939381%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/29566246

407. Klevens RM, Canary L, Huang X, Denniston MM, Yeo AE, Pesano RL, et al. The Burden of Hepatitis C Infection – Related Liver Fibrosis in the United States. 2016;63(8):1049–55.

408. De Lédinghen V, Barreiro P, Foucher J, Labarga P, Castéra L, Vispo ME, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. J Viral Hepat. 2008;15(6):427–33.

409. Puoti M, Lorenzini P, Cozzi-Lepri A, Gori A, Mastroianni C, Rizzardini G, et al. Incidence and Progression to Cirrhosis of New HCV infections in Persons Living with HIV. Clin Microbiol Infect. 2017;23(4).

410. Bailey H, Nizova N, Martsynovska V, Volokha A, Malyuta R, Cortina-Borja M, et al. HCV co-infection and markers of liver injury and fibrosis among HIV-positive childbearing women in Ukraine: Results from a cohort study. BMC Infect Dis [Internet]. 2016;16(1):1–10. Available from: http://dx.doi.org/10.1186/s12879-016-2089-7

411. Silver D, Karnik G, Osinusi A, Silk R, Stabinski L, Doonquah L, et al. Effect of HIV on liver fibrosis among HCV-infected African Americans. Clin Infect Dis. 2013;56(9):1280–3.

412. Martin-Carbonero L, Benhamou Y, Puoti M, Berenguer J, Mallolas J, Quereda C, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. Clin Infect Dis [Internet]. 2004;38(1):128–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14679458

413. Béguelin C, Suter A, Bernasconi E, Fehr J, Kovari H, Bucher HC, et al. Trends in

HCV treatment uptake, efficacy and impact on liver fibrosis in the Swiss HIV Cohort Study. Liver Int. 2018;38(3):424–31.

414. Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: A consensus definition. HIV Med. 2011;12(1):61–4.

415. Fleishman JA, Yehia BR, Moore RD, Gebo KA. The economic burden of late entry into medical care for patients with HIV infection. Med Care. 2010;48(12):1071–9.

416. Lanoy E, Mary-Krause M, Tattevin P, Perbost I, Poizot-Martin I, Dupont C, et al. Frequency, determinants and consequences of delayed access to care for HIV infection in France. Antivir Ther. 2007;12:89–96.

417. Hansen JF, Hallager S, Øvrehus A, Weis N, Brehm Christensen P, Pedersen C. Late presentation for care among patients with chronic hepatitis C: Prevalence and risk factors. Open Forum Infect Dis. 2018;5(1):1–3.

418. Chhatwal J, He T, Hur C, Lopez-Olivo MA. Direct-Acting Antiviral Agents for Patients With Hepatitis C Virus Genotype 1 Infection Are Cost-Saving. Clin Gastroenterol Hepatol [Internet]. 2017;15(6):827-837.e8. Available from: http://dx.doi.org/10.1016/j.cgh.2016.09.015

419. D.Marshall A, Pawlotsky J-M, V.Lazarus J, Aghemo A, J.Dore G, Grebely J. The removal of DAA restrictions in Europe – One step closer to eliminating HCV as a major public health threat. J Hepatol. 2018;69(5):1188–96.

420. Halfon P, Bourlière M, Pénaranda G, Deydier R, Renou C, Botta-Fridlund D, et al. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. Comp Hepatol. 2005;4(6):1–7.

421. CDC Centers for Disease Control and Prevention. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS

Among Adolescents and Adults. MMWR Recomm Reports. 1992;41(RR-17).

422. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. J Acquir Immune Defic Syndr. 2010;55(2):262–70.

423. Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, et al. Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfected patients: Impact of protease inhibitor therapy. Hepatology. 2001;34(2):283–7.

424. Ragni M V., Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis. 2001;183(7):1112–5.

425. Gourlay A, Noori T, Pharris A, Axelsson M, Costagliola D, Cowan S, et al. The human immunodeficiency virus continuum of care in European Union Countries in 2013: Data and Challenges. Clin Infect Dis. 2017;64(12):1644–56.

