

Novel Screening Strategies for HIV, Hepatitis B and C infection

**A thesis submitted to the University of Dublin, Trinity College, for the
degree of Doctor in Clinical Medicine**



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I would like to thank the patients who attend St James's Hospital, who throughout both testing and follow-up care, have contributed with the greatest importance and without which these studies could not have taken place. I would like to thank Professor Colm Bergin, my research supervisor and clinical mentor for the past 5 years, for his endless advice, support and help. I would like to thank Anne Moriarty, Viral Liaison Nurse and Siobhan O'Dea, Research Nurse at St James's Hospital, whose hard work was essential for the successful running of these projects. Lastly, I would like to thank my husband Liam for all his support throughout my clinical and research training.

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Summary

Introduction: Despite prevention measures in place, rates of Human Immunodeficiency Virus (HIV) infection have failed to decline in Ireland in recent years. From 2015 to 2016, a 6% increase was seen in notifications of newly diagnosed HIV infection. In 2015, almost 50% of those who are newly diagnosed present at a late stage of infection. It is estimated that 25% of those with HIV in the United Kingdom (UK) are unaware of their diagnosis. High numbers of chronic hepatitis B infection continue to be diagnosed in Ireland every year; the majority of these patients are from countries of high prevalence. Rates of newly diagnosed hepatitis C infection have fallen slightly in recent years, but this is thought to be due to a change in the reporting policy to those with active infection only. It is thought that over 50% of those with hepatitis C in Ireland are unaware of their infection. The HIV UNAIDS 90-90-90 plan outlines a target for 2020, where 90% of those with HIV infection be diagnosed, 90% of those are linked to care and 90% of those are on effective anti-retroviral therapy (ART). The National Hepatitis C Treatment Programme aims to see progression towards eradication of hepatitis C by 2026. Risk based screening nationally are the most common screening practices in Ireland.

Widespread opt-out testing for HIV and hepatitis B takes place in antenatal settings and in sexual health clinics. Risk-based screening is almost always used for hepatitis C testing. It was proposed to undertake a research programme to understand current HIV presentation patterns and the current landscape of blood borne virus cascade of care, to introduce a pilot blood borne virus screening programme, to examine the feasibility and acceptability of such a programme and to examine the sero-prevalence of infection in a high-prevalence cohort. We aimed to understand the demographics of those diagnosed, measure linkage to care rates,

monitor patients through their treatment pathways and examine ways to improve the testing and follow up service.

Methods: Retrospective cohort studies examining HIV, hepatitis B and C retention in care rates and treatment outcomes were undertaken at our centre. A nested case control study examining factors associated with non-retention in HIV care was performed. A retrospective cohort study of those who presented with late HIV infection at our centre from 2002 and 2014 was then performed. A cross sectional pilot study was then performed, where 10,000 patient samples in St James's Hospital Emergency Department were tested on an opt-out basis for HIV, hepatitis B and C infection. Uptake rate of testing was recorded. Patients were diagnosed and linked to care and demographics were recorded. Given high rates of poor engagement to hepatitis C care, a retrospective cohort study of those with known hepatitis C infection was then performed to understand factors associated with non-engagement in hepatitis C care. Success of this pilot study led to the implementation of blood-borne virus (BBV) testing as routine care. Referrals to the Department of Genito-Urinary Medicine and Infectious Diseases (GUIDE) were recorded and tracked to monitor retention in care and triage/treatment outcomes. A quality improvement programme was then undertaken to explore ways to improve hepatitis C retention in care.

Results: Patients with heterosexual mode of acquisition and of an older age were more likely to present at a late point in their HIV illness, suggesting a non-risk based HIV screening approach is necessary. In our BBV cohort, retention in HIV care rates are comparable with international standards but can be improved upon to meet the UNAIDS 90-90-90 target. Hepatitis B and C retention in care rates are poor. No significant demographic is associated with hepatitis B disengagement from care and reasons for disengaging are poorly understood. Results of a nested case-control study showed that the non-Irish, heterosexual population are

more likely to disengage from HIV care. Following the introduction of a pilot Emergency Department (ED) opt-out BBV study, a high feasibility and acceptability rate was found. High sero-prevalence for all 3 infections was found, and a high proportion of those with previously known hepatitis C were not attending care. Cases were diagnosed and linked/re-linked to care. Factors associated with non-engagement in hepatitis C care included active intravenous drug use. Success of this pilot project led to the introduction of routine testing in the ED. Results show ongoing overall high sero-prevalence rates. Despite intensive counselling and one to one patient contact following diagnosis, rates of attendance for hepatitis C care continue to be low. A quality improvement programme was introduced to find ways to improve the poor hepatitis C retention in care rate. Despite multiple interventions employed to try to improve these rates, little improvement was seen. This programme provided the team with valuable experience in Quality Improvement tools that can be used to deliver quality healthcare.

Conclusion: Patients need to be diagnosed with infections they are unaware of and linked to care. We have shown that this is possible, and the healthcare infrastructure in place can serve these patients well. We need to make improvements in our healthcare service in the areas of BBV retention in care and increased BBV testing overall. Improved healthcare staff education on the need for widespread BBV testing, the need to understand predictors of non-retention in care and the need to be better aware of HIV clinical indicant conditions is required. Lastly, BBV screening programmes need to be expanded nationally to allow for widespread testing.

My Research Role

Study Inception and Design

I independently designed all the studies outlined in this thesis. I researched background methods to ensure robust study design and communicated my plans with my research supervisor.

Ethics submissions

I wrote ethics submissions, patient information leaflets and study protocols for the Emergency Department Viral Screening (EDVS) Study, the General Practice (GP) Migrant Screening Study and the Qualitative Barriers to HIV Care Semi-Structured interview. I answered multiple queries from the ethics committees and for the EDVS Study I sent programme reports and reports on breach of protocol as required to the Ethics Committee involved.

Database Management and Statistical analysis

As part of the retrospective cohort studies outlined in this thesis, including hepatitis B and C retention and engagement in care studies and HIV late presenter retrospective cohort study, I independently designed a suitable database, and coded variables accordingly to allow for effective database management. The HIV retention in care nested case control study required my development of a database that allowed matching each case to control in a 1:4 ratio. Data then required cleaning, coding and sorting with subsequent statistical analysis. For the Emergency Department Viral Screening Cross Sectional Study, I developed a working database from the beginning of the project, and then subsequently coded and sorted all variables to describe results accurately. On initiation of the Emergency Department Viral Screening Programme, I developed a working database that is updated in real-time by a clinical nurse

specialist, which allows for ongoing recording of output from the programme that allows for close monitoring of programme activity and has now recorded a large amount of useful clinical data.

I chose the appropriate statistical tests, performed all statistical analysis on SPSS and present the results myself for all research presented in this study.

Business planning

I wrote a business plan that was submitted to the Chief Executive Officer of St James's Hospital and the Social Inclusion Unit at the HSE. As a result, €400,000 funding per year was granted to begin and continue routine blood borne viral screening in St James's Emergency Department, the first global initiative of its kind.

Funding

I applied for and secured non-restrictive grant funding at an early point in my research to fund a Viral Liaison Nurse Specialist, whose role involves the follow up the patients with positive tests. This funding was obtained from MSD Pharmaceuticals. I was then successfully awarded the Gilead UK and Ireland HIV and Hepatitis Fellowship 2016 (competitive international grant funding) to self-fund my research since I began in the full-time role 18 months ago.

Committee membership and leadership

I formed and led the EDVS Committee, with input from the Microbiology, ED, Hepatology and IT department at St James's Hospital that met on a weekly basis throughout the 10-month pilot study. Prior to commencement of the EDVS routine screening programme, I formed a working sub-group committee to collectively decide on a revised Standard Operation Procedure document, that I then wrote and have updated on 2 occasions where required. As EDVS

Medical Lead for routine BBV screening, I led the programme, chaired all the meetings and in this role I ensured smooth and effective running of the programme.

QI leadership

I was team leader for the Quality Improvement (QI) programme at the Department of Genito-Urinary Medicine and Infectious Diseases at St James's Hospital. I led and directed the team and identified multiple QI processes and interventions during the programme. Results have been presented nationally at the HSE National Patient Safety Conference and also at the International Healthcare Improvement Conference in Orlando, Florida.

Collaboration

Throughout this research, I have collaborated with many research colleagues both in St James's Hospital and Trinity College Dublin. Specifically, the EDVS study and ongoing routine programme involves ongoing collaboration between GUIDE, ED, Hepatology, Microbiology and IT departments at St James's Hospital. I have recently collaborated with the Centre for Global Health at TCD to develop and conduct semi-structured qualitative interviews to understand true barriers for HIV retention in care.

Presentation of research

I have written and presented the research outlined in this thesis at multiple national and international conferences. I have familiarised myself with the techniques required for presentation of various research topics. I have written up the research outlined in this thesis also and have recently published this research in multiple international journals. As a result, I have now been invited and have undertaken peer review for international academic journals.

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List of Abbreviations

AI: Advanced Immunodeficiency

AIDS: Auto-immune Deficiency Syndrome

AFP: Alpha-foeto protein

ART: Anti-retroviral Therapy

BBV: Blood Borne Virus

CDC: Centre for Disease Control

CNS: Clinical Nurse Specialist

DAA: Direct Acting Anti-Viral

DDI: Drug-drug interaction

DNA: Did Not Attend

EASL: European Association of Liver Diseases

ED: Emergency Department

EDVS: Emergency Department Viral Screening

EOT: End of Treatment

EU/EEA: European Union/Eastern European A

eAg: Hepatitis B e Antigen

FDA: Food and Drug Authority

GP: General Practice

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HPSC: Health Protection Surveillance Centre

HSE: Health Service Executive

ICORN: Irish Hepatitis C Research Outcomes Network

IDSi: Infectious Disease Society of Ireland

IT: Information Technology

IQR: Inter-Quartile Range

IVDU: Intravenous drug users

LPS: Late Presenters

MI: Moderate Immunodeficiency

MSM: Men who have sex with men

ND: Non-Detectable

NRI: No risk identified

PCR: Polymerase Chain Reaction

PEP: Post-Exposure Prophylaxis

PrEP: Pre-Exposure Prophylaxis

PWID: People who inject drugs

RITA: Recent HIV Infection Testing Algorithm

RNA: Ribonucleic Acid

SD: Standard Deviation

SVR: Sustained Viral Response

TDF: Tenofovir

UK: United Kingdom

USA: United States of America

WHO: World Health Organisation

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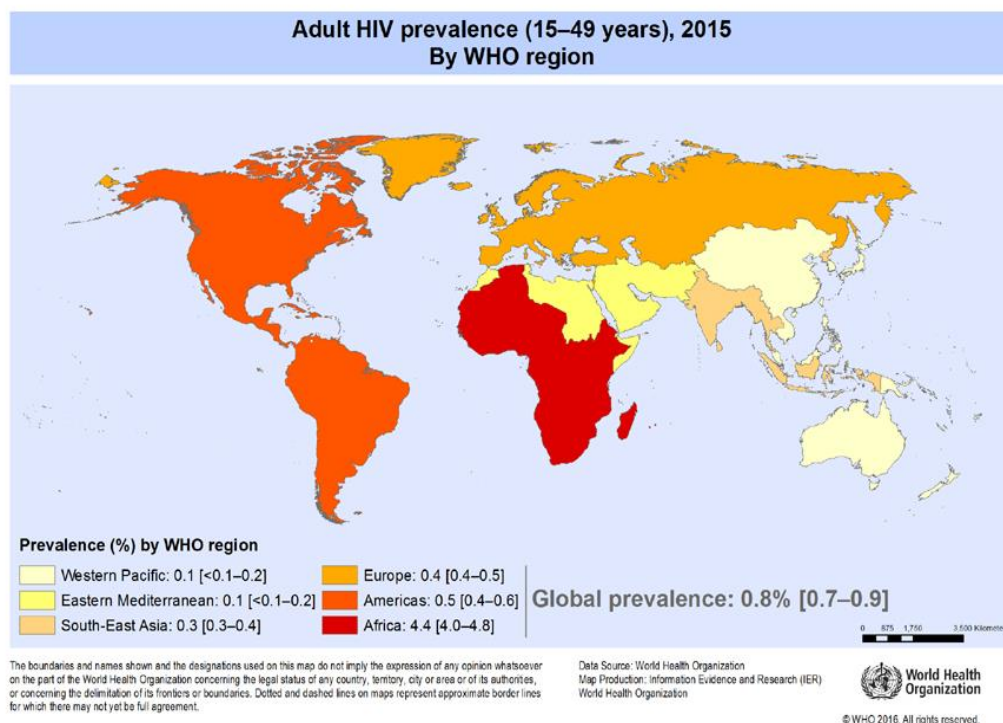
Chapter 1: Introduction

1.1 Epidemiology of HIV

1.1.1 Global HIV Epidemiology

In 2015, it was estimated that 36.7 million people are living with HIV worldwide. 1.1 million people died of AIDS related illnesses worldwide in 2015 and the burden of the epidemic continues to vary worldwide. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.4%) living with HIV and accounting for nearly 70% of the people living with HIV worldwide. (1) (Figure 1-1)

Figure 1-1: Adult HIV prevalence by WHO region



Source: World Health Organisation. Global Health Observatory data. Adult HIV prevalence (15-29 years), 2015.

In the United States, figures from the Centre for Disease Control and Prevention (CDC) show that in 2015, an estimated 39,513 people were diagnosed with HIV. (2) While many risk groups for acquisition for HIV are recognised worldwide, including heterosexual contact and injection drug use, in the western world Men who have sex with men (MSM) are now the group at highest risk of HIV acquisition. In the United States, MSM and bisexual males represent 2% of the adult population, but they experience disproportionate rates of HIV infection, accounting for 67% of new HIV cases respectively in 2015. (3)

In EU/EEA countries, in 2015, 29,747 people were newly diagnosed with HIV. In these countries, where 31 European countries contribute to data, MSM transmission is also now the predominant mode of HIV transmission, accounting for 42% of the total number of new diagnoses in 2015. (4)

1.1.2 Epidemiology of HIV in Ireland

In Ireland rates of newly diagnosed HIV infection have increased in recent years. Provisional data from the Health Protection and Surveillance Centre for 2016 show that 512 people were newly diagnosed with HIV-1 infection in Ireland, representing a 6% increase from 2015 (n=485). (Figure 1-2) MSM was the predominant mode of acquisition, accounting for 46% of all new HIV notifications. (5) From 2005 to 2015, the number of new diagnoses among MSM has increased threefold (from 60 to 183) and the median age at diagnosis has dropped from 37 to 31 years. (6) Proportions of heterosexual transmissions continue to decrease, accounting for 18% of new diagnoses. (7) In 2015, there were 45 new diagnoses among people who inject drugs (PWID) (9.2%) which is an increase on recent years, and likely reflects the recently recognised HIV outbreak among PWID in the Dublin area. (8) Rates of HIV new diagnoses

among PWID were lower in 2016; 19(4%) of all diagnoses occurred in those with IVDU as mode of acquisition. (7) (Figure 1-3a, Figure 1-3b)

For those diagnosed and living with HIV in Ireland, a HIV prevalence rate of over 2 per 1000 among 15-59 year olds in the Dublin area has been reported and the overall Irish HIV prevalence is 1.09 per 1000. (9)

1.1.2.1 Undiagnosed HIV Infection

In the United Kingdom, around 13,500 (13%) people living with HIV in 2015 remained undiagnosed, and of those living with HIV, it is estimated that heterosexual male and female risk group represent the highest proportion amongst risk groups who are unaware of their diagnosis (Figure 1-4) (10) Similar figures in the Irish population are unknown, and it is unknown whether figures are similar to the UK, given potential differences in demography of migration between the UK and Ireland.