426. Raymond A, Hill A, Pozniak A. Large disparities in HIV treatment cascades between eight European and high-income countries – analysis of break points. J Int AIDS Soc [Internet]. 2014;17(4(Suppl 3)):2013–4. Available from: http://www.jiasociety.org/index.php/jias/article/view/19507

427. Hajarizadeh B, Grebely J, McManus H, Estes C, Razavi H, Gray RT, et al. Chronic hepatitis C burden and care cascade in Australia in the era of interferon-based treatment. J Gastroenterol Hepatol. 2017;32(1):229–36.

428. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V. The treatment cascade for chronic hepatitis C virus infection in the United States: A systematic review and meta-analysis. PLoS One. 2014;9(7):3–9.

429. Zuckerman A, Douglas A, Nwosu S, Choi L, Chastain C. Increasing success and evolving barriers in the hepatitis C cascade of care during the direct acting

antiviral era. PLoS One [Internet]. 2018;13(6):1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0199174

430. Anderson ES, Galbraith JW, Deering LJ, Pfeil SK, Todorovic T, Rodgers JB, et al. Continuum of Care for Hepatitis C Virus Among Patients Diagnosed in the Emergency Department Setting. 2017;64(Xx Xxxx):1–7.

431. Hawks L, Norton BL, Cunningham CO, Fox AD. The Hepatitis C virus treatment cascade at an urban postincarceration transitions clinic. J Viral Hepat. 2016;23(6):473–8.

432. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. Int J Drug Policy [Internet]. 2017;47(March 2016):77–85. Available from: http://dx.doi.org/10.1016/j.drugpo.2017.05.022

433. Janjua NZ, Kuo M, Yu A, Alvarez M, Wong S, Cook D, et al. The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada: The BC Hepatitis Testers Cohort (BC-HTC). EBioMedicine [Internet]. 2016;12:189–95. Available from: http://dx.doi.org/10.1016/j.ebiom.2016.08.035

434. Machado SM, Almeida-neto C De, Capuani L, Regina F, Abreu M, Catharina A, et al. Hepatitis C among blood donors: cascade of care and predictors of loss to follow-up. 2017;1–8.

435. Maier MM, Ross DB, Chartier M, Belperio PS, Backus LI. Cascade of care for hepatitis C virus infection within the US veterans health administration. Am J Public Health. 2016;106(2):353–8.

436. Noska AJ, Belperio PS, Loomis TP, Backus LI. Engagement in the Hepatitis C Care Cascade Among Homeless Veterans, 2015. Public Health Rep. 2017;132(2):136–9.

437. Simmons R, Ireland G, Irving W, Hickman M, Sabin C, Ijaz S, et al. Establishing

the cascade of care for hepatitis C in England—benchmarking to monitor impact of direct acting antivirals. J vi. 2018;25(5):482–90.

438. Wade AJ, Macdonald DM, Doyle JS, Gordon A, Roberts SK, Thompson AJ, et al. The cascade of care for an Australian community-based Hepatitis C treatment service. PLoS One. 2015;10(11):1–12.

439. Moradpour D, Grakoui A, Manns MP. Future landscape of hepatitis C research - Basic, translational and clinical perspectives. J Hepatol [Internet]. 2016;65(1 Suppl):S143-55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27641984

440. Tsui JI, Ko SC, Krupitsky E, Lioznov D, Chaisson CE, Gnatienko N, et al. Insights on the Russian HCV care cascade: minimal HCV treatment for HIV/HCV co-infected PWID in St. Petersburg. Hepatol Med Policy [Internet]. 2016;1(1):13. Available from: http://hmap.biomedcentral.com/articles/10.1186/s41124-016-0020-x

441. Saris J, van den Berk G, Moha DA, van der Meer J, Brinkman K, van der Valk M. Successful implementation of hepatitis C virus treatment in two large HIV clinics in Amsterdam. Aids [Internet]. 2017;31(12):1779–80. Available from: http://insights.ovid.com/crossref?an=00002030-201707310-00019

442. Roberson JL, Kan VL. Hepatitis C Virus Continuum of Care in the Interferon and Direct-Acting Agent Eras Among HIV-Coinfected Patients. AIDS Res Hum Retroviruses [Internet]. 2017;33(5):405–6. Available from: http://online.liebertpub.com/doi/10.1089/aid.2016.0170

443. Cachay ER, Hill L, Wyles D, Colwell B, Ballard C, Torriani F, et al. The hepatitis C cascade of care among HIV infected patients: A call to address ongoing barriers to care. PLoS One. 2014;9(7):3–9.

444. Pesano RL. Testing and reporting practices for improved management of hepatitis C. Antivir Ther. 2012;17(7):1403–7.

445. Lourenço L, Hull M, Nosyk B, Montaner JSG, Lima VD. The need for standardisation of the HIV continuum of care. Lancet HIV [Internet]. 2015;2(6):225–6. Available from: http://dx.doi.org/10.1016/S2352-3018(15)00086-7

446. Safreed-Harmon K, Blach S, Aleman S, Boe Kielland K, Bollerup S, Cooke G, et al. The Consensus Hepatitis C Cascade of Care: standardized reporting to monitor progress toward elimination. Clin Infect Dis. 2019;69(12):2218–27.

447. Rappold M, Rieger A, Gisinger M, Sarcletti M, Schmied B, Geit M, et al. The Hepatitis C Continuum of Care Among HIV Infected Individuals in Austria. In: 25th Conference on Retroviruses and Opportunistic Infections (CROI) 2018 March 4-7. Boston, MA, USA; 2018.

448. Chapko MK, Dufour DR, Hatia RI, Drobeniuc J, Ward JW, Teo CG. Cost-effectiveness of strategies for testing current hepatitis C virus infection. Hepatology. 2015;62(5):1396–404.

449. Reiberger T, Obermeier M, Payer BA, Baumgarten A, Weitner L, Moll A, et al. Considerable under-treatment of chronic HCV infection in HIV patients despite acceptable sustained virological response rates in a real-life setting. Antivir Ther. 2011;16(6):815–24.

450. Higgs P, Sacks-Davis R, Gold J, Hellard M. Barriers to receiving hepatitis c treatment for people who inject drugs: Myths and evidence. Hepat Mon. 2011;11(7):513–8.

451. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: From cascade to continuum to control. Clin Infect Dis. 2013;57(8):1164–71.

452. Lesko CR, Edwards JK, Moore RD, Lau B. A longitudinal, HIV care continuum: 10-year restricted mean time in each care continuum stage after enrollment in care, by history of IDU. AIDS. 2016;30(14):2227–34.

453. Meissner EG. Update in HIV–hepatitis C virus coinfection in the direct acting antiviral era. Curr Opin Gastroenterol [Internet]. 2017 May;33(3):120–7. Available from: http://insights.ovid.com/crossref?an=00001574-201705000-00004

454. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. Clin Infect Dis. 2001;33(4):562–9.

455. Re V Lo, Wang L, Devine S, Baser O, Olufade T. Hepatic decompensation in patients with HIV/Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV) triple infection versus HIV/HCV coinfection and the effect of Anti-HBV Nucleos(t)ide therapy. Clin Infect Dis. 2014;59(7):1027–31.

456. World Health Organization (WHO). Combating hepatitis B and C to reach elimination by 2030 [Internet]. World Health Organization. 2016. Available from: https://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/.

457. World Health Organization (WHO). Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021. 2019.

458. United Nations Office on Drugs and Crime; World Drug Report 2018. Booklet 1: Executive Summary - Conclusions and policy implications Implications [Internet]. 2018. Available from: https://www.unodc.org/wdr2018/prelaunch/

459. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. Lancet Glob Heal [Internet]. 2017;5(12):e1208–e1220. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2214109X1730373X

460. Ingiliz P, Christensen S, Kimhofer T, Hueppe D, Lutz T, Schewe K, et al. Sofosbuvir and Ledipasvir for 8 Weeks for the Treatment of Chronic Hepatitis C Virus (HCV) Infection in HCV-Monoinfected and HIV-HCV-Coinfected Individuals: Results from the German Hepatitis C Cohort (GECCO-01). Clin Infect Dis. 2016;63(10):1320–4.

461. Burton MJ, Naggie S. Real-world effectiveness of DAA therapies in human immunodeficiency virus/Hepatitis C virus coinfection: 996 veterans can't be wrong. Clin Infect Dis. 2017;64(12):1721–3.

462. Gayam V, Hossain MR, Khalid M, Chakaraborty S, Mukhtar O, Dahal S, et al. Real-World Clinical Efficacy and Tolerability of Direct-Acting Antivirals in Hepatitis C Monoinfection Compared to Hepatitis C/Human Immunodeficiency Virus Coinfection in a Community Care Setting. Gut Liver. 2018;12(6):694–703.