1.1.2.2. Late HIV Presentation

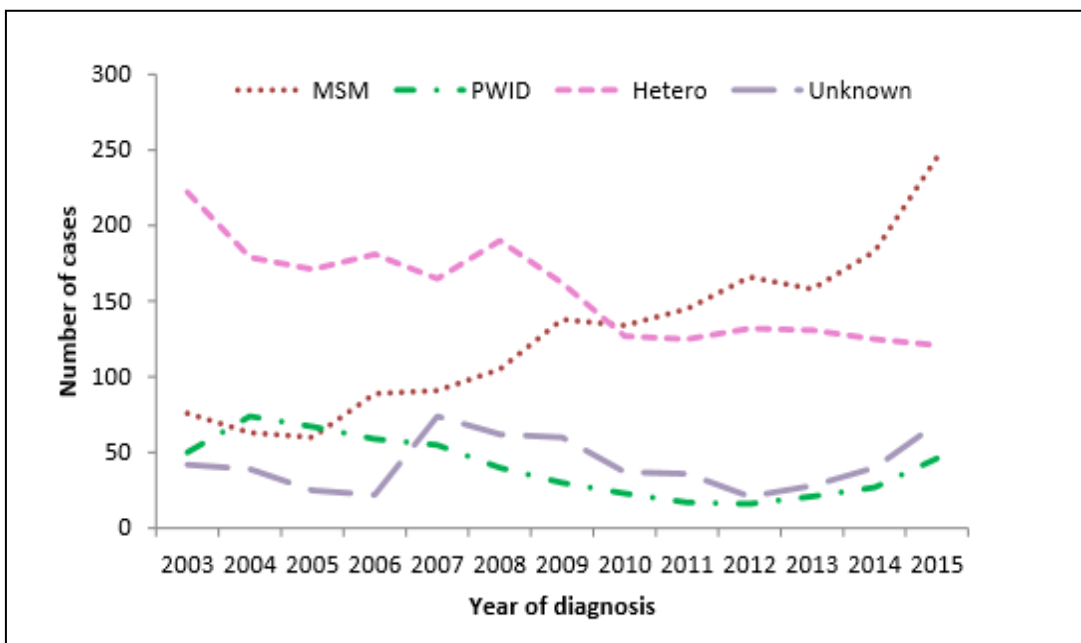
In EU/EEA countries, a significant proportion of patients present at a late stage of HIV infection. Close to half (48%) of people newly diagnosed for whom information about CD4 cell count at the time of HIV diagnoses was available, were late presenters with CD4 cell counts below 350 cells per mm³, including 28% with advanced HIV infection (CD4 <200 cells/mm³). (11). In Ireland, forty five percent of new diagnoses in 2015 were late presenters (CD4 count of less than 350 cells/mm³ or an AIDS defining illness at diagnosis). This is very similar to proportions in preceding years (47% in 2014, 49% in 2013). Late presentation was less common among MSM (36%) and PWID (53%) than among heterosexuals (51% in females and 67% in males). (12)

Figure 1-2: HIV diagnoses and diagnosis rate (per 100,000 population), 2003 - 2015



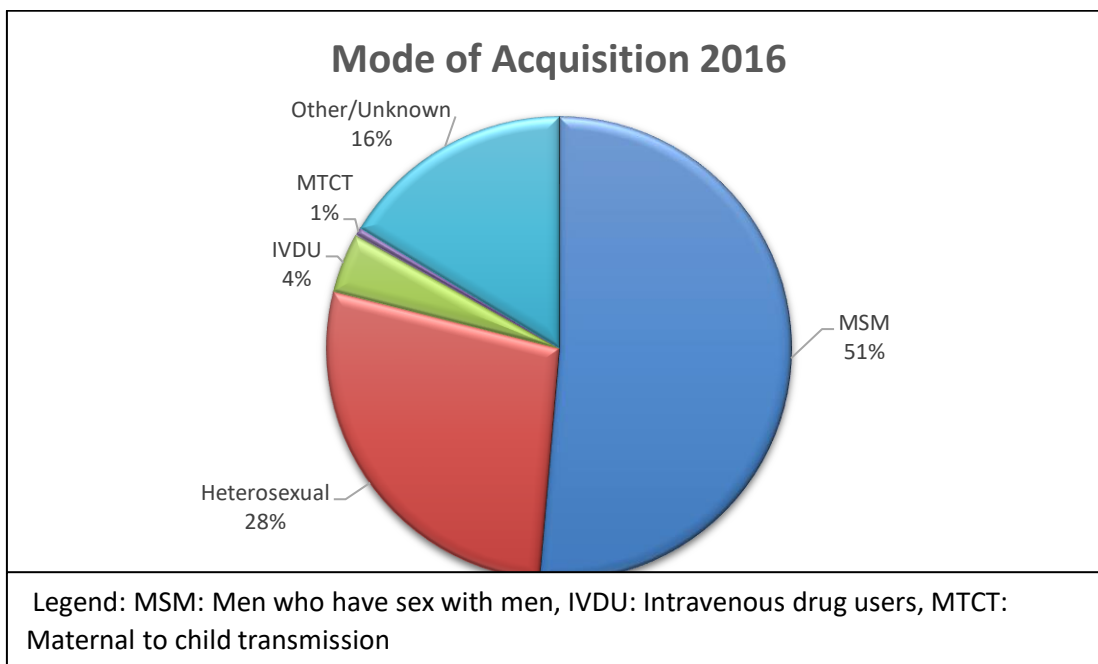
Source: Health Protection Surveillance Centre HIV in Ireland 2015 Report. 5th October 2016.

Figure 1-3a: HIV by Probable Route of Transmission 2003-2015



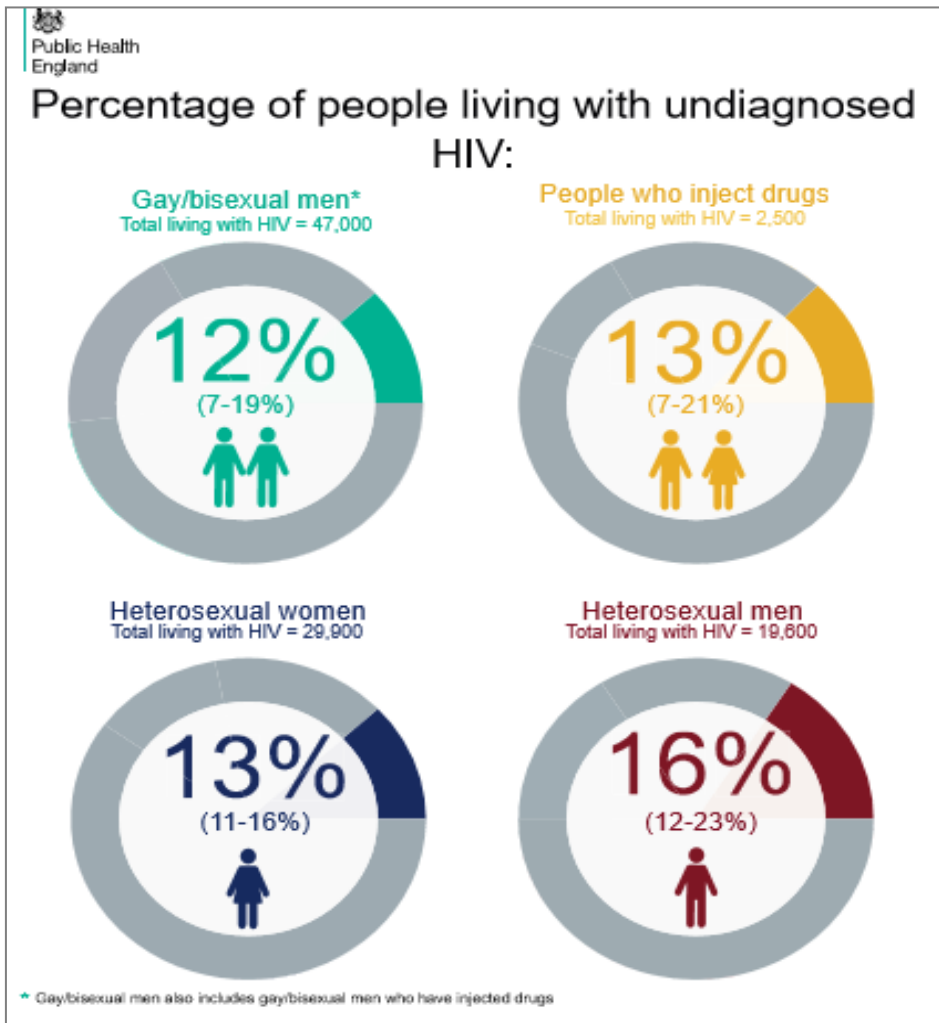
Source: Health Protection Surveillance Centre HIV in Ireland 2015 Report. 5th October 2016.

Figure 1-3b: Mode of HIV Acquisition per Risk Category 2016



Source: Health Protection Surveillance Centre HIV in Ireland 2016 Report. 3rd October 2017.

Figure 1-4: Who is most affected by Undiagnosed HIV? – Public Health England



Source: Public Health England. HIV in the UK: 2016 Report

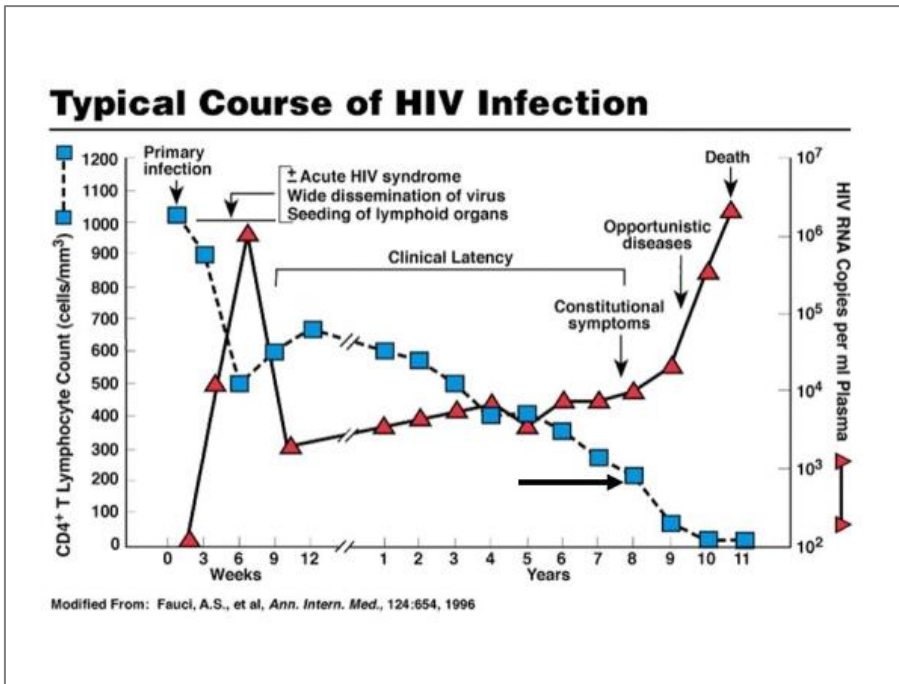
1.1.3. Natural History of HIV-1 infection

The US Centre for Disease and Control describes 4 stages of HIV infection:

- 1) **Acute Retroviral Syndrome:** This is an illness with flu-like symptoms like infectious mononucleosis. It can occur a few days after HIV infection but can also occur several weeks after the person is infected. The symptoms can range from mild to severe and usually disappear on their own after 2 to 3 weeks. Most people do not develop any symptoms or have very mild symptoms only.
- 2) **Stage 1 (HIV infection):** This is where there are no AIDS-related clinical conditions and the CD4+ cell count is at least 500 cells/ml or the percent of CD4+ cells is at least 29% of all lymphocytes.
- 3) **Stage 2 (HIV infection):** There are no AIDS-related conditions and the CD4+ cell count is 200 to 499 or the percent of CD4+ cells is 14% to 28% of all lymphocytes.
- 4) **Stage 3 (AIDS):** The CD4+ cell count is lower than 200, the percent of CD4+ cells is less than 14% of all lymphocytes, or an AIDS-related condition is present. (13)

(See Figure 1-5)

Figure 1-5: Natural History of HIV infection



Source: Aidsmap: www.aidsmap.com, adapted by Prof Luc Kestens 2005

1.1.4 HIV Prevention

Many HIV prevention methods including access to condoms, HIV testing and linkage to care, antiretroviral therapy and prevention programmes for those with HIV and their partners and for people at high risk for HIV infection are proven to work and are recommended by the CDC.

1.1.4.1 Randomised Controlled Trials

While various HIV prevention measures have been studied, and many have proven successful, few have been proven to be successful at reducing the risk of HIV transmission at randomised controlled trial. A review of randomised controlled trials of HIV prevention methods found that of 39 interventions tested, only 5 showed significant evidence of protection. (14) These included 3 trials on male circumcision (15,16,17), the Mwanza trial of sexually transmitted infection treatment for HIV prevention (18) and the RV 144 trial of a prime-boost vaccine regimen in Thailand. (19)

1.1.4.2 HIV post-exposure prophylaxis (PEP)

Due to ethical and practical concerns with the conduction of a randomised controlled trial to evaluate the efficacy of PEP, no such trial has been conducted. One informative case-control study showed that taking a course of zidovudine monotherapy after occupational needle-stick exposure reduced the risk of HIV infection by approximately 81 percent. (20)

Other observational studies following sexual exposure or injecting drug use have been conducted. One such study included 891 people who had requested post-exposure prophylaxis after possible non-occupational HIV exposure (e.g. sexual exposure or injecting drug use). Six out of the 700 that returned for testing after 12 weeks were HIV positive. However, it was

difficult to determine the exact moment of exposure and PEP efficacy as all six had been exposed over a six-month period preceding PEP use. (21) Furthermore, in a South African study of 480 rape survivors taking a 6-week course of zidovudine and lamivudine, only one woman became HIV positive. (22) Due to success demonstrated with the use of multi-drug regimens for HIV treatment, these are used for PEP also, but multi-drug regimens have not been studied for this purpose.

There is a distinct lack of definitive evidence to show that PEP can be effective in non-occupational settings. Studies have generally concluded that PEP 'might' reduce the risk of HIV infection and it is widely available for this purpose, but none have been able to say that it is a definite preventative measure.

1.1.4.3 HIV pre-exposure prophylaxis (PrEP)

HIV pre-exposure prophylaxis has been studied as a method of HIV prevention in both the MSM and heterosexual population. The Pre-exposure Prophylaxis Initiative (iPrEx) trial of pre-exposure prophylaxis for MSM showed a 41% reduction in HIV incidence in those receiving an oral combination of daily tenofovir/emtricitabine. (23) CAPRISA 004 trial showed a 39% reduction in HIV incidence with the use of tenofovir gel. (24) Partners PrEP study showed a 67-75% reduction in HIV incidence in sero-discordant couples (25) while TDF2 showed a protective efficacy of 62% with the use of daily tenofovir/emtricitabine in heterosexual couples in Botswana. (26) However, a placebo-controlled trial of PrEP in African women (FEM-PrEP) was discontinued early when it was deemed unlikely that the intervention could show a protective effect in the study population. (27) More recently, the Ipergay study that enrolled 400 MSM in Canada and France evaluated the safety and efficacy of "on-demand" use of PrEP in the high risk MSM population, where PrEP is taken between 2-24 hours before sexual intercourse, and

again at 24 hours and 48 hours following intercourse. Results showed a relative reduction of 86% in the incidence of HIV infection with the use of on demand PrEP. As a result, on demand PrEP with oral Truvada ART is highly effective to reduce the incidence of HIV-infection in high risk MSM and a good safety profile was also observed. (28) The United Kingdom PROUD trial evaluated the efficacy of immediate daily PrEP against deferred PrEP at one year. Results showed a relative risk reduction of HIV infection of 86% in those who immediately received daily PrEP. (29)

In 2014 the CDC provided new guidelines for the expanded use of Pre-Exposure Prophylaxis in the US, where PrEP is now recommended as one prevention option for sexually-active adult MSM at substantial risk of HIV acquisition. (30) These guidelines were updated in 2017 (31) and have been implemented into routine practice in both sexual health clinics and primary care clinics also, with 170,000 prescriptions issued in the United States since 2012 (32). Further studies are required to investigate the use of PrEP on a widespread basis and as part of an integrated programme as a valuable and successful HIV prevention strategy.

1.1.4.4 Anti-Retroviral Therapy as Prevention

The benefits of ART are now well recognized, and it has also previously been shown that those in care for HIV in Ireland have high rates of viral suppression, with 94% of patients on treatment having HIV RNA < 50cpm. (33) The personal benefits of an earlier diagnosis are many: earlier access to ART, reduced mortality, reduced risk of cardiovascular diseases, malignancies, slower progression of hepatitis B and C if co-infected and overall improved outcomes. The public health benefits of earlier diagnoses mean reduced onward transmission.

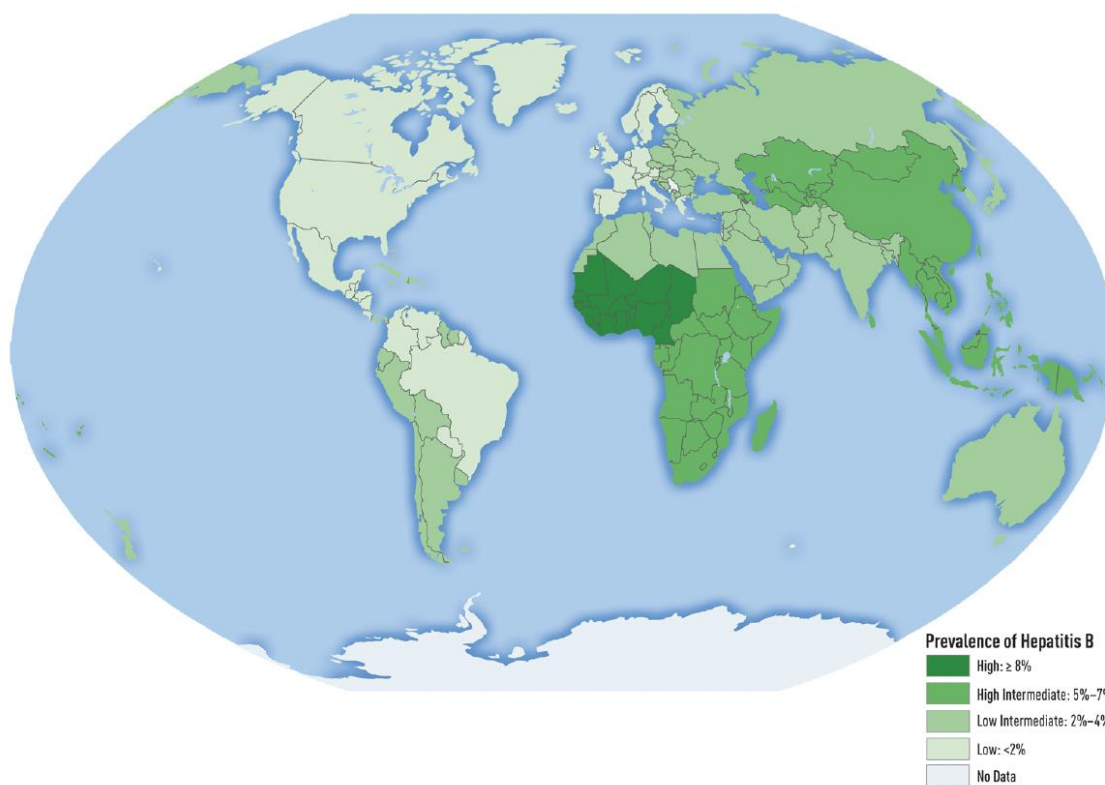
ART treatment immediately after diagnosis is now seen as a key preventative measure as over 50% of HIV transmissions are from people who are undiagnosed. (34) The HPTN 052 Study has shown that ART for HIV positive individuals in a serodiscordant relationship results in a 96% reduction in HIV transmission to a seronegative heterosexual partner. (35) Since then, the Partner Study has shown that no phylogenetically linked HIV transmission occurred amongst 1114 MSM and heterosexual serodiscordant couples enrolled during median follow up of 1.3 years per couple. (36)

1.2 Epidemiology of Hepatitis B

1.2.1 Global Epidemiology of Hepatitis B

The World Health Organisation (WHO) estimates that 240 million people have chronic hepatitis B infection, worldwide. (Figure 1-6) More than 686,000 people die every year due to complications of hepatitis B, including cirrhosis and liver cancer. Prevalence is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. (37)

Figure 1-6: Global Adult Hepatitis B prevalence



MAP 3-4. PREVALENCE OF CHRONIC HEPATITIS B VIRUS INFECTION AMONG ADULTS¹

¹ Disease data source: Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012; 30(12): 2212-2219.