463. Neukam K, Morano-Amado LE, Rivero-Juárez A, Mancebo M, Granados R, Téllez F, et al. HIV-coinfected patients respond worse to direct-acting antiviral-based therapy against chronic hepatitis C in real life than HCV-monoinfected individuals: a prospective cohort study. HIV Clin Trials [Internet]. 2017;18(3):126–34. Available from: http://doi.org/10.1080/15284336.2017.1330801

464. Arias A, Aguilera A, Soriano V, Benítez-Gutiérrez L, Lledó G, Navarro D, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther. 2017;22(4):307–12.

465. Yee BE, Nguyen NH, Jin M, Lutchman G, Lim JK, Nguyen MH. Lower response to simeprevir and sofosbuvir in HCV genotype 1 in routine practice compared with clinical trials. BMJ Open Gastroenterol. 2016;3(1):e000056.

466. Bhattacharya D, Belperio PS, Shahoumian TA, Loomis TP, Goetz MB, Mole LA, et al. Effectiveness of All-Oral Antiviral Regimens in 996 Human Immunodeficiency Virus/Hepatitis C Virus Genotype 1-Coinfected Patients

Treated in Routine Practice. Clin Infect Dis. 2017;64(12):1711–20.

467. Boesecke C, Ingiliz P, Berger F, Lutz T, Schewe K, Schulze zur Wiesch J, et al. Liver Cirrhosis as a Risk Factor for Direct-Acting Antiviral Therapy Failure in Real-Life Hepatitis C Virus/Human Immunodeficiency Virus Coinfection. Open Forum Infect Dis. 2017;4(3):349–51.

468. Berenguer J, Gil-Martin Á, Jarrin I, Moreno A, Dominguez L, Montes M, et al. All-oral Direct-Acting Antiviral Therapy Against Hepatitis C Virus (HCV) in Human Immunodeficiency Virus/HCV–Coinfected Subjects in Real-World Practice: Madrid Coinfection Registry Findings. Hepatology. 2018;68(1):32–47.

469. Piroth L, Wittkop L, Lacombe K, Rosenthal E, Gilbert C, Miailhes P, et al. Efficacy and safety of direct-acting antiviral regimens in HIV/HCV-co-infected patients – French ANRS CO13 HEPAVIH cohort. J Hepatol [Internet]. 2017;67(1):23–31. Available from: http://dx.doi.org/10.1016/j.jhep.2017.02.012

470. Milazzo L, Lai A, Calvi E, Ronzi P, Micheli V, Binda F, et al. Direct-acting antivirals in hepatitis C virus (HCV)-infected and HCV/HIV-coinfected patients: real-life safety and efficacy. HIV Med [Internet]. 2017;18(4):284–91. Available from: http://www.wiley.com/bw/journal.asp?ref=1464-2662%0Ahttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emex&NEWS=N&AN=612481962

471. Monforte ADA, Cozzi-Lepri A, Ceccherini-Silberstein F, De Luca A, Caputo S Lo, Castagna A, et al. Access and response to direct antiviral agents (DAA) in HIV-HCV co-infected patients in Italy: Data from the Icona cohort. PLoS One. 2017;12(5):30–41.

472. Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, Jaroszewicz J, Zarębska-Michaluk D, Nazzal K, et al. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C: AMBER study. Aliment Pharmacol Ther. 2016;44(9):946–56.

473. Flisiak R, Łucejko M, Mazur W, Janczewska E, Berak H, Tomasiewicz K, et al. Effectiveness and safety of ledipasvir/sofosbuvir ± ribavirin in the treatment of HCV infection: The real-world HARVEST study. Adv Med Sci. 2017;62(2):387–92.

474. Hunyady B, Abonyi M, Gerlei Z, Gervain J, Horváth G, Jancsik V, et al. Ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin in HCV genotype 1 infected patients who failed previous protease inhibitor therapy. Clin Exp Hepatol. 2018;4(2):83–90.

475. National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. US Department of Health and Human Services. 2014.

476. Singer JD. Using SAS PROC MIXED to Fit Multilevel Models, Hierarchical Models, and Individual Growth Models. J Educ Behav Stat. 1998;23(4):323–55.

477. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015;373(8):705–13.

478. Sulkowski MS, Eron OJ, Wyles D, Trinh R, Lalezari J, Wang C, et al. Ombitasvir, Paritaprevir Co-dosed with Ritonavir, Dasabuvir, and Ribavirin for Hepatitis C in Patients Co-infected with HIV-1 a Randomized Trial. JAMA - J Am Med Assoc. 2015;313(12):1223–31.

479. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med [Internet]. 2015;373(8):714–25. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1503153

480. Chung RT, Ghany MG, Kim AY, Marks KM, Naggie S, Vargas HE, et al. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for Testing, Managing, and Treating Hepatitis C Virus infection. Clin Infect Dis.

2018;67:1477–92.

481. Mcginnis J, Mccombs J, Mehta D, Fox S. Analysis of the Impact of HIV Co-Infection on Hepatitis C Treatment Effectiveness for Patients Using New Direct-Acting Antivirals. J Hepatol. 2016;64(2):S219–20.

482. Randazzo A, Leith D, Demma S, Macdonald D. THU-172-It's the ribavarin, stupid: an analysis of >10, 000 hepatitis C treatment monitoring encounters and the factors associated with side-effects and non-adherence. J Hepatol [Internet]. 2019;70(1):e237–8. Available from: https://doi.org/10.1016/S0618-8278(19)30447-5

483. Laprise C, Baril J-G, Dufresne S, Trottier H. Atazanavir and Other Determinants of Hyperbilirubinemia in a Cohort of 1150 HIV-Positive Patients: Results from 9 Years of Follow-Up. AIDS Patient Care STDS. 2013;27(7):378–86.

484. Prescribing Information for REBETOL, MERCK, 2020 [Internet]. [cited 2020 Dec 16]. Available from: https://www.merck.com/product/usa/pi_circulars/r/rebetol/rebetol_pi.pdf

485. Prescribing Information for REYATAZ, Bristol-Myers Squibb, 2018 [Internet]. [cited 2020 Dec 16]. Available from: https://packageinserts.bms.com/pi/pi_reyataz.pdf

486. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. Hepatology. 2016;64(2):405–14.

487. Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. Vol. 25, Journal of Viral Hepatitis. 2018. p. 220–7.

488. Lambers FAE, Prins M, Thomas X, Molenkamp R, Kwa D, Brinkman K, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually

acquired acute hepatitis C virus infection in HIV-infected MSM MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study group. AIDS. 2011;25(17):21–7.

489. Martinello M, Grebely J, Petoumenos K, Gane E, Hellard M, Shaw D, et al. HCV reinfection incidence among individuals treated for recent infection. J Viral Hepat. 2017;24(5):359–70.

490. Pineda JA, Núñez-Torres R, Téllez F, Mancebo M, García F, Merchante N, et al. Hepatitis C virus reinfection after sustained virological response in HIV-infected patients with chronic hepatitis C. J Infect. 2015;71(5):571–7.

491. Marco A, Guerrero RA, Vergara M, Gallego C, Solé C, Planella R, et al. Reinfection in a large cohort of prison inmates with sustained virological response after treatment of chronic hepatitis C in Catalonia (Spain), 2002–2016. Int J Drug Policy [Internet]. 2019;72:189–94. Available from: https://doi.org/10.1016/j.drugpo.2019.05.014

492. Islam N, Krajden M, Shoveller J, Gustafson P, Gilbert M, Buxton JA, et al. Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study. Lancet Gastroenterol Hepatol [Internet]. 2017;2(3):200–10. Available from: http://dx.doi.org/10.1016/S2468-1253(16)30182-0

493. Young J, Rossi C, Gill J, Walmsley S, Cooper C, Cox J, et al. Risk factors for hepatitis C virus reinfection after sustained virologic response in patients coinfected with HIV. Clin Infect Dis. 2017;64(9):1154–62.

494. Ingiliz P, Wehmeyer MH, Boesecke C, Schulze Zur Wiesch J, Schewe K, Lutz T, et al. Reinfection With the Hepatitis C Virus in Men Who Have Sex With Men After Successful Treatment With Direct-acting Antivirals in Germany: Current Incidence Rates, Compared With Rates During the Interferon Era. Clin Infect Dis. 2019;1–7.

495. Rossi C, Butt ZA, Wong S, Tyndall MW, Krajden M, Naveed Z. Hepatitis C virus

reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. J Hepatol [Internet]. 2018;69(5):1007–14. Available from: https://doi.org/10.1016/j.jhep.2018.07.025

496. Berenguer J, Gil-Martin Á, Jarrin I, Montes ML, Domínguez L, Aldámiz-Echevarría T, et al. Reinfection by hepatitis C virus following effective all-oral direct-acting antiviral drug therapy in HIV/hepatitis C virus coinfected individuals. AIDS. 2019;33(4):685–9.

497. Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. Drug Alcohol Depend. 2008;93(1–2):148–54.

498. Ingiliz P, Krznaric I, Stellbrink HJ, Knecht G, Lutz T, Noah C, et al. Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: No influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. HIV Med. 2014;15(6):355–61.

499. Martin TCS, Martin NK, Hickman M, Vickerman P, Page EE, Everett R, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. AIDS. 2013;27(16):2551–7.

500. Mehta SH, Cox A, Hoover DR, Wang X, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. Lancet. 2002;359(9316):1478–83.

501. Osburn WO, Fisher BE, Dowd KA, Urban G, Liu L, Ray SC, et al. Spontaneous Control of Primary Hepatitis C Virus Infection and Immunity Against Persistent Reinfection. Gastroenterology [Internet]. 2010;138(1):315–24. Available from: http://dx.doi.org/10.1053/j.gastro.2009.09.017

502. Abdel-Hakeem MS, Shoukry NH. Protective immunity against hepatitis C: Many shades of gray. Front Immunol. 2014;5(JUN):1–19.

503. Thomson EC, Fleming VM, Main J, Klenerman P, Weber J, Eliahoo J, et al.

Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut. 2011;60(6):837–45.

504. Boesecke C, et al. Fueling the epidemic: Low rates of spontaneous clearance of acute HCV coinfection. 25th Conference on Retroviruses and Opportunistic Infections; March 4-7, 2018; Boston. Abstract 129. Available from: http://www.natap.org/2018/CROI/croi_154.htm

505. Aisyah DN, Shallcross L, Hully AJ, O'Brien A, Hayward A. Assessing hepatitis C spontaneous clearance and understanding associated factors—A systematic review and meta-analysis. Vol. 25, Journal of Viral Hepatitis. 2018. p. 680–98.

506. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020;73(5):1170–218.

507. Soriano V, Mocroft A, Rockstroh J, Ledergerber B, Knysz B, Chaplinskas S, et al. Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. J Infect Dis. 2008;198(9):1337–44.

508. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson K. Viral infections in short-term injection drug users: The prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health. 1996;86(5):655–61.

509. Des Jarlais DC, Diaz T, Perlis T, Vlahov D, Maslow C, Latka M, et al. Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New York City. Am J Epidemiol. 2003;157(5):467–71.

510. Peters L, Mocroft A, Soriano V, Rockstroh J, Kirkby N, Reiss P, et al. High rate of hepatitis C virus (HCV) recurrence in HIV-infected individuals with spontaneous HCV RNA clearance. HIV Med [Internet]. 2014 Jun;15(10):615–

20. Available from: http://doi.wiley.com/10.1111/hiv.12160

511. Sacks-Davis R, Grebely J, Dore GJ, Osburn W, Cox AL, Rice TM, et al. Hepatitis c virus reinfection and spontaneous clearance of reinfection - The InC3 study. J Infect Dis. 2015;212(9):1407–19.

512. Chkhartishvili N, Gabunia P, Abutidze A, Korkotashvili G, Chokoshvili O, Dvali N, et al. HCV reinfection among HIV patients after DAA therapy in the country of Georgia. In: Conference on Retroviruses and Opportunistic Infections [Internet]. Boston, Massachusetts; 2020. Available from: https://www.croiconference.org/abstract/hcv-reinfection-among-hiv-patients-after-daa-therapy-in-the-country-of-georgia/

513. Doyle JS, Santen DK van, Iser D, Sasadeusz J, O'Reilly M, Harney B, et al. Micro-elimination of hepatitis C among people with HIV coinfection: declining incidence and prevalence accompanying a multi-center treatment scale-up trial. Clin Infect Dis [Internet]. 2020; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0924977X16300050%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/27139079

514. Hosseini-Hooshyar S, Martinello M, Yee J, Read P, Baker D, Post JJ, et al. Low hepatitis C virus reinfection rate despite ongoing risk following universal access to direct-acting antiviral therapy among people living with HIV. AIDS. 2020;34(9):1347–58.