Source: Centers for Disease Control and Prevention. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012; 30(12):2212–2219

1.2.2 Epidemiology of Hepatitis B in Ireland

In 2015 there were 502 new diagnoses of chronic hepatitis B reported (38). Case rate has increased since 2012 (n=389); this is thought possibly to be due to higher immigration rates to Ireland since 2012. (39) Nationally, the hepatitis B prevalence rate is estimated to be <0.5%. (40)

In 2015, the Health Protection and Surveillance Centre (HPSC) notifications showed risk factor for acquisition was only reported for a minority of chronic cases. However, some information on country of birth or asylum seeker status was available for 50% (n=251). Of these, 90% (n=225) were either born in a hepatitis B endemic country (hepatitis B surface antigen prevalence >2%) or were asylum seekers. (41).

Complications of chronic hepatitis B infection include cirrhosis, decompensated disease, hepatocellular carcinoma and death. Early treatment of infections where indicated can prevent disease progression; the complications of disease progression may represent a significant burden of care to the Irish healthcare system.

1.2.3 Hepatitis B Treatment

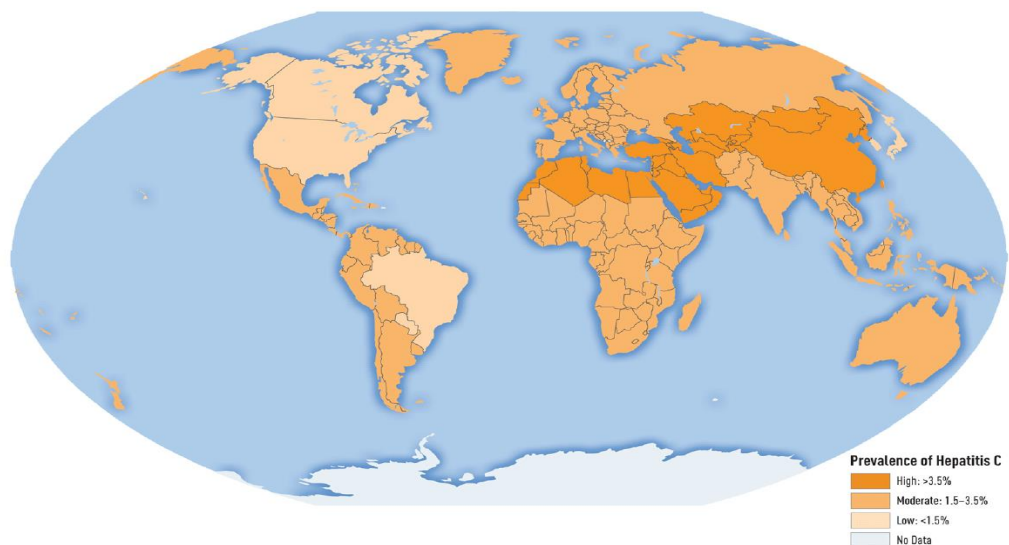
The goal of treatment for chronic hepatitis B is to prevent cirrhosis, hepatocellular carcinoma and liver failure. Antiviral therapy suppresses hepatitis B replication and decreases hepatic inflammation and fibrosis, reducing the threat of serious clinical disease. Since the introduction of effective treatment in the form of interferon alfa, several nucleoside and nucleotide analogues have been approved for use in adults with chronic hepatitis B, together with pegylated interferon alfa. Current oral first line therapies for hepatitis B now include tenofovir disoproxil fumarate (TDF) and entecavir. These oral treatment regimens are most frequently used rather than pegylated interferon alfa, allowing for a well-tolerated, effective treatment option that is widely available in developed countries. With multiple treatment options that are effective and safe, the key questions now are which patients need immediate treatment and which patients can be monitored and have treatment delayed. (42)

1.3 Epidemiology of Hepatitis C

1.3.1 Global Hepatitis C Epidemiology

Globally, an estimated 170 million people are living with chronic active hepatitis C infection and almost 500,000 were estimated to have died from hepatitis c related liver disease in 2010. (Figure 1-7) The prevalence is higher ($\geq 2\%$) in several countries in Latin America, Eastern Europe and the former Soviet Union, and certain countries in Africa, the Middle East, and South Asia; the prevalence is reported to be highest (approximately 10%) in Egypt. The most frequent mode of transmission in the United States and most developed countries is through sharing drug-injection equipment. In countries where hepatitis C is more common ($\geq 2\%$ prevalence), the predominant mode of transmission is from unsafe injections and other health care exposures where infection control practices are poor. (43)

Figure 1-7: Global Prevalence of Chronic Hepatitis C Infection



MAP 3-5. DISTRIBUTION OF HEPATITIS C VIRUS INFECTION¹
¹ Disease data source: Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. "Global Epidemiology of Hepatitis C Virus Infection; New Estimates of Age-Specific Antibody to HCV and Seroprevalence." *Hepatology* 2013; 57:1333-1342.

Source: Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global Epidemiology of Hepatitis C Virus Infection; New Estimates of Age-Specific Antibody to HCV and Seroprevalence. *Hepatology*. 2013; 57:1333-1342.

1.3.2 Epidemiology of Hepatitis C in Ireland

Reported hepatitis C prevalence in Ireland is between 0.5 and 1.2%. (44) It is estimated that between 20,000 and 50,000 people have hepatitis C infection and the majority of these remain undiagnosed. (45) Of those, only the minority (approximately 14,500) are diagnosed and fewer still (approximately 8,000) have engaged in tertiary level care. (46)

In 2015, 675 new cases of hepatitis C were reported in Ireland, giving a crude notification rate of 14.7/100,000 population. The most common risk factors reported were injecting drug use (76%, n=194), sexual exposure (5%) and receipt of blood or blood products (7%). (46)

1.3.3 Hepatitis C Treatment

Newer successful direct-acting anti-viral therapies for hepatitis C have recently been introduced. However, the current high cost of such newer effective therapies has limited the widespread use of such agents to the entire hepatitis C positive population. Research into treatment strategies for hepatitis C suggest that treating hepatitis C is cost effective at all levels of fibrosis. Studies looking at treatment regimens with interferon, ribavirin and direct acting anti-viral therapy suggest that if there are constraints on the budget that treatment with these drug regimens is most cost effective in those with advanced liver disease thus supporting the use of clinical prioritisation. (47, 48)

With the availability of these new drug treatments, research has focused on optimising treatment strategies. A recent study has shown that the total number of hepatitis C infections is projected to decline in nearly every country studied due to a reduction in risk factors for new infections (e.g. screening of blood supply), aging of the infected population and the corresponding increase in mortality, and treatment of infected individuals. (49) However even though the total number of infected individuals is expected to decline, those who remain infected are expected to progress to more advanced stages of liver disease and thus a sharp increase in hepatocellular carcinoma, liver related deaths, decompensated cirrhosis and cirrhosis cases is anticipated. The Department of Health Public Health Plan for the Pharmaceutical Treatment of Hepatitis C suggests that the hepatitis C burden will not be controlled by the current treatment strategies and that increased treatment and /or higher efficacy therapies would be needed to keep the number of hepatitis C individuals with advanced liver disease and liver-related deaths from increasing.

Mathematical modelling and simulation model studies in both Germany and Belgium show that successful diagnosis and treatment of even a small number of patients can contribute significantly to a reduction in disease burden in those countries. The research further suggests that the largest reduction in hepatitis C related morbidity and mortality occurs when increased diagnosis and treatment is combined with therapies with higher efficacy rates. This would require a significant increase in those being diagnosed and subsequently treated. This research also suggests that increased treatment and drug efficacy had most impact on morbidity and mortality when the patients being treated had more advanced fibrosis of the liver. However, it also suggests that to have the largest impact on transmission of hepatitis C infection among active intravenous drug users requires treating all patients with any signs of fibrosis. To eliminate hepatitis C infection would require treating all these patients. The most effective treatment strategy was to treat those with more significant fibrosis (> F2-3) and once that pool of patients had been depleted to expand to treat all patients including those with F0-F1. This research would suggest that to manage the existing deteriorating cohort of patients in most countries a strategy for management of the disease will require the provision of screening for undiagnosed cases paralleled to the treatment of patients. (50,51)

1.4 Current BBV Screening Practices

Screening for HIV, hepatitis B and hepatitis C offers a health benefit to the individual by early diagnosis of an infection the individual was previously unaware of and prevents onward transmission. These viruses are world-wide public health problems resulting in a significant impact on healthcare resource utilisation and costs (52, 53). Furthermore, these infections disproportionately affect socially marginalised groups.

1.4.1 International BBV Screening Practices

CDC guidelines in the USA recommend an opt-out HIV screening approach. In the UK it is recommended that HIV testing is considered where HIV prevalence rates exceed 2/1000. (54) In the US, the CDC recently recommended one-time hepatitis C screening of all persons born between 1945 and 1965, in addition to risk factor-based screening already in place. (55) CDC hepatitis B testing guidelines suggest testing those with exposure factors to hepatitis B. (56) In 2016, the World Health Organisation published guidelines on testing and treatment of Hepatitis B and C infection, to provide a major improvement in detection and treatment of both viral infections. (57)

1.4.2 Current BBV Screening Practices in Ireland

In Ireland, risk-based testing for HIV, hepatitis B and hepatitis C is most commonly offered. Despite the known prevalence in Dublin, universal HIV and hepatitis B screening is performed on an opt-out basis only in antenatal care and sexual health clinics. Hepatitis C screening is not routinely undertaken in antenatal care and sexual health settings but is routinely undertaken at blood donation. Despite common risk demography for acquisition in migrants, men who

have sex with men and PWID with significant rates of hepatitis C reported in the Rotunda and Coombe Maternity hospitals, only risk based targeted hepatitis C screening strategies are operational in most maternity hospitals and the universal screening of migrants has not yet been undertaken. (58, 59)

Offering routine HIV testing incurs a cost per test, however in 2005 the Centre for Disease Control in the United States reported that routine testing was cost effective if one undiagnosed person is found per 1000 tests performed. It must be noted that at the time this did not include modelling regarding the costs saved in reduction of onward transmission. Further modelling in France has also shown that one test carried out per lifetime will be cost effective for the general population. (60)

Chapter 2

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Chapter 2

2.1 Late HIV Presentation St James's Hospital

2.1.1 Introduction

The WHO estimates that worldwide, 37 million people are living with HIV, and now recommend anti-retroviral therapy for all those with HIV infection. It is estimated that currently worldwide, only 54% of people are aware of their infection status. (61)

Late HIV presentation can be defined as those presenting for HIV care with a CD4 cell count of less than 350 cells/mm. (62, 63) Late presentation with HIV infection has a negative impact on outcome for the individual. Those who are unaware of their positive HIV status cannot benefit from widely available treatment options. As a result, late presentation for HIV care is associated with higher morbidity and mortality, even after treatment with antiretroviral therapy. (64,65) Late presenters also carry a lower chance of recovery of CD4 T lymphocytes following treatment, (66) and without treatment carry a risk of HIV transmission while unaware of their HIV status. Furthermore, costly inpatient hospital admissions may be avoided with appropriate management of HIV at an earlier point.

2.1.2 Late HIV Presentation in Ireland

In 2016, 512 new HIV diagnoses were notified in Ireland, giving a crude notification rate of 11.2 per 100,000 population. This is an increase of 6% compared with 2015 and can be accounted for by an increasing number of HIV notifications among migrant MSM and PWID. Between 2010 and 2013, the annual rate of new HIV diagnoses had been relatively stable in Ireland, ranging from 7.0 to 7.5 per 100,000 population. The highest number of new diagnoses ever reported in MSM was in 2015, comprising 50.9% of new HIV diagnoses in Ireland. In the 10

years since 2005, the number of new diagnoses among MSM has increased threefold (from 60 to 183) and in 2015, there were 49 (10%) new diagnoses among PWID, the highest number reported in this risk group since 2009.

In Ireland, the Health Protection and Surveillance Centre (HPSC) report that 45% of new HIV diagnoses in 2015 were late presenters, with CD4 less than 350 cells/ml or an AIDS defining illness at diagnosis. This number reflects similar proportion over recent years. Late presentation was less common among MSM and PWID than among heterosexuals. Regular testing among MSM and PWID is likely to be a major reason for this. The groups with the highest proportions presenting late were male heterosexuals, people aged 50 years and over and people born in sub-Saharan Africa. However, the lower proportion of late diagnoses among MSM and PWID may also be a result of more recently acquired infections in these population groups. Based on previous HIV testing history, 20% of infections in MSM, and 23% in PWID were acquired in the previous 2 years. (66) While CD4 count is currently one of the parameters used to define late HIV presentation, it is important to note that early HIV infection often is associated with low CD4 count. This suggests that the current definition of late HIV presentation may need to be revised.

2.1.3 Study Aims

The primary aim of this study was to identify factors associated with late HIV presentation (LPS, CD4 cell count < 350 cells/mm³) and to further examine differences between those with moderate immunodeficiency (MI, CD4 200–350 cells/mm³) and advanced immunodeficiency (CD4 < 200 cells/mm³). We sought to determine opportunities missed to diagnose HIV earlier in

this patient cohort. A secondary aim was to identify changing trends of late HIV presentation from 2002 to 2014 at our centre.

2.2 Methods

2.2.1 Study design and population

This was a retrospective cohort study. Appropriate in-hospital approval for research activity was obtained (ref 2015/109). Retrospective electronic chart review was undertaken. Patients with a new diagnosis of HIV infection who presented for care at our HIV centre over 2014, 2012, 2007 and 2002 with newly diagnosed HIV infection were included. Time intervals were chosen to reflect the possible changing demographics of our cohort over time. Data collection had previously taken place at our department for 2002, 2007 and 2012. These time-points were chosen as part of a cyclical departmental audit reviewing patient-care outcomes. Following on from this, data were then collected for the most recent year that had passed (2014). Patients who had already received care for their HIV infection at another centre were excluded from the study.

2.2.2 Variable of interest

The primary variable of interest was CD4 cell count (cells/mm³) at presentation. Patients were identified by a departmental patient database; these were new attenders for HIV care over defined time-points (2014, 2012, 2007 and 2002). By electronic chart review, various demographic data including age, gender, risk group, geographic origin, previous HIV testing status, previous investigation of unexplained symptoms prior to HIV diagnosis, clinical indicator condition at time of diagnosis and CD4 cell count at presentation of new HIV diagnoses over

2014 were collected on Excel Database. HIV transmission risk group was categorised as MSM, IDU, heterosexual and other/unknown. Using data available, further comparison was then made between variables of this group and those of late presenters from three previous time-points over the past decade. (2002, 2007 and 2012). These variables included age, gender, mode of acquisition, country of origin and CD4 cell count at presentation. Data were coded anonymously, and statistical analysis was performed using Graphpad InStat. Wilcoxon, ANOVA and χ^2 tests were used to compare variables. Late presentation (LPS) was defined as those who presented with a CD4 cell count of <350 cells/mm³. Moderate immunodeficiency (MI) was defined with an initial CD4 cell count between 200 and 350 cells/mm³ and advanced immunodeficiency (AI) was defined as an initial CD4 cell count of <200 cells/mm³.

2.3 Results

In 2014, a total number of 231 patients were referred for management of newly diagnosed HIV infection. Seventy-five (32.6%) patients presented with a CD4 cell count of <350 cells/mm³ (LPS). Of these, 55 (73.3%) were male and 20 (26.7%) were female. Mean (SD) age at presentation was 39.7 (11) years. Most patients (n: 33, 44%) were Irish. Mean (SD) CD4 cell count was 166 (109) cells/mm³. See Figure 2-1 for information on probable route of transmission and geographic origin and see Table 2-1 for detailed demographic information for each presentation stage.

Figure 2-1 New HIV Diagnoses by Route of Transmission and Geographic Origin 2014

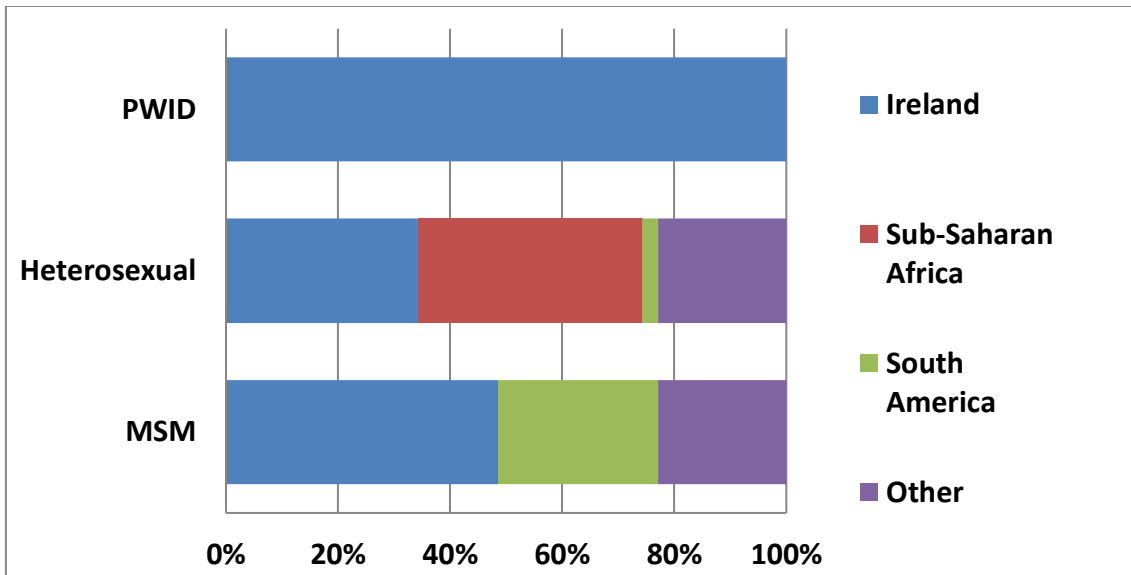


Table 2-1 Detailed Demographic Information for all Presentation Stages 2002-2014

	2002			2007			2012			2014		
	n	MI	AI	n	MI	AI	n	MI	AI	n	MI	AI
Total No Patients (n)	220	99(45)	47(21.36)	215	92(42.79)	45(20.93)	200	78(39)	40(20)	231	32(13.8)	43(18.5)
Gender												
Male(%)	112(50.9)	46(46.46)	24(51.06)	140(65.12)	49(53.26)	26(57.78)	159(79.5)	58(74.36)	23(57.5)	187(81)	26(81.2)	29(67.4)
Female(%)	108(49.1)	53(53.53)	23(48.94)	75(35.88)	43(46.74)	19(42.22)	41(20.5)	20(25.64)	17(22.5)	44(19)	6(18.8)	14(32.5)
Mean Age at Presentation (SD)	31.73(8.6)	32.56(8.78)	35.27(9.8)	34(9)	33.03(9.15)	34.86(9.15)	35.32(9.59)	36.96(10.03)	36.32(10.2)	35.8(9.8)	38(12)	40.8(9.8)
Region of origin												
Ireland	89(40.45)	39(39.39)	19(40.42)	117(54.42)	45(48.91)	25(55.56)	98(49)	39(50)	19(47.5)	91(39.4)	15(46.8)	18(41.8)
SSA	113(51.36)	51(51.51)	20(42.55)	64(29.77)	39(42.39)	17(37.78)	33(16.5)	18(23.08)	13(32.5)	29(12.5)	5(15.6)	8(18.6)
South America	2(0.9)	1(1.01)	0	2(0.93)	0	0	20(10)	2(2.56)	0	47(20.3)	6(18.75)	5(11.6)
Other	15(6.8)	9(9.09)	8(17.02)	32(14.88)	8(8.69)	3(6.67)	49(24.5)	19(24.36)	8(10)	64(27.7)	5(15.6)	12(28)
Acquisition Risk Group												
HS	137(62.27)	68(68.68)	35(74.47)	92(42.79)	48(52.17)	23(51.1)	71(35.5)	47(60.26)	24(60)	61(26.4)	11(34.3)	24(55.8)
MSM	40(18.18)	14(14.14)	6(12.76)	65(30.23)	14(15.22)	4(8.89)	119(59.5)	25(32.05)	12(30)	153(66.2)	19(59.3)	16(37.2)
PWID	40(18.18)	15(15.15)	5(10.64)	55(25.58)	29(31.52)	17(37.78)	9(4.5)	6(7.69)	4(10)	14(6)	2(6.25)	2(4.65)
Other	3(1.36)	2(2)	1(2.13)	3(1.39)	1(1.08)	1(2.22)	1(0.5)	0(0)	0(0)	3(1.29)	0	1(2.3)
Mean CD4 (SD)	428.2(279.1)	189.4(104.41)	95.4(62.37)	427.4(310.99)	186.1(105.61)	94.3(65.93)	415(239.66)	187.82(111.26)	94.6(66.83)	463(281.2)	275(38.3)	84.8(64.6)

Table Legend: MI: Moderate Immunodeficiency (CD4: 200-350), AI: Advanced Immunodeficiency (CD4: <200), SSA: Sub-Sahara Africa, HS: Heterosexual, MSM: Men who have sex with men, PWID: People who inject drugs, SD: Standard deviation

2.3.1 Moderate immunodeficiency in 2014 (n: 32)

Most patients (n: 23, 72%) were tested in healthcare settings outside our hospital. Seventeen (53.1%) patients had previously been tested for HIV infection. Eight (50%) of these patients had a HIV test within 2 years prior to HIV diagnosis and 7 (88%) of these were MSM.

2.3.2 Advanced immunodeficiency in 2014 (n: 43)

Eighteen (42%) patients were tested in healthcare settings outside our hospital. Seventeen (39.5%) had previously been tested for HIV infection. Eleven (65%) of these had a HIV test within 2 years of diagnosis and 6 (54.5%) of these were MSM. See Table 2-2 for a detailed description of factors associated with moderate and advanced immunodeficiency presentation.

2.3.3 Comparison of groups over time

Proportions of male LPS compared with female LPS have increased over time ($p < 0.001$). With this, proportions of MSM compared with other risk groups diagnosed over time have increased ($p < 0.001$) (Figure 2-2). A decreased proportion of those with heterosexual risk in the LPS group was seen over time, however in 2014, the risk group most likely to present as LPS was heterosexual: HS (58%) vs. MSM (22.8%). Proportions of LPS from Sub-Saharan Africa in comparison with other geographic origins have decreased from 2002 to 2014 ($p < 0.0001$). In contrast to this, proportions of LPS attending from South America have increased significantly from 2002 to 2014 ($p < 0.001$). As rates of those from Sub-Saharan Africa have fallen, another significant proportion (44%) of LPS with heterosexual mode of acquisition in 2014 was from Ireland. No overall significant age difference was seen amongst LPS over time ($p: 0.593$). However, a direct comparison between 2002 and 2014 shows a significant difference in age, where LPS are presenting at an older age in 2014 than in 2002 ($p < 0.001$) (Table 2-1).

The overall proportion of LPS newly diagnosed with HIV attending our centre for care has decreased over time ($p < 0.001$). However, the proportion of those who presented with advanced immunodeficiency (AI) over time has not significantly changed ($p : 0.69$) (Figure 2-4). Within risk category analysis shows that the percentage of MSM LPS has decreased, as has the percentage of males, females and those from Sub-Saharan Africa. No significant decrease in proportions of LPS in the heterosexual risk group was seen, with 100% of the heterosexual risk group diagnosed in 2012 presenting with a CD4 cell count of less than 350 cells/mm³. These findings reflect the overall decreased proportion of those presenting late since 2002. See Table 2-3 and Figure 2-3 for percentage rate change over time amongst each category.

Figure 2-2 Risk of Acquisition of HIV 2002-2014

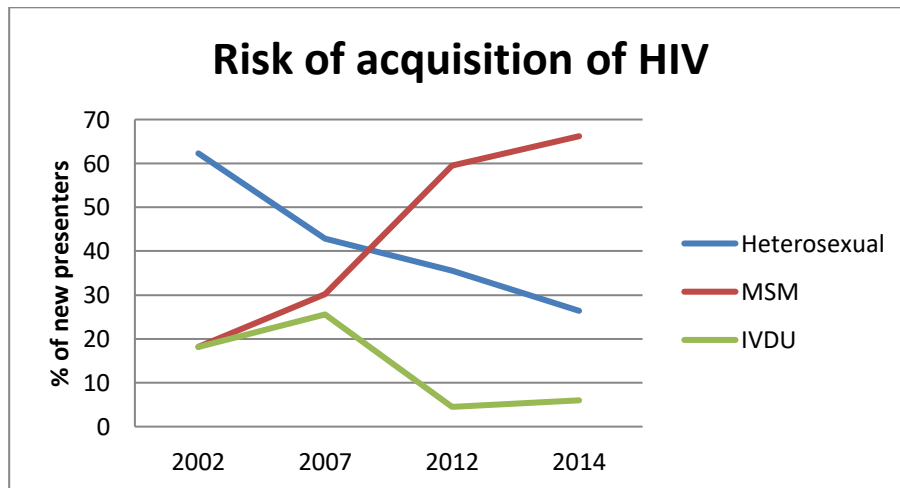


Table 2-3: Rate of change over time (% of each category who presented with CD4 count <350)

	2002	2007	2012	2014	P value
Males	63	53.6	51	29.4	<0.001
Females	70	83	58	45	<0.001
MSM	50	28	31	23	<0.003
HS	75	77	100	57	<0.098
SSA	63	87	93	45	<0.016

Figure 2-3 Percentage of each category presenting with Late HIV Infection

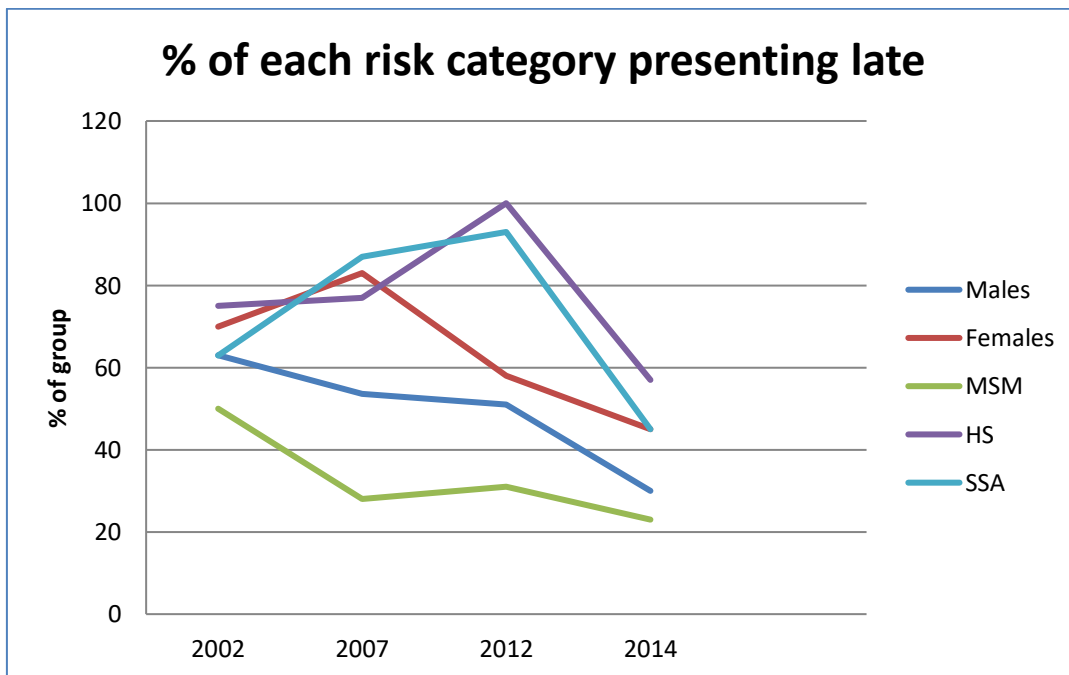
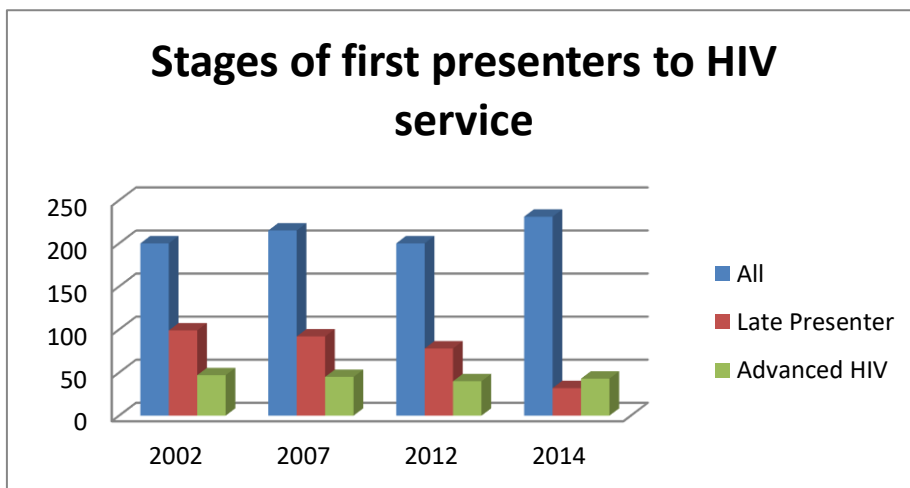


Figure 2-4 Stages of First Presenters to HIV Ambulatory Care Service 2002-2014



2.4 Discussion

Over time, proportions of those with newly diagnosed HIV-1 infection presenting at a late stage in their illness are decreasing. Proportions of those with very late presentation presenting over the past 12 years, with a CD4 cell count of $<200 \text{ cells/mm}^3$, remain unchanged. The demographics of those with late HIV presentation are changing over time. Those with heterosexual mode of acquisition, older patients and those from South America are more likely to present with late HIV infection in recent years.

Despite current HIV prevention strategies in place, including earlier introduction of ART and the widespread availability of post-exposure prophylaxis our findings show that a significant portion of those presenting with HIV continue to present at a late point in their illness, with a subsequent risk for negative impact on overall morbidity and mortality. These data have shown that in 2014, several patients presented to a range of healthcare facilities for investigation of unexplained symptoms that later were diagnosed as HIV clinical indicator illness, without

having a HIV test done, including medical and surgical outpatients, general practice and Emergency Departments. High rates of missed opportunities for HIV diagnosis have previously been reported; one US study reports 35% of individuals newly diagnosed with HIV infection had previously attended a healthcare provider over the preceding 1 year with HIV associated signs and symptoms. (67) The missed opportunities identified in this study further highlights the ongoing need for appropriate physician education on HIV clinical indicant illness, the need for expanded HIV testing and the removal of barriers to performing a HIV test for patients.

Comparison between those presenting with moderate and advanced immunodeficiency in 2014 shows a significantly smaller number of those with advanced immunodeficiency had previously undergone HIV testing. At least 50% of patients in both groups had previously tested for HIV in the 2-year period prior to testing positive; the majority (69%) of these were MSM, reflecting high rates of HIV testing in this risk group. Early HIV infection with low CD4 cell count needs to be considered as a possible explanation for higher rates of LPS MSM diagnoses with higher testing rates and suggests the definition for late HIV presentation needs to be revised. It also highlights the role for newer laboratory techniques to be developed and evaluated to distinguish recent and established HIV infection.

One example of a newer laboratory technique that is now used as part of the Irish HIV surveillance system is the Recent Infection Testing Algorithm (RITA). This involves the testing of blood samples of those with HIV infection to differentiate recent versus long-standing HIV infection. The purpose of using this algorithm is to better understand HIV incidence at population level. The RITA Pilot Project was conducted at the National Virus Reference Laboratory from January to March 2016. Aims of this pilot project were to assess the feasibility of integrating the testing algorithm into national routine surveillance. Rates of recent infection were determined over a 3-month period.

Recent infections could be determined using the Sedia HIV-1 Limiting Antigen Avidity enzyme immunoassay and clinical data was extracted from CIDR in October 2016. A new HIV diagnosis was determined to be recent if avidity was less than 1.5, unless the patient was already on ART when tested, had a CD4 count of less than 200 cells/mm, a viral load of less than 400 copies/ml or if an AIDS defining illness was reported at time of diagnosis. 16(14%) of those tested were found to have true early infection. Where data was available from surveillance data, most of these patients with new infection were MSM (n=10) and infection was acquired in Ireland (n=8). While a small sample size was used, and clinical data was incomplete, the RITA algorithm was found to be a valuable addition to HIV reporting and it is feasible to apply RITA to Irish Surveillance Data. (Personal Communication Dr Cillian de Gascun).

When comparison was made between patterns of demographics of those presenting in 2014 and over three other time points since 2002, currently the rate of LPS in all risk groups is decreasing, however similar proportions of those with advanced immunodeficiency continue to present. Furthermore, people are likely to be older when presenting as LPS. These findings reflect those which have been found at national level. (68) Rates of LPS in our cohort are lower than that found internationally. The Cohere Observational Cross-European study of LPS from 34 countries showed a LPS rate of 48.7% in 2013, with overall highest rates of LPS from 2010 to 2013 in heterosexual males and females. (69) While risk factors for late HIV presentation seen in this study are similar to our cohort, rates of LPS are higher than seen in our cohort. A possible explanation for this is that AIDS defining illness was not included as a definition for LPS in our cohort because we used CD4 count as a marker for HIV presentation stage only. Furthermore, a 2015 meta-analysis of gender differences at risk of late HIV presentation showed male gender to be at higher odds of late HIV presentation, similar to our cohort. (70) A review of HIV presentations in the United States over a 10-year time period, with LPS defined

as CD4 cell count of <350 only, showed rates of LPS decreased over this time period, with LPS rates of 53% seen most recently in 2007. The effect of the use of earlier ART in the US cohort in more recent times remains to be seen. (71)

Various intervention strategies have been employed in recent years to reduce the rates of late HIV diagnosis, missed opportunities for HIV testing and the detrimental sequelae of such an outcome. In the United States, to accelerate progress toward reducing undiagnosed HIV infection, the CDC and its partners have pursued an approach that includes expanding HIV testing in communities with high HIV infection rates (72) It has previously been shown that barriers amongst healthcare providers exist, including lack of time to conduct testing and staff feeling ill-prepared to answer patient queries. (73,74) It is possible that our patients did not have a HIV test previously for these reasons.

2.4.1 Limitations

This study has several limitations that are inherent with a retrospective cohort study. We were unable to ascertain the true timing of HIV acquisition in our patients. As late presenters were categorised based on CD4 cell count only, it is likely that a proportion of these patients included in the data analysis had recently acquired infection. Because of limitations with retrospective chart review, the authors did not use the LP consensus definition, (75) where AIDS defining illness was not included in our definition of LPS. Because of this, it is possible that rates of LPS are lower in our cohort than seen internationally.

2.5 Conclusions

Potential targets for future HIV testing include testing initiatives at other healthcare settings and GP practices, where a large proportion of those LPS were diagnosed. In line with higher rates of HIV diagnosis in MSM, the proportion of MSM LPS as compared with other risk groups is increasing. A significantly smaller number of MSM were diagnosed with advanced immunodeficiency, representing the higher frequency of HIV tests performed for this risk group. With this in mind, our knowledge that the heterosexual risk group is now most likely to present as LPS in 2014 and given high rates of recent previous testing in the MSM group, it is evident that other non-MSM risk groups need to be targeted for HIV testing, including those patients who have not yet identified as MSM and are not engaged in the practice of regular HIV testing. Given the increasing age of patients who are presenting with late HIV, all age and risk groups should be considered for a HIV test. To employ these interventions effectively, widespread HIV testing in expanded urban healthcare facilities needs to be implemented.

Furthermore, the need to augment the education of healthcare providers with early introduction to the topic (eg undergraduate medical and nursing students), to re-emphasise the need for HIV clinical suspicion in all risk and age groups and to increase the awareness of the role for widespread HIV testing in areas of differing prevalence and demography has been highlighted by this study. Further strategies need to be employed to diagnose and treat HIV early, to prevent onward HIV transmission and avoid adverse healthcare consequence.

Table 2-2 Late Diagnosis 2014 Demographics

	Late Presenters (Cd4 <350) n=32 n(%)	Advanced HIV (Cd4 <200) n=43 n(%)	p Value	
Previous HIV Test				
Yes	19 (59.4)	17 (39.5)	0.0071, OR: 2.25	
No	13 (40.6)	26 (60.5)		
Site of HIV Diagnosis				
GMHS	9 (28.1)	4 (9.3)	0.0009, OR: 3.93	
WHP	0 (0)	1 (2.3)		
Abroad	0 (0)	1 (2.3)		
Medical Inpatient	0 (0)	5 (11.6)		
Respiratory OPD	0 (0)	1 (2.3)		
Oncology OPD	0 (0)	1 (2.3)		
GP	8 (25)	9 (21)		0.61
EDVS	2 (6.3)	3 (7)		
Other Hospital	5 (15.6)	10 (23.2)		0.28
GUIDE STI Clinic	6 (18.8)	8 (18.6)		1.00
Colorectal SVUH	1 (3.1)	0 (0)		
Entrance to Country	1 (3.1)	0 (0)		
Previous Investigations				
Yes	2 (6.3)	9 (21)	0.0032, OR: 0.24	
No	30 (93.7)	34 (79)		

Nature of Previous Investigations	30 (93.7)	34 (79)	
None	2 (6.3)	4 (9.3)	
CXR (GP)	0 (0)	1 (2.3)	
CT, Mantoux, CXR	0 (0)	2 (4.6)	
ED visits for non-specific viral infection	0 (0)	1 (2.3)	
Bronchoscopy	0 (0)	1 (2.3)	
PUO Investigated at other hospital			
Clinical Indicator Illness			
No	18 (56.3)	11 (25.6)	0.22
Weight loss	2 (6.3)	8 (18.6)	
Blood dyscrasias	1 (3.1)	2 (4.6)	
Diarrhoea	1 (3.1)	1 (2.3)	
Oropharyngeal candidiasis	0 (0)	1 (2.3)	
TB	0 (0)	2 (4.6)	
HPV	1 (3.1)	2 (4.6)	
VZV	0 (0)	1 (2.3)	
HSV 2	2 (6.3)	1 (2.3)	
Non-specific myalgia	0 (0)	1 (2.3)	
Myositis	0 (0)	3 (7)	
PCP			

Cerebral Toxoplasmosis	0 (0)	5 (11.6)	
Burkitts Lymphoma	1 (3.1)	1 (2.3)	
Recurrent LRTI	0 (0)	1 (2.3)	
Septic Arthritis	0 (0)	1 (2.3)	
HIV Seroconversion Illness	0 (0)	1 (2.3)	
Cervical Lymphadenopathy	3 (9.4)	1 (2.3)	
Anal Carcinoma	1 (3.1)	0 (0)	
Abnormal CXR	1 (3.1)	0 (0)	
	1 (3.1)	0 (0)	

Table 2-2 Legend: GMHS: Gay Mens Health Service, WHP: Womens Health Project, OPD: Out-patient Department, GP: General Practice, EDVS: Emergency Department Viral Screening Study, STI: Sexually Transmitted Infection, SVUH: ST Vincents University Hospital, CXR: Chest X Ray, CT: Computed Tomography Scan, ED: Emergency Department, PUO: Pyrexia of Unknown Origin, TB: Tuberculosis, HPV: Human Papilloma Virus, VZV: Varicella Zoster Virus, HSV: Herpes Simplex Virus, PCP: Pneumocystis Cariini Infection, LRTI: Lower Respiratory Tract Infection

Chapter 3

Chapter 3: Cascades of Care

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Chapter 3 Cascades of Care

3.1 Background

The implementation of widespread blood borne virus screening programmes cannot proceed unless a robust clinical-care structure is in place, to ensure efficient delivery of patient care. Within this, rates of retention in care and treatment delivery need to be determined for our cohort (at the Department of Genito-Urinary Medicine and Infectious Diseases, St James's Hospital, Dublin 8). Furthermore, where required, we need to understand the reasons why people disengaged from care so we can improve our service delivery, to prevent this from happening and to ensure new patients remain engaged.

3.2 HIV Retention in care

3.2.1 Introduction

Retention to HIV care is crucial for patient survival, to prevent onward transmission and avoid emergence of drug resistance. Continuous retention in HIV care has been associated with prevalent HIV-1 viral suppression. (76) The UNAIDS global HIV targets of 90% diagnosed, 90% on antiretroviral treatment (ART) and 90% suppressed suggest that testing and ART are the tools necessary to reach these targets. Without an adequate retention in HIV care, reaching these targets will not be possible.

ART is now thought to have a clinical benefit to all individuals with HIV infection, thus international HIV treatment guidelines now recommend ART for all HIV-1 infected individuals who are ready to start. (77)

Furthermore, ART has a public health benefit beyond that of the individual, with reduction in transmission at both individual and population levels with ART now established – Treatment as Prevention (TasP). (78,79)

3.2.1.2 HIV Retention in Care – International Data

In the United States, the Center for Disease Control estimate that more than 1.2 million people are living with HIV infection, and almost 1 in 8 (12.8%) are unaware of their infection (82). The CDC also estimates that less than 50% of persons diagnosed with HIV receive regular HIV care (83). In comparison, in the United Kingdom, a HIV retention in care rate of 95% was reported in 2014 (91).

3.2.1.3 HIV Retention in Care – Irish Data

In Ireland, in 2016, 512 new HIV diagnoses were made. This was an increase of 6% as compared to 2015. (80) It was estimated that 3254 people were attending specialist services for HIV care in 2010 in Ireland. For the 3202 patients where data was available, 2574(80.4%) were on ART. HIV RNA values were available on 2528(98.2%) of patients on ART; 2208(87.3%) of these had HIV viral load responses of < less than 50 copies per ml. (81) With the lack of a National HIV Disease Registry, more up to date accurate numbers of those currently diagnosed and living with HIV in Ireland is not available.

3.2.1.4 Factors Associated with Poor HIV Retention in Care

Numerous factors that negatively affect HIV retention in care have been reported. These factors can be both patient related and disease related. Patient related factors previously identified include stigma (84, 85) associated with a positive infection status, logistic and

financial difficulties in transportation to an ambulatory clinic (84), younger age (84) and lack of education and social support (86, 87). In less developed countries, patient related factors such as not having yet started ART (88), travelling long distances to receive care, (88), TB co-infection (88) and competing life activities (85) all negatively affect retention in HIV care. Disease related factors associated with poor retention in HIV care that have been previously identified include feeling too sick to attend clinic, depression and mental illness (85).

3.2.1.5 Study Aims

The primary aim of our study was to describe the prevalence of retention in HIV care at our centre from 2007 to 2014 inclusively. A secondary aim was to examine patient factors associated with both retention and non-retention in HIV care over this time and to describe an intervention to link those who had previously disengaged back to care.

3.2.2 Methods

3.2.2.1 Study Sample and Data Collection

For this study, retention in care was defined as evidence of HIV care provision at our ambulatory HIV clinic within a 1-year time-period before the study time point. 1 year was chosen as the time interval based on the recommendation by Medland et al, following a systematic review of data sources recording the HIV care cascade in the United States (89). All patients who disengaged from HIV care for greater than a one-year time-period, from 2007 to 2014 were identified with a departmental database. Appropriate institutional ethical approval was obtained. Retrospective electronic chart review of patients was undertaken, and demographics were recorded on a confidential departmental Excel database. Patients who

were disengaged from care for greater than one year but subsequently re-attended over the eight-year time-period of follow up were categorised as “poor-attenders” but were included in study analysis.

3.2.2.2 Definitions of Variables

For each patient, variables including age, gender, mode of acquisition, use of anti-retroviral therapy, CD4 count and HIV viral load at the time of disengagement were recorded. Variables including missing values were then coded and exported to SPSS version 23. SPSS was then used to describe and compare patient demographics in both retained and non-retained groups.

3.2.2.3 Statistical analysis

A nested case control study was performed. Cases matched for HIV positivity and attendance over the same year time-period were identified and controls were matched to cases at a 4:1 ratio. Demographics for both cases and controls were retrospectively recorded from electronic chart review. Variables including missing values were then coded and exported to SPSS version 23. SPSS was used to describe patient demographics in both retained and non-retained groups. Univariate and multivariable analysis for this dataset was then carried out. T-test independent samples of means, Mann-Whitney U and Chi-squared tests were used for continuous and categorical variables respectively. Re-coded variables were then used to perform binary logistic and multivariable logistic regression. Weighted odds-ratio was then interpreted for independent variables, using a 95% confidence interval and a p value of less than 0.05 to determine statistical significance.

3.2.3 Results

3.2.3.1 Description of Total Cohort

1250 patients were included in this study. 250 patients had disengaged from HIV care from 2007 to 2014 and the remaining 1000 patients were randomly selected as controls, matched on a 4:1 ratio for same year of attendance and HIV-1 infection. Age range was 19-78, Median Age (IQR): 42(36,50). 641 (51.3%) patients were Irish and 842 (67.4%) were male. 463 (37%) were heterosexual, 471 (37.7%) were MSM and 291 (23.3%) had a history of intravenous drug use (IDU) as mode of acquisition. 317 (25.4%) of patients had a CD4 count below 350 cells/mm³. Most patients (n=930, 74.6%) had a CD4 count of >350 cells/mm³ and 612 (66%) of these had a CD4 count of >500 cells/mm³. 950 (76%) of patients were taking ART and 769 (81%) of these 950 patients had a suppressed HIV-1 viral load. (See Table 3-1)

3.2.3.2 Description of non-engaged group (Cases)

250/2289 (10.9%) of patients attending our ambulatory HIV clinic had disengaged from HIV care from 2007 to 2014. 21 (8.4%) of these patients subsequently re-engaged in HIV care. From retrospective review we found that 7 (2.8%) patients died over the study period, figures may be higher. 153 (61.2%) were male. 126 (50.4%) were heterosexual: 15(12%) of these were Irish, 84(66%) were Sub-Saharan African, 81 (32.4%) were MSM and 40 (16%) were PWID. Only 87 (34.8%) of patients who disengaged were Irish and 90 (36%) were from Sub-Saharan Africa. Of significance 88.4% of the heterosexual risk group were non-Irish.

4 (1.6%) patients had a CD4 count of <50 and 59 (23.6%) patients had a CD4 count of <350 at the time of disengagement from HIV care. 140 (56%) patients were taking ART at the time of disengaging from care, and only 59 (42%) of these patients had a suppressed HIV-1 viral load at the time of disengagement from care.

As compared to the total cohort, 15% (81/471) of MSM had disengaged from care, 25% (126/263) of heterosexuals and 18% (40/291) of PWID had disengaged from care.

Telephone follow up of 243/250 (97.2%) patients was undertaken. Successful contact was made with 47 (18.8%) of patients. When interviewed over the phone, 34 (72.3%) stated they were willing to return and 17 (50%) of these 34 patients have re-engaged in care at our centre to date. A further 11 (23.4%) patients are now attending another centre and 2 (4.2%) have not disclosed why they will not follow up for care.

3.2.3.3 Univariate analysis of Engaged and Disengaged Groups

Mean age of patients who were retained in care was higher than that for those patients who had disengaged ($p < 0.001$, 95% CI: 2.24-4.93). Prior to disengaging, a higher proportion of patients who had disengaged from care had not been receiving ART ($p < 0.001$). No significant gender difference was found between cases and controls ($p: 0.056$).

Most patients who had disengaged from care were non-Irish (65.2%) as compared with those who retained in care (44.6%); this difference was statistically significant ($p < 0.001$).

No change in distribution of CD4 counts was observed between cases and controls (p: 0.181).

A significantly higher proportion of patients who disengaged from care were heterosexual (50.4%) as compared to those who retained in care (33.7%); (p value: <0.001, 95% CI: 0.378 – 0.662). Conversely, a significantly lower proportion of those with intravenous drug use as mode of acquisition (16%) had disengaged from care, as compared with 25.1% of those in the retained in care group (p: 0.002). 32.4% of those who disengaged from care were MSM, as compared to 39% of those who were retained in care. This difference was not found to be statistically significant (p: 0.058). See table 3.1 for description of patient characteristics.

Table 3-1 Description of Patient Characteristics / Univariate Analysis

	Total Cohort	Retained in Care	Disengaged	p value
	N=1250	N=1000	N=250	
	N (%)	N (%)	N (%)	
Median Age (years)	42	43	39.5	<0.001, CI: 2.24 – 4.95
Geographic Origin				
Ireland	641 (51.3)	554 (55.4)	87 (34.8)	<0.001
SSA	333 (27)	243 (24.3)	90 (36)	
South America	55 (4.4)	34 (3.4)	21 (8.4)	
SE Asia	29 (2.3)	23 (2.3)	6 (2.4)	
Other	192 (15.3)	146 (14.6)	46 (18.4)	
Gender				
Male	842 (67)	689 (68.9)	153 (61.2)	0.056
Female	408 (33)	311 (31)	97 (38.8)	
Risk				
HS	463 (37)	337 (33.7)	126 (50.4)	<0.001
MSM	471 (38)	390 (39)	81 (32.4)	0.058

IDU	291 (23)	251 (25.1)	40 (16)	<0.001
Other	25 (2)	22 (2.2)	2 (0.8)	
CD4				
<50	21 (1.7)	17 (1.7)	4 (1.6)	0.181
50-200	88 (7)	74 (7.4)	14 (5.6)	
200-350	208 (16.7)	167 (16.7)	41 (16.4)	
350-500	318 (25)	260 (26)	58 (23.2)	
>500	612 (49)	482 (48.2)	130 (52)	
Viral Load				
Suppressed	788 (63)	710 (71)	78 (31.2)	<0.001
Not suppressed	388 (31)	224 (22.4)	164 (65.6)	
Just started	42 (3.3)	42 (4.2)	0	
New diagnosis	16 (1.3)	16 (1.6)	0	
ART				
On ART	950 (76)	810 (81)	140 (56)	<0.001
Not on ART	297 (23.7)	187 (18.7)	110 (44)	

Table 3-1 Legend: SSA: Sub-Saharan Africa, SE Asia: South East Asia, ART: Anti-Retroviral Therapy, HS: Heterosexual, IDU: Intravenous Drug Use, MSM: Men who have sex with men

3.2.3.4 Multivariable analysis of predictors for disengagement in care

Patients from Ireland were less likely to disengage from HIV care (OR: 0.567, CI: 0.397 – 0.811, p: 0.002). Those with a suppressed HIV-1 viral load were also less likely to disengage from HIV care (OR: 0.191, CI: 0.128-0.284, p:<0.001). While viral suppression was identified as a predictor, this is also a surrogate marker for disengagement. Patients on ART were less likely to disengage from care, but results were not found to be statistically significant. (OR: 0.914, CI: 0.611-1.368, p value: 0.663)

Considering other independent predictors including age, gender, ethnicity and immune status, heterosexual mode-of-acquisition, intravenous drug use and MSM were all associated with a higher risk of disengagement from care. These results were not found to be statistically significant. Male gender was associated with disengagement from HIV care, but results were not statistically significant (OR: 1.14, CI: 0.782 – 1.664, p value: 0.495).

See Table 3-2 for description of logistic multi-variable regression model.

Table 3-2: Multivariable Regression Model

	Retained	Non-retained	B	OR	95% CI	p value
	n=1000	n=250				
	n(%)	n(%)				
Age (median, IQR)	43 (28,58)	39.5 (28,52)	0.252	1.286	0.937-1.765	0.119
Gender	689 (68.9)	153 (61.2)	0.131	1.140	0.782-1.664	0.495
Irish	554 (55.4)	87 (34.8)	-0.567	0.567	0.397-0.811	0.002
CD4 <200	91 (9.1)	18 (7.2)	-0.407	0.666	0.372-1.192	0.171
HS	337 (33.7)	126 (50.4)	0.616	1.852	0.507-6.761	0.351
MSM	390 (39)	81 (32.4)	0.032	1.032	0.281-3.789	0.962
IDU	251 (25.1)	126 (50.4)	0.056	1.057	0.3281-3.983	0.934
ART	810 (81)	140 (56)	-0.090	0.914	0.611-1.368	0.663
VL	710 (71)	59 (23.6)	-1.658	0.191	0.128-0.284	0.000

Legend Table 3-2: IQR: Interquartile Ratio, HS: Heterosexual, MSM: Men who have sex with men, IDU: Intravenous drug use, ART: Anti-retroviral therapy, VL: Viral Load

3.2.4 Discussion

HIV retention in care rates at our centre are overall comparable with international figures (90, 91), and rates occur over a time where patient demography in Ireland is changing over time (92).

Regarding geographic origin, the highest proportion of those who disengaged from care (36%) was from Sub-Saharan Africa, representing a higher proportion than the Irish group who disengaged (34.8%). 88% of the heterosexual risk group that disengaged were not from Ireland. From 2000-2011 in Ireland, as seen throughout Europe, a large proportion of those attending for HIV care with newly diagnosed HIV, were from the asylum seeker population (93) and it is possible that some of these patients have either relocated to another HIV centre with further provision of accommodation elsewhere in the country. It is also possible that these patients moved abroad.

56% of patients were on ART at the time of disengagement; 12% of these were females who had stopped ART post-partum, and did not return for care after cessation of ART. With HIV treatment guidelines change, this is no longer part of normal practice, as ART is continued throughout both pregnancy and the post-partum period.

These data highlight the need for a national HIV disease registry; an intervention undertaken in our department to contact these patients who were lost to follow up was successful, but only for a limited number who were contactable; 81.2% of patients who disengaged from care were not contactable, where registered phone numbers were out of service or the person could not be reached. This information suggests that a better way of maintaining patient demographics at each clinic appointment needs to be employed. The use of self-service kiosks as an efficient way for patients to update contact details including phone numbers and addresses at each

clinic visit, so they can be successfully contacted at an early point should they disengage was advised and has now been introduced (in 2016).

32.4% of patients who had disengaged from care were taking ART but did not have a suppressed viral load at the time of disengagement. This suggests a history of erratic ART use and possible intermittent clinic attendance.

While on univariate analysis, gender does not appear to be a factor associated with disengagement from HIV care, on multi-variable analysis males were more likely to disengage from HIV care.

In our study, patients who had disengaged from care were younger than those retained in care. Literature has previously described this as a factor associated with poor retention in care. (86) Those who had disengaged from care were less likely to have received ART and to have a suppressed HIV viral load, over this 8-year period,

The heterosexual risk group was most likely to disengage from care, with significantly higher rates of retention seen in the MSM and IDU risk groups. We have previously understood from literature that those with a history of intravenous drug use can have poor rates of healthcare attendance, but we also know that PWID frequently attend hospital services. It is possible that these patients engage in a more frequent manner due to such attendances with higher rates of points of contact with healthcare providers.

Multivariable analysis shows that when confounding for other independent predictors of non-retention in HIV care, non-Irish patients are more likely to disengage from care. Those with a suppressed HIV-1 viral load were more likely to engage in care, but those on ART alone were not found to be significantly more likely to engage in care. Use of this model with multiple

covariates shows that when other independent predictors are considered, few predictors are significantly associated with non-retention in HIV care.

A semi-structured interview has taken place, where reasons for disengaging from HIV care were explored with patients who have since re-engaged in care. Various themes for disengaging from care were identified, following interviews with patients. These included competing life events, a rigid hospital appointment system and poor communication with HIV service providers. Also, factors associated with motivation to re-attend were elucidated. These were patient changes in HIV symptoms that prompted re-attendance and also family, friend and hospital staff support to re-attend. These results were presented to the department staff and have given a better insight into reasons for disengagement. (Personal Communication Dr Almida Lynam, St James's Hospital).

The effect of implementation of the recommendation for immediate commencement of ART will need to be monitored over the coming years.

3.2.4.1 Limitations

This study has some limitations including those that are inherent in a single centre retrospective study. We do not have accurate records of those who may have passed away since disengaging. Individual patient reasons for defaulting from care were not elicited. A semi-structured interview has since taken place to explore patient reasons for disengagement from care. Patients were matched for year of attendance but not for other demographic factors. This decision was made to allow examination of other demographics as possible predictors for disengagement from care.

3.2.5 Conclusion

While we have identified specific characteristics of this patient group, including that the younger, non-Irish heterosexual risk group is at the highest risk of disengaging from care, anecdotal evidence suggests that perhaps this cohort have been re-located to another part of the country or have travelled abroad. This information highlights the previously made call for a national HIV disease registry, so we can fully understand the dynamic nature of our HIV cohort as it changes over time.

3.3 Hepatitis B Retention in Care / Treatment Outcomes

3.3.1 Background

Current clinical practice at the GUIDE Viral Hepatitis Clinic includes the care of patients with Hepatitis B mono-infection and HIV/hepatitis B co-infection. In 2012, given concerns related to perception of poor hepatitis B retention in care, a designated database was established. While one-third of the world population have serological evidence of exposure to chronic hepatitis B, and only 5% of these patients have chronic infection, rates of treatment for chronic hepatitis B remain low. Data available for hepatitis B mono-infection retention in care rates are limited. We aimed to describe the demographics of patients attending this clinic including rates of retention in care, to audit measures of clinical practice involving the care of patients with hepatitis B mono-infection at our viral hepatitis clinic, in accordance with EASL guidelines and to explore factors associated with hepatitis B retention in care.

3.3.2 Methods

A retrospective chart review identifying a set of pre-determined demographics relating to patient characteristics, socioeconomic patient status and disease staging was undertaken. Patient attendance in the past one year was also recorded. All patients with hepatitis B mono-infection attending the GUIDE clinic were included. The patient cohort was identified from a departmental database. Appropriate in-house ethical approval was obtained. Retrospective electronic chart review of these patients was undertaken. Patient demographics and variables of interest were collected on an Excel database, kept on a confidential password protected hard-drive. Data was then anonymised and analysed on SPSS V.23, using descriptive statistics, non-parametric T tests and Chi squared/Fishers tests.

3.3.3 Results

3.3.3.1 Patient Demographics

144 patients were identified in the cohort. 91(64%) of patients had remained in care in the preceding year. Patient Demographics: Mean Age (SD) was 37.28 (10.83) years. 105 (73%) patients were males. 23(16%) were Irish /Western European, the remainder were from other geographic origins including Sub-Saharan Africa, South-East Asia and Eastern Europe. Mode for hepatitis B acquisition included heterosexual (n=87, 60%), MSM (n=21, 14.6%), Vertical (n=18, 12.5%) and Other (n=18, 12.5%). Most patients (n=137, 95%) had no documented history of intravenous drug use. 73 (50.7%) of patients were employed. 143(99%) were of fixed abode. 3 patients had hepatitis C co-infection and 2 had hepatitis D co-infection. 1 patient lost hepatitis B sAg spontaneously and did not undergo subsequent surveillance and investigation. (See Table 3.3a)

3.3.3.2 Adherence with Guidelines Baseline disease assessment:

Most patients (n=103, 71.5%) were hepatitis B e antigen negative. 22(15%) were e antigen positive. 17 (11.8%) did not have e antigen recorded at baseline. In the most recent year of clinical contact, most patients (n=107, 74%) had a low hepatitis B viral load (Log +1 to Log +3). 14 patients (10%) had a suppressed hepatitis B viral load. Mean ALT in the most recent clinical year was 43.18 mmol/L (normal range 7-56 units/litre). Synthetic function (albumin) was normal in 99% of patients. Alpha-foetoprotein was checked in 128 (88.8%) of patients attending the clinic. 19 (13%) of patients had undergone a fibroscan and 18(12.5%) had undergone liver biopsy (4: FO, 6 F1, 3 F2, 2 F3, 1 F6.) In total, 2 patients were cirrhotic. 76% had a screening liver ultrasound performed. Regarding disease stage at baseline assessment, 96 (66.6%) were chronic healthy carriers, 22 were immune tolerant, 12 had immune clearance and 3 had reactivation. 7 were unknown. See Table 3-3a.

Table 3-3a Baseline Characteristics of Hepatitis B Attendees

	Total n=144 N (%)
Age Mean (SD)	37.28 (10.83)
Gender Male Female	105 (73) 39 (27)
Nationality Irish Sub-Saharan African SE Asia Eastern Europe Other	22 (15) 42 (29) 9 (6) 34 (24) 37 (26)
Risk Factor HS MSM Vertical Other	87 (60) 21 (14.6) 18 (12.5) 18 (12.5)
History of IDU Yes No	7 (4.9) 137 (95)
Employed Yes No	73 (50.7) 71 (49.3)
No Fixed Abode No Yes	143 (99) 1 (1)
eAg status Positive Negative Not recorded	22 (15) 103 (71.5) 19 (13)
HBV VL ➤ >Log +3 ➤ Log +1 --3 ➤ ND ➤ Not checked	18 (12.5) 107 (74.3) 15 (10.4) 4(3)

ALT Mean (mmol/L)	43.18
Synthetic Function (albumin) Normal Abnormal	143 (99) 1 (1)
AFP checked Yes No	128 (88.8) 16 (11.2)
Fibroscan done Yes No	19 (13) 125 (87)
Liver Biopsy done Yes No	18 (12.5) 126 (87.5)
Ultrasound Screening Yes No	110 (76) 34 (24)
Staging Chronic Healthy Carriers Immune tolerant Immune Clearance Reactivation Unknown	96 (66.6) 22 (15.3) 12 (8.3) 3 (2) 11 (7.6)

3.3.3.3 Treatment and Measurement of Outcomes:

26(18%) had undergone or were currently undergoing treatment for chronic hepatitis B management. 25(96%) were e antigen positive at baseline. Of these, 13 had complete virological response, (defined as hepatitis B viral DNA not detected), 12 were partial responders and 1 was within the time-period for assessment of response. Regarding e Antigen monitoring of response, 1 had lost eAg and 1 had not. 17 (65%) did not have an e Ag checked after starting treatment and 6 have unknown eAg status post treatment commencement.

Monitoring for co-infection: 129(90%) were tested for Hepatitis C and 139 (96.5%) were tested for HIV. 2 were tested for and were positive for hepatitis D co-infection. 115 (79.9%) patients were either immune or had received the hepatitis A vaccine, 9 still required the HAV vaccine. 19 did not have hepatitis A serology checked. See Table 3-3b.

Table 3-3b. Treatment Outcomes and Monitoring

	Total n=143 N (%)
On treatment	26 (18)
eAg positive	25 (96)
Complete Virological Response	13 (50)
Partial Virological Response	12 (46)
Treatment just commenced	1 (4)
eAg Monitored on treatment (n=26)	
Yes	2 (7.7)
No	17 (65)
Unknown	6 (27.3)
Co-infection testing	
HCV	
Yes	129 (90)
No	15 (10)
HDV	
Yes	2 (1.4)
No	142 (98.6)
Hepatitis A Immune	
Yes	115 (80)
No	9 (6.3)
Serology not checked	19 (13)

Table Legend: HCV: Hepatitis C virus, HDV: Hepatitis Delta virus

3.3.3.4 Engagement in Care

91 (63%) of patients have remained in care at this clinic. When certain demographics were compared, no significant difference between those who engaged in care or those who had disengaged was found for variables including age (p:0.8), geographic origin(p:0.8), gender (p:0.7) or mode of acquisition (p:0.47). See Table 3-3c for details. .

Table 3-3c. Engagement in Care n=143

	Engaged in Care N=91 N(%)	Disengaged from Care N=52 N(%)	p value
Age (years) Mean (SD)	37(11.5)	37.5(9.3)	0.8
Geographic Origin			0.8
Ireland/Western Europe	16(18)	5(11)	
Eastern Europe	21(23)	13(25)	
Sub-Saharan Africa	25(27)	17(32)	
South East Asia	6(7)	3(7)	
Other	23(25)	14(26)	
Gender			0.7
Male	65(71)	39(75)	
Female	26(29)	13(25)	
Risk Factor			0.47
Heterosexual	58(64)	28(55)	
MSM	12(13)	9(17)	
IDU	0(0)	1(2)	
Other	21(23)	14(26)	

Table Legend: MSM: Men who have with men, IDU: Intravenous Drug Use

3.3.4 Discussion

We have identified that some patients still require a liver ultrasound as part of work-up. Given low rates of timely eAg status monitoring, this needs to be improved upon, both before and following treatment. AFP levels should be checked for all patients at baseline. A small proportion of patients still require checking of hepatitis A immunity and hepatitis A vaccination provided for those who are non-immune. These recommendations have been disseminated at departmental level; I presented the study findings at a departmental audit day, that all clinic staff attended. I gave a recommendation to staff that Hepatitis eAg status should be specifically checked on routine clinic bloods, as part of assessment of treatment outcomes. Limitations for this study include the retrospective nature of data collection; it is possible that we do not have access to patient demographics collected when the patient has attended another hospital prior to transfer to St James's Hospital.

Rates of disengagement are lower than that for hepatitis C infection but higher than those with HIV infection. Most of these patients were living in a fixed residence, were employed and did not have a history of intravenous drug use. Given that different factors including homelessness, intravenous drug use and lack of employment are negatively associated with retention in healthcare, it should be expected that higher rates of retention in care should be observed. However, notably, most of our hepatitis B mono-infected patient population are from a migrant population. It is possible that these people have either moved abroad or to another part of Ireland, and thus have not truly disengaged from care. True figures of such cases are unknown due to the lack of national hepatitis B disease registry.

3.3.5 Conclusion

All patients who require treatment according to EASL guidelines are being treated accordingly. The treatment cascade for patients with hepatitis B mono-infection often requires clinical surveillance on at least a six-monthly basis, and for many no treatment is ever given. While clinical surveillance is still necessary in this cohort, it is possible that many stop attending due to perceived lack of clinical input. A detailed semi-structured interview is necessary to further understand reasons for hepatitis B disengagement from care.

3.4 Hepatitis C retention in care / treatment outcomes

3.4.1 Background

Rates of retention in hepatitis C care have internationally been recognised as low for many years (94,95) Globally, treatment uptake for hepatitis C remains low. (104) Treatment uptake is particularly low in PWID estimated to be as low as only 2-4% of those eligible.

(102,103,105,106) Those who are engaged in methadone replacement therapy, have a history of intravenous drug use or active psychiatric disorders show high rates of discontinuation of treatment for hepatitis C. (96)

For intravenous drug users, it is possible that the healthcare provider may affect treatment rates by being reticent about starting treatment in this cohort. The provider may have concerns about treatment adherence, the impact of psychiatric co-morbidities, alcohol and

drug consumption and potential hepatitis C re-infection. (101) Fortunately, the hepatitis C treatment landscape is changing. A growing body of literature shows that many of these provider concerns should not preclude consideration for hepatitis C treatment, as adherence among cohorts of intravenous drug users is similar to that of other patients, (99,100,101) Further research has shown that intravenous drug users are interested in accessing and commencing hepatitis C treatment (97,98) and have rates of hepatitis C treatment success comparable with other populations (99).

Hepatitis C patients co-infected with HIV have accelerated liver disease progression and historically lower rates of sustained viral response (SVR) compared to mono-infected when treated with pegylated interferon and ribavirin. Direct Acting Antivirals (DAA) are newer Hepatitis C therapies that are directed at multiple sites of the hepatitis C virus. They inhibit or prevent many viral proteins being produced by the virus. (107)

The use of Direct Acting Antivirals has improved SVR rates in co-infected patients however the necessity to avoid drug-drug interactions (DDIs) and toxicities with co-administration of ART require significant ART changes prior to commencing DAAs. (108)

Our primary aim was to determine rates of retention in hepatitis C care in our current cohort awaiting treatment attending GUIDE Viral Hepatitis Clinic at St James's Hospital. Our secondary aim was to assess the treatment outcomes of the co-infected cohort attending the GUIDE Viral Hepatitis Clinic, compared against the mono-infected cohort and to assess rates of ARV switch to avoid DDIs and toxicities.

3.4.2 Methods

All patients with a positive HCV PCR result attending the GUIDE viral hepatitis clinic were identified from a database at the National Virus reference Laboratory, UCD, Dublin 4. Retrospective electronic chart review was then undertaken. Demographics including retention in care, fibroscan result, where available, and treatment outcome were recorded.

To examine treatment outcomes specifically in those who have received DAA therapy, all patients treated since December 2012 were included in the analysis. Demographic, virological and drug treatment data were collected from the electronic patient and pharmacy records and entered on a database. Outcomes were described at SVR12, PCR negative at end of treatment but awaiting SVR12 (EOT=ND), Failed/stopped treatment and Treatment Ongoing. Data are reported as median (IQR) and differences between the mono-infected and co-infected groups were assessed using Student T test and Pearson's Chi square test.

3.4.3 Results

Since 2012, 715 patients have attended the GUIDE clinic for hepatitis C care. Of these, 179 (25%) have been treated, 536 (75%) still require treatment.

Of the 536 remaining to be treated, 262 (49%) of these patients with HCV are engaged in care, having been seen in clinic in the preceding 12 months.

207 (38.6%) have hepatitis C co-infection and 329 (61.4%) have hepatitis C mono-infection. 173 (32%) have undergone a fibroscan, and 42 (24.2%) of these are eligible for treatment, with a fibroscan score of greater than 8.5 kPa. However, 26 (57%) of these patients eligible for

treatment have reasons documented for being currently unable to start, including patient wishes, non-suppressed HIV viral load and other medical issues.

3.4.3.1 Treatment outcomes:

179 patients have been treated since 2012, including those prior to introduction of IFN-free DAA therapy. 123 (69%) of these patients were infected with HCV genotype 1. Overall SVR rates of 82.4% have been recorded.

149 patients were treated with treatment that included DAA therapy, of which 95 were co-infected with HIV. Of the co-infected cohort, median age was 47yrs, 78 (82.1%) male, 55 (57.9%) acquired hep C through intravenous drug use and most prevalent genotype was genotype 1. The only significant between-group differences were the DAA regimen choice and Hep C genotype (Table 3-3). Of the 79 (83.2%) co-infected patients who completed treatment 94% had either a SVR12 or were PCR negative at end of treatment, compared to 92% in the mono-infected cohort. 55% of co-infected patients required changes to their ART regime, with the most common switch off protease inhibitors and non-nucleoside reverse transcriptase inhibitors to integrase inhibitors. This compares to a switch rate of 17% overall in the clinic, calculated on audit data from 2014. There was no HIV viral escape detected in patients following switch of ART to facilitate DAA therapy.

Table 3-4a: Characteristics and Outcome Data: Mono-infected versus Co-Infected Patients

with HCV

	Mono-Infected	Co-Infected	p value
N=	54	95	
Age (Median IQR)	46 (36,52)	47.5 (42, 52)	0.121 (-0.63-5.37)
Male	48 (85.2%)	78 (82.1%)	0.348
Ethnicity			
Caucasian	51 (94.5%)	95 (100%)	0.116
African	2 (3.7%)	0	
Asian	1 (1.8%)	0	
Transmission risk			
IVDU	36 (66.7%)	55 (57.9%)	0.302
Sexual	5 (9.3%)	10 (10.5%)	1.000
Transfusion	1 (1.8%)	11 (11.6%)	1.000
Other	2 (3.7%)	3 (3.2%)	
Unknown	10 (18.5%)	16 (16.8%)	
Genotype			
1	47 (87.0%)	66 (69.5%)	0.017
2	0	0	
3	6 (11.1%)	25 (26.3%)	0.035
4	1 (1.9%)	4 (4.2%)	

DAA Regimen			
Sof/LDV/RBV	17 (31.5%)	39 (41.0%)	0.293
Sof/Dac/RBV	8 (14.8%)	25 (26.3%)	0.008
IFN/RBV/Sim	7 (13.0%)	0	0.001
Ifn/Rbv/Tel	18 (33.3%)	20 (21%)	0.119
IFN/RBV/Boc	4 (7.4%)	0	0.016
Abbvie 3d	0	11 (11.6%)	0.008
SVR			
SVR12	29 (53.7%)	55 (57.9%)	0.731
Failure/stopped tx	9 (16.7%)	13 (13.7%)	
Ongoing	9 (16.7%)	8 (8.4%)	
EOT=ND	7 (13.0%)	19 (20.0%)	
Antiretroviral Regime Switches made		52 (54.7%)	
PI to integrase		27 (52%)	
NNRTI to integrase		17 (32%)	
PI to PI		3 (6%)	
NNRTI to NNRTI		3 (6%)	
NRTI to NRTI		1 (2%)	
NRTI discontinuation		1 (2%)	

Table 3-4c SVR Outcomes by HCV Therapy

	Sof/Dac/ RBV n=33	Sof/LDV/ RBV n=56	Abbvie 3d n=11	Ifn/Rbv/ Tel n=38	IFN/RBV/ Boc n=4	IFN/RBV /Sim N=7	P value
SVR 12	13(39)	27(48)	7(63)	31(82)	3(75)	3(43)	<0.0001
Failure/ Stopped tx	3(9)	9(16)	1(9)	5(13)	1(25)	3(43)	
Ongoing	10(30)	5(9)	0(0)	2(5)	0(0)	0(0)	
EOT=ND	7(21)	15(27)	3(27)	0(0)	0(0)	1(14)	

Table 3-4b Fibroscan Results

	Mono-Infected	Co-Infected	P value
Fibroscan Completed	31 (57.4%)	62 (65.3%)	0.3102
Fibroscan Score (Median IQR)	10.9 (8.7,14.2)	12.1 (9.3, 17.1)	
Fibroscan Score			
<6.5kPa	3 (9.7)	4 (6)	0.4353
6.5-8.5 kPa	6 (19)	7 (11)	0.1649
>8.5 kPa	8 (26)	17 (27)	1.000
>11 kPa	14 (45)	34 (55)	0.2030
Liver Biopsy	3 (5.6%)	4 (5.3%)	1.000
F0	1	0	
F1	0	2	
F2	0	0	
F3	1	1	
F4	0	1	
F5	1	1	

3.4.4 Discussion

Rates of non-retention in care in our hepatitis C cohort continue to be much higher than the National HSE DNA rate of 7.5%. (109) This is a commonly observed phenomenon in the hepatitis C cascade of care seen both nationally and internationally. However, of those patients who were engaged in care, a high proportion of these patients were triaged appropriately for treatment, and the majority were treated where approval was in place to do so.

No significant difference in Fibroscan scores was found between the mono-infected and co-infected groups in this cohort. Most patients in both groups had a high score of greater than 11kPa, indicating significant liver fibrosis. A higher proportion of patients who received interferon-containing regimens had SVR 12, but it should be noted that a large proportion of patients being treated with an interferon-sparing regimen had treatment ongoing at the time of data collection. Of those patients who were treated, overall, high SVR rates were observed. These rates are higher than those that have been seen in recent clinical trials internationally. (110,111,112). In January 2017 the fibroscan threshold of 8.5 kPa to access DAA therapy was lifted, thus all patients with chronic hepatitis C infection are now eligible for treatment.

In this, the largest cohort of co-infected patients treated to date in Ireland with DAA therapy, there was no significant difference of SVR 12 between co-infected and mono-infected groups. The ART switch rate was considerably higher than overall clinic rate to avoid DDIs and toxicities associated with co-prescription of DAAs.

3.4.5 Conclusion

Valuable experience has been gained in the HCV DAA era, enabling effective treatment delivery to both mono-infected and co-infected HCV patients. However, much work remains to be completed to improve retention in care rates for those with active hepatitis C infection, so infection can be successfully treated and progression towards elimination of HCV is seen nationally by 2026, in line with both the Department of Health Multiannual Pharmaceutical Plan for the Treatment of HCV (113) and with targets outlined in the National Hepatitis C Treatment Programme.

Chapter 4

Chapter 4 HIV, Hepatitis B and C viral testing in an urban Emergency Department: A Pilot Study

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4.1 Introduction

Screening for infectious diseases including HIV, hepatitis B and hepatitis C offers a health benefit to the individual and prevents onward transmission. These viruses are world-wide public health problems resulting in a significant impact on population health, healthcare resource utilisation and costs. [114,115]

4.1.1 Current Screening Practices

CDC guidelines in the USA recommend an opt-out HIV screening approach. In the UK it is recommended that HIV testing is considered where HIV prevalence rates exceed 2/1000. [116] In the US, the CDC recently recommended one-time hepatitis C screening of all persons born between 1945 and 1965, in addition to risk factor-based screening already in place. [117] CDC hepatitis B testing guidelines suggest testing those with exposure risk factors to hepatitis B. [118]

In Ireland risk-based testing for HIV, hepatitis B and hepatitis C is most commonly offered. Despite the known prevalence in Dublin, universal HIV and hepatitis B screening is performed on an opt-out basis only in antenatal care and sexual health clinics. Common risk demography exists for hepatitis C acquisition in migrants, men who have sex with men and persons who inject drugs (PWID) as for HIV and hepatitis B infection. Significant rates of hepatitis C have been reported amongst PWID in the point prevalence studies undertaken in Dublin maternity hospitals also. [119,120] Despite these factors, only risk based targeted hepatitis C screening strategies are operational in Ireland and in most maternity hospitals. The universal screening of migrants has not yet been undertaken and overall there has been no integrated programme to screen patients for multiple blood-borne viral (BBV) infections with panel testing in a healthcare setting.

The offer of HIV testing in healthcare settings that do not routinely test for BBV infections including Out-Patient Clinics, General Practice, Acute Care Units and Emergency Departments has been shown to be acceptable and feasible. [121] Similar screening strategies include a universal point of care testing approach in an acute admission unit; this appeared to be an effective, feasible, acceptable and low-cost approach to HIV screening. [122] The emergency department is a desirable target for HIV testing within hospitals as it serves a high-throughput population of diverse attendees. Our ED serves a population with a very high diagnosed prevalence of HIV (2.25 per 1000) and this busy ED has 46,000 attendances per year.

4.2 Aims/Methods

4.2.1 Study Aims

The primary aim of this study was to assess the feasibility and acceptability of this approach of panel testing for HIV, hepatitis B and C in a busy urban ED where opt-out testing was performed on patients having bloods done as part of routine clinical care.

The secondary aim of this study was to determine the sero-prevalence of these three viral infections in this ED and to determine the new diagnosis rate of new viral infections. New and previously known and disengaged patients were linked back to care for early treatment to prevent morbidity/mortality and to prevent onward transmission. This was the first initiative of

its kind to take place in Ireland and this project was one of the first global initiatives to undertake testing for all 3 infections in an ED.

4.2.2 Methods

This was a cross-sectional study conducted at a large urban Emergency Department in Dublin, Ireland. Collaboration between the Departments of Genito-Urinary Medicine and Infectious Diseases (GUIDE), Emergency Medicine, Hepatology, Microbiology, in partnership with the HSE Social Inclusion Unit, Infectious Diseases Society of Ireland (IDSI) and Ireland Hepatitis C Research Outcomes Network (ICORN), allowed for the opt-out screening of all patients who had bloods taken as part of routine clinical care. Patients who were alert and had the ability to give verbal consent to testing were included. Prior to project commencement and throughout the project, the research nurse and I delivered didactic teaching sessions and workshops to nursing and medical staff in the ED to provide background information for the pilot study and to explain the testing protocol. ED staff in our centre attend weekly teaching sessions on various aspects of care for the ED patient. Dates were agreed upon with the co-ordinator of these sessions for the EDVS research nurse and I to allocate these slots monthly to give an update of results and to introduce and re-familiarise the staff with the study background and protocol. Monthly sessions were especially necessary given the turnover of staff and shift-patterns held by staff.

I wrote weekly progress updates in chart and written format and sent these to the ED staff to inform them of study blood uptake and details of positive tests found.

All patients over the age of 18 with the capacity to consent were included, as outlined in ethical approval granted by our local ethics committee. I designed posters in agreement with the EDVS Committee and placed these in the ED waiting room and triage areas. Patient

information leaflets were created and approved by the ethics committee; I then made these available at various care stages throughout the Emergency Department, including at reception and at triage. I arranged to have patient information leaflets translated into the 7 most common languages. A mobile phone was purchased that was solely for the use of the EDVS study team and this contact number was provided on both patient information leaflets and on separate smaller slips for those patients who had further questions for the study team or to find out their results.

ED staff advised patients that an extra serum sample would be taken when undergoing phlebotomy as part of routine clinical care at no extra cost, and this sample would be tested for HIV, hepatitis B and hepatitis C viral infection. The patient was given the option to opt-out following a set time of 20 minutes to consider his/her options. (Figure 4-1) Verbal consent was obtained in all cases in line with good clinical practice and current international clinical guidelines [123]. Written consent was deemed unnecessary as stated in these guidelines and is no longer part of routine clinical practice. When a study blood sample was taken this was recorded in the Emergency Department patient case notes.

Patients were informed that they would be contacted 3 working days after their initial ED visit, if the blood test taken was reactive. Patients were also informed that they would not be contacted if results were negative.

Appropriate ethical approval was obtained from the St James's Hospital/Adelaide and Meath, National Children's Hospital (SJH/AMNCH) Research Ethics Committee. (REC reference 2014/01) The consent process was approved by this committee. Following submission of first ethical approval protocol to our local research and ethics committee, concerns were raised by the ethics committee around the issue of the Emergency Department as a suitable site for the patients to consider having a HIV test taken. A rebuttal was sent to the ethics committee and a meeting was convened between the Principal Investigators of the study and Ethics Committee Members. Following delivery of a presentation and communication to the committee regarding the rate of undiagnosed infection and the importance of evaluation such an intervention, the decision was made to grant ethics for testing once a 20-minute isolation period was provided to the patient to consider his/her options before agreeing to have a test taken.

Given potential common risk demography for all three infections, panel testing for all three infections was performed in the possible scenario that a patient disclosed one blood borne viral infection to the healthcare staff member at the time of screening, or where the patient had study bloods taken at an earlier point in the study.

I managed results governance and delivery during the project, with the assistance of a research nurse assigned to the project. We contacted patients requiring follow up bloods or with a reactive blood test using contact details the patient provided at ED reception. We then took follow up bloods at the study facility (GUIDE department) and we linked appropriate patients to care. Those who had previously disengaged from care were also identified in the study; we then co-ordinated linkage back to care for these patients also. I recorded patient demographics for those who had a positive test by reviewing electronic and paper chart records.

Considering a range of previous opt-in rates (23% - 66%) reported for HIV testing in Emergency Departments [124,125,126], and a previous study which showed a higher patient offer rate with an opt-out approach [127] we set target uptake rate at greater than 50%. We defined uptake rate as the number of study bloods taken when the patient was undergoing phlebotomy as part of routine clinical care, proportional to the total number of bloods taken in the Emergency Department over the study period.

New diagnosis rate and study prevalence were defined as the number of new cases per 1000 tested and number of positive tests per 1000 tested for BBV respectively.

Figure 4-1. Patient Testing and Results Process.

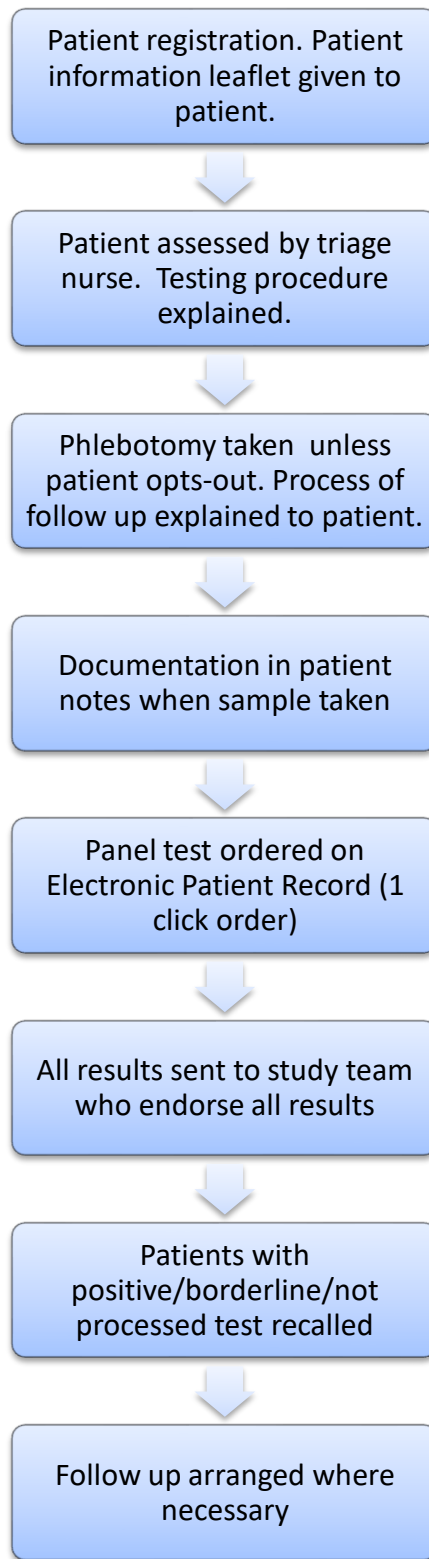
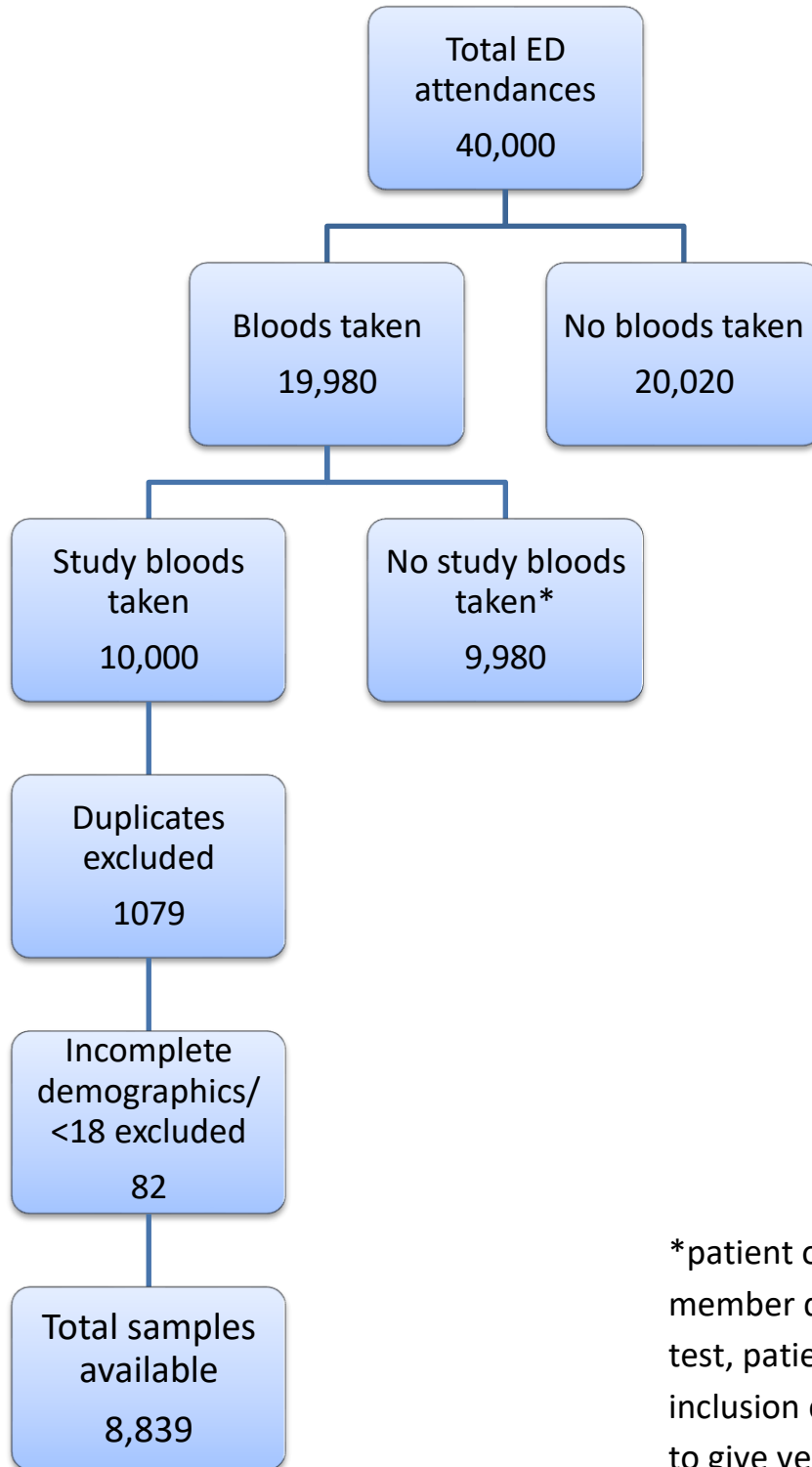


Figure 4-2 Description of Patient Numbers Tested.



*patient opted-out, staff member did not perform test, patient did not fulfil inclusion criteria (ie unable to give verbal consent for testing)

4.3 Results

10,000 serum samples were tested for HIV antibody/antigen, hepatitis B surface antigen and hepatitis C antibody from March 2014 to January 2015. A sustained cumulative target testing uptake rate of 50.1% was obtained. Of all ED blood samples taken, the proportion of study bloods taken was greater than 80% on specific days selected, where uptake of study bloods was examined using Emergency Department patient notes.

1079 subjects had a sample tested greater than once during the study period. 74 subjects under the age of 18 and 8 subjects with incomplete demographics were excluded from analysis. Once it was noted, a letter was drafted to the Ethics Committee to explain and record the breach in protocol where 74 patients under 18 were tested for BBV infection, all with negative results. Following exclusion of these patients and removal of duplicates, a total of 8,839 individual patient test results were available for analysis. (Figure 4-2) Median age (IQR) for this group tested was 45 (32,66). Age range was 18-102 years. 4463 (50.4%) were male subjects.

4.3.1 HIV

97 subjects who underwent testing had a positive HIV test. Age range (years) was 20-60. Median (IQR) years was 39(33,43). 68 patients (61.8%) were male. 7 of these patients were new diagnoses and 90 of these patients were previously known. 89 (98.8%) of patients with previously known infection were linked to care at the time of testing, and one further patient was re-linked to care as result of study team intervention.

Of the 7 newly diagnosed patients, 4 were male, age range was 23-51 and median (IQR) age was 29.5(38,43.5). (Table 4-1) Mode of acquisition included 3 MSM, 3 Irish female patients with heterosexual contact with a person from a country of high prevalence and 1 male with a history of previous intra-venous drug use. 4 (57.1%) of these patients presented to the ED with no clinical indicators for HIV infection. 3 (42.9%) presented with clinical indicators including *Pneumocystis Jirovecii* pneumonia (n=2) and pyrexia of unknown origin (n=1), with a subsequent diagnosis of Multicentric Castleman's disease. Five of these patients presented at a late point in their illness, with a CD4 count of less than 350 cells/mm³. Two of these patients had a CD4 count of less than 50 cells/mm³ at presentation, one of less than 200 cells/mm³ and the remaining two had a CD4 count of less than 350 cells/mm³. One patient was experiencing HIV seroconversion at the time of testing based on viral load result, avidity and HIV antibody results. HIV -1 viral load measured for this patient was greater than 10 million copies/mL, posing a very high risk of onward transmission. 1 patient (MSM) had previously tested for HIV; this test was negative 1 year prior to diagnosis. All 7 patients have been successfully commenced on ART, in the setting of interim results of a large-scale randomised clinical trial that recently showed significant clinical benefits for those patients commenced on ART at an earlier point in their illness, thus supporting the US recommendation that all asymptomatic HIV positive patients take ART irrespective of CD4 count. [128] (Table 4-2)

Of those with previously diagnosed HIV infection, 70 (77.6%) were Irish. Other countries of origin included United Kingdom (n=1), Brazil (n=5), Greece (n=1), Latvia (n=1), Lithuania (n=1), Russia (n=1), Sub-Saharan Africa (n=7), Poland (n=2) and Pakistan (n=1).

49 (50.5%) and 2 (2%) patients were co-infected with hepatitis C and B viral infection respectively. All these patients were aware of their co-infection status.

Emergency Department new diagnosis and prevalence rates for HIV infection were 0.8 and 11 per 1000 respectively. Patients were recalled and linked to care where appropriate. (Table 4-3)

4.3.2 Hepatitis B

A total of 44 patients had a positive blood test for hepatitis B surface antigen. 23 of these patients were known and 20 were new diagnoses. One patient is currently lost to follow up. Of the 20 newly diagnosed patients, with chronic hepatitis B infection, 16 were male, age range was 29-78 and median (IQR) age was 44(34-57). (Table 4-1) 6(30%) of these patients are from Ireland, other countries of origin included Afghanistan (n=1), China (n=3), Romania (n=3) Brazil (n=1), Eastern Europe (n=2), Pakistan (n=1), Philippines (n=1) and sub-Saharan Africa (n=2). Mode of acquisition included vertical transmission (n=9), MSM (n=1), PWID (n=1) and a further 9 patients (45%) had no identifiable risk when a full clinical history was taken at subsequent out-patient assessment. (Table 4-2)

8 (34.8%) of those with previously diagnosed HBV infection were Irish. Other countries of origin included Italy (n=1), Brazil (n=1), Latvia (n=1), Sub-Saharan Africa (n=8), Thailand (n=1) and Pakistan (n=3).

ED new diagnosis and prevalence rates for chronic hepatitis B infection were 2.26 and 5 per 1000 respectively. Patients were recalled and linked to care where appropriate. (Table 4-3)

4.3.3 Hepatitis C

447 patients had a positive blood test for hepatitis C antibody. 58 of these tests were newly diagnosed infection and 373 were previously diagnosed. 16 are currently lost to follow up, have not received their results and attempts to actively contact these patients are being pursued. These patients did not have complete demographics recorded at registration, (eg no fixed abode status) so were unable to be contacted. I met with administration staff during the project to explain the importance of recording as much demographic information as possible to prevent this happening. Following discussion with our IT department, I arranged an electronic notification to alert any care provider who logs in to the relevant patient records that we are trying to find this patient and contact details are provided on the alert to contact me. Also, these patient details have been registered on a homeless service list that encompasses all the Dublin area, so the manager of this service is aware to contact us should he find any of these patients.

Of the newly diagnosed group (n=58), 15% (n=12) had a negative PCR during study follow up. Age range for this group was 18-69, median (IQR) age was 25(36,49). (Table 4-1) 47(81%) were male. Country of origin included Ireland (n=52), Morocco (n=1), Pakistan (n=1), China (n=1), Asian (n=1) and Latvia (n=2).

Of the 43 patients with newly diagnosed hepatitis C linked to care, 32 had a history of intravenous drug use, 1 with a history of nasal cocaine use, 6 had no risk identified on assessment, 1 reported due to blood transfusion, 1 nosocomial acquisition and 2 heterosexual risk. 39 (93%) were Irish. Of those 32 patients who had a history of intravenous drug use, 12 were actively injecting drugs, 18 previously injected drugs and 2 had unknown active injection

drug use status. 16 (50%) of these patients with a history of intravenous drug use were receiving methadone replacement therapy. (Table 4-2)

364 (97.6%) of those with previously diagnosed hepatitis C infection were Irish. Other countries of origin included United Kingdom (n=1), Afghanistan (n=1), Latvia (n=1), Poland (n=2), Ukraine (n=1), Congo (n=1), China (n=1) and country of origin for one patient is unknown.

3 newly diagnosed patients seroconverted to hepatitis C viral infection during the study duration, with an initial negative hepatitis C antibody test followed by newly diagnosed positive serology during the study period on re-attendance to the Emergency Department. 2 of these patients carried risk of intravenous drug use for acquisition and 1 patient reported no identifiable risk for acquisition. 1 newly diagnosed patient was treated for hepatitis C 10 years previously and after a subsequent positive PCR (Polymerase Chain Reaction) was diagnosed with re-infection because of ongoing intravenous drug use.

ED new diagnosis and prevalence rates for hepatitis C viral infection were 6.5 and 50.5 per 1000 respectively. Patients were recalled and linked to care where appropriate. (Table 4-3)

Table 4-1. Positive Patient Age Distribution

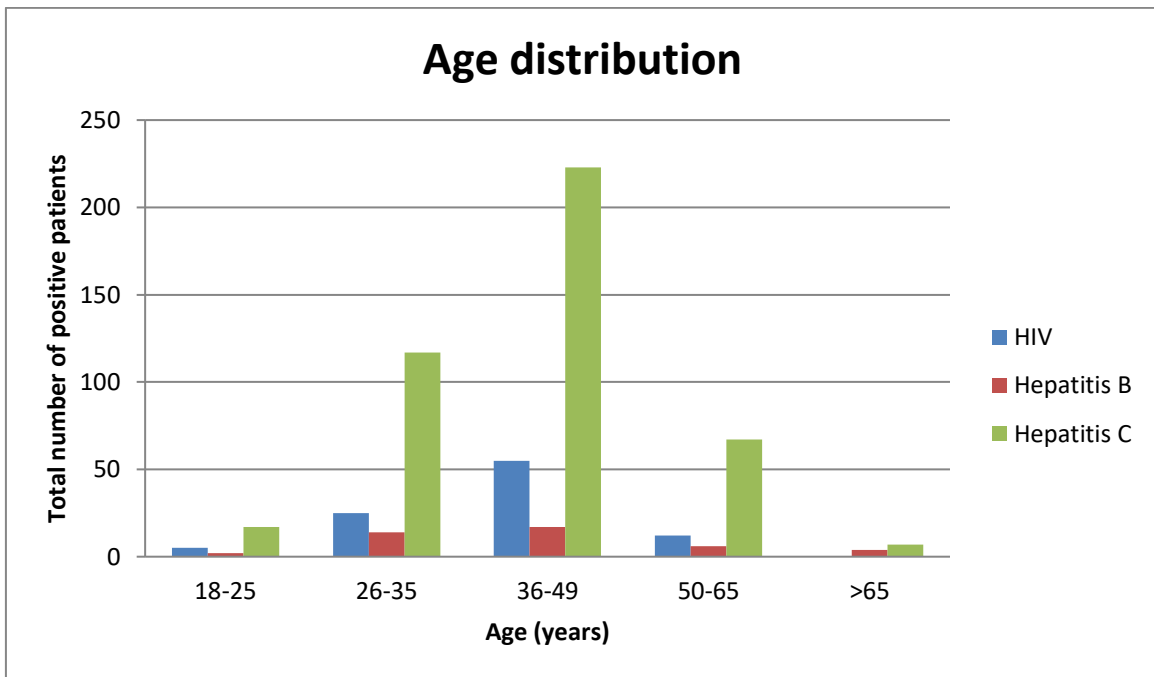


Table 4-2. Positive Patient Demographics

	HIV	Hepatitis B	Hepatitis C
	n(%)	n(%)	n(%)
Age			
New	7	20	58
<i>Range</i>	23-51	29-78	18-69
<i>Median, (IQR)</i>	29.5 (38,43.5)	44 (34, 57)	25 (36,49)
Known	90	23	373
<i>Range</i>	20-60	21-72	18-81
<i>Median (IQR)</i>	47.5 (33,44.5)	42 (33.5,45)	39 (34,46)
Gender			
New	7	20	58
<i>Male</i>	4 (57.1)	16 (80)	47 (81)
<i>Female</i>	3 (42.9)	4 (20)	11 (19)
Known	90	23	373
<i>Male</i>	57 (63.3)	16 (69.6)	235 (63)
<i>Female</i>	33 (36.7)	7 (30.4)	138 (37)
Risk			
New	7	20	58
<i>MSM^a</i>	3 (42.8)	1 (5)	0
<i>IVDU^b</i>	1 (14.3)	1 (5)	37 (63.8)
<i>HS^c</i>	3 (42.8)	0	2 (3.4)
<i>NRI^d</i>	0	9 (45)	14 (24.1)
<i>Vertical/COHP^e</i>	0	9 (45)	3 (5.1)

Nasal DU^f	0	0	2 (3.4)
Known	90	23	373
IVDU^b	48 (53.3)	5 (21.8)	333 (89.3)
HS^c	12 (13.3)	13 (56.5)	5 (1.3)
Blood Transfusion	0	1 (4.3)	4 (1)
Anti D	0	0	5 (1.3)
NRI^d	0	2 (8.7)	21 (5.6)
Nasal DU^f	0	0	1 (0.3)
Vertical^e	0	1 (4.3)	2 (0.5)
Haemophilia	0	0	1 (0.3)
MSM^a	30 (33.3)	1 (4.3)	1 (0.3)
Active IVDU			
New	7	20	58
Active IVDU^b	1 (14.3)	1 (5)	37 (63.8)
Known	90	23	373
Active IVDU^b	17 (18.8)	0 (0)	135 (40.5)
High Risk Postal Codes			
New	7	20	58
Dublin area	7 (100)	18 (90)	54(93.1)
Known	90	23	373
Dublin area	63 (70)	19 (82.6)	221 (59.2)
Homelessness			

New	7	20	58
<i>No fixed abode</i>	2 (28.5)	1 (5)	19 (32.7)
Known	90	23	373
<i>No fixed abode</i>	20 (22.2)	3 (13)	125 (33.5)

Table 1 Legend: ^aMSM: Men who have sex with men, ^bIVDU: Intravenous drug users, ^cHS: Heterosexual, ^dNRI: No risk identified, ^eCOHP: Country of high prevalence, ^fNasal DU: Nasal drug use

Table 4-3. Description of Linkage to Care

N=8,839	N(%)
<p>Total HIV cases</p> <p>New HIV+ cases</p> <p><i>Now linked</i></p> <p><i>Unlinked</i></p> <p>Known HIV+ cases</p> <p><i>Linked</i></p> <p><i>Unlinked</i></p>	<p>97</p> <p>7</p> <p>7 (100)</p> <p>0 (0)</p> <p>90</p> <p>90 (100)</p> <p>0 (0)</p>
<p>Total hepatitis B sAb+ cases</p> <p>New hepatitis B sAg+ cases</p> <p><i>Now linked</i></p> <p><i>Linkage ongoing</i></p> <p>Known hepatitis B sAg+ cases</p> <p><i>Linked</i></p> <p>Undetermined new / known – contact ongoing</p>	<p>44</p> <p>20</p> <p>19 (95.0)</p> <p>1 (5.0)</p> <p>23</p> <p>23 (100)</p> <p>1 (2.27)</p>
<p>Total hepatitis C Ab+ cases</p>	<p>447</p>

New HCV Ab+ cases	58
<i>Now linked</i>	43 (74.1)
<i>Linkage not required (PCR –ve)</i>	11 (18.9)
<i>Unlinked</i>	4 (6.89)
Known HCV Ab+ cases	373
<i>Linked</i>	202 (54.1)
<i>Relinked</i>	80 (21.4)
<i>Relinkage not required (PCR –ve)</i>	64 (17.1)
<i>Unlinked</i>	27 (7.2)
Undetermined new / known – contact ongoing	16 (3.5)

4.4 Discussion

This study demonstrates the novel use of panel testing as a method of screening for blood-borne viruses including HIV, hepatitis B and hepatitis C viral infection in a busy urban ED. No previous studies have been conducted examining this method as a screening strategy in the ED setting.

A high uptake rate was seen from an early point in the study, with 50.1% of all bloods in the ED taken over the study period containing an extra sample for viral screening. ED staff members reported to me that it was easier to take the bloods on a regular basis instead of consideration of risk before the patient underwent phlebotomy. The medical teams at our hospital gave me feedback that the process of blood-borne viral screening being performed at the stage of presentation to the hospital allowed for a faster assessment process and formulation of differential diagnosis by including immune-suppression or hepatitis as a factor in clinical decision making. Also, occupational health assessment of donor risk of BBV infection can happen in a shorter time as the majority of ED and admitted patients now have a recent HIV, hepatitis B and C results available on the electronic patient record.

A broad range of ages were tested and as testing was undertaken on an opt-out basis, patient risk was not considered prior to screening, thus the assumption is held that all risk groups were possibly screened.

A high Emergency Department study prevalence was seen for all three viral infections, with a positive HIV blood test in 1.1% of attendees having study bloods taken. This prevalence rate is much higher than the results of previous work that determined the rate of those living with

HIV in the greater Dublin area to be at least 0.2% and suggests that HIV screening should be performed as routine in those undergoing venepunctures or accessing secondary care.

Furthermore, 5% of all attendees undergoing study bloods had a positive hepatitis C antibody test and a significant number of HIV/Hepatitis C co-infection was noted. Both these rates reflect our inner-city cohort with high prevalence of intravenous drug use in this group.

Based on these results, to optimise patient outcomes and to reduce the risk of onward transmission, we successfully advocated to have implement this practice as standard of care, in partnership with the HSE Acute Hospitals Division, National Social Inclusion Unit and the HSE Population Health and Wellbeing Directorate. I wrote a media press release, approved by the CEO of the hospital. This was widely disseminated through national newspapers and websites on World Hepatitis Day 2015, when routine testing began at St James's Hospital ED.

This study had some limitations. Due to the study design of opt-out testing as part of routine clinical care in a busy ED and limitations with our electronic medical record system, we were unable to ascertain a refusal rate of HIV tests offered, or to obtain patient feedback to establish acceptability of patients at the time of routine screening. Furthermore, risk demography of patients was not routinely collected at the time of testing, thus electronic patient records were relied upon to collect this risk demography after screening. ED prevalence and new diagnosis rates reflect those who had study bloods done only, thus these reported figures may be an over –representation of viral infection prevalence in the ED attendees.

Conversely, the HIV new diagnosis rate found was lower than those found in previous studies [129,130]. This study design incorporated an opt-out approach, where patients having phlebotomy done as part of clinical care were given the option to opt out of BBV testing. In previous studies, an “opt-in” approach has been utilised, where patients are approached and offered the tests, and different testing methods have been used including salivary point of care tests in these studies. It is possible that due to the exclusion of greater than 50% of ED attendees over the study period who did not have bloods taken, the HIV new diagnosis rate found was lower than if this cohort had also undergone testing.

Many challenges were faced during this study: from an early stage of the project we dealt with an exceptionally high number of results and patients being diagnosed as positive. Each result either positive or negative required endorsement by myself or the appointed research nurse. Patient follow up required a significant amount of time and effort to ensure each patient was appropriately counselled, linked and supported by allied health professionals after diagnosis. Despite these challenges, 91% of patients with newly diagnosed active hepatitis C infection were linked to care and 75% of those with previously unlinked, active hepatitis C infection were re-linked to care. This is a much higher linkage to care rate than that reported in similar hepatitis C screening studies recently conducted internationally. (131) 100% of HIV and 95% of all hepatitis B patients are linked to care. Furthermore, a high uptake rate of testing was obtained and stigma for BBV testing has been reduced in our hospital by publicising the initiative and incorporating it as routine practice.

We learned that a large amount of time was required to follow up patients and that a dedicated Viral Liaison Nurse was required to follow up these patients once testing transitioned to routine care. Also, a high number of duplicates were found as patients

attended the ED more than once during the study period (Figure 4-2). Furthermore, it is possible that staff did not include the EDVS test on some patients because this needed to be actively included in the care set by clicking on the test, for each patient encounter. We sought to overcome these issues once routine testing was introduced, in July 2015. (section 4.6)

As previously described, ED staff attended regular teaching sessions on study protocol and updated results. These helped the testing process because staff were familiar with the study protocol and how to explain the testing process and follow-up with the patients. By providing teaching to the ED staff, this provided us also with a unique opportunity to hear candid staff feedback, so we could learn from it and make changes during both pilot and programme. ED staff education was key to the success of the pilot study.

From conducting these sessions, we learned from feedback that while delivering didactic teaching to staff was appreciated, a more successful approach was to discuss the project on a one-to-one basis. When possible, the study team were present at the morning clinical handover at the main staff hub on the ED floor to address this issue. We created progress charts and weekly e mails with results were sent to study investigators in the ED. A more effective approach for future studies would be to place these weekly on a well-visited noticeboard, for all busy staff to quickly see as they worked. Lastly, while teaching sessions were delivered to ED staff regularly, wider regular teaching sessions to other departments involved in the study including laboratory staff and hepatology staff would have improved communication and helped us answer any questions the staff would have had.

A very small proportion of those patients testing positive for blood