515. Martin TC, Rauch A, Salazar-vizcaya L, Martin NK. Understanding and addressing HCV reinfection among men who have sex with men. 2018;32(2):395–405.

516. Hoornenborg E, Coyer L, Boyd A, Achterbergh RCA, Loeff MFS van der, Bruisten S, et al. High incidence of HCV in HIV-negative men who have sex with men using pre-exposure prophylaxis. J Hepatol. 2020;72(5):855–64.

517. Charre C, Cotte L, Kramer R, Miailhes P, Godinot M, Koffi J, et al. Hepatitis C

virus spread from HIV-positive to HIV-negative men who have sex with men. PLoS One. 2018;13(1):1–10.

518. Ramière C, Charre C, Miailhes P, Bailly F, Radenne S, Uhres A, et al. Patterns of Hepatitis C Virus Transmission in Human Immunodeficiency Virus (HIV)–infected and HIV-negative Men Who Have Sex With Men. Clin Infect Dis. 2019;69(12):2127–35.

519. Medrano J, Barreiro P, Resino S, Tuma P, Rodríguez V, Vispo E, et al. Rate and Timing of Hepatitis C Virus Relapse after a Successful Course of Pegylated Interferon plus Ribavirin in HIV-Infected and HIV-Uninfected Patients. Clin Infect Dis. 2009;49(9):1397–401.

520. Lazarus J V., Laut KG, Safreed-Harmon K, Peters L, Johnson M, Fätkenheuer G, et al. Disparities in HIV clinic care across Europe: findings from the EuroSIDA clinic survey. BMC Infect Dis [Internet]. 2016;16(1):335. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1685-x

521. UNAIDS. Fact sheet - World AIDS Day 2020 [Internet]. 2020. Available from: https://www.unaids.org/en/resources/fact-sheet

522. Swindells S, Andrade-Villanueva J-F, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression | Enhanced Reader. N Engl J Med [Internet]. 2020 [cited 2021 Aug 23];382(12):1112–23. Available from: chrome-extension://dagcmkpagjlhakfdhnbomgmjdpkdklff/enhanced-reader.html?openApp&pdf=https%3A%2F%2Fwww.nejm.org%2Fdoi%2Fpdf%2F10.1056%2FNEJMoa1904398%3FarticleTools%3Dtrue

523. Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Vol. 40, Liver International. 2019. p. 522–9.

524. Girardi E, Puoti M, Mussini C, Tavelli A, Mastrorosa I, Silberstein FC, et al. The

hepatitis C continuum of care among HIV infected individuals in the Icona study network. J Hepatol [Internet]. 2018;68(Supplement 1):S178–9. Available from: http://dx.doi.org/10.1016/S0168-8278(18)30568-3

525. He T, Lopez-Olivo MA, Hur C, Chhatwal J. Systematic review: cost-effectiveness of direct-acting antivirals for treatment of hepatitis C genotypes 2-6. Aliment Pharmacol Ther. 2017;46(8):711–21.

526. Abozeid M, Alsebaey A, Abdelsameea E, Othman W, Elhelbawy M, Rgab A, et al. High efficacy of generic and brand direct acting antivirals in treatment of chronic hepatitis C. Int J Infect Dis [Internet]. 2018;75:109–14. Available from: https://doi.org/10.1016/j.ijid.2018.07.025

527. Sacks-Davis R, Doyle JS, Rauch A, Beguelin C, Pedrana AE, Matthews G V., et al. Linkage and retention in HCV care for HIV-infected populations: early data from the DAA era. J Int AIDS Soc. 2018;21:e25051.

528. Salazar-Vizcaya L, Kouyos RD, Zahnd C, Wandeler G, Battegay M, Darling KEA, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology. 2016;64(6):1856–69.

529. Treloar C, Rance J, Backmund M. Understanding barriers to hepatitis c virus care and stigmatization from a social perspective. Clin Infect Dis. 2013;57(SUPPL.2):51–5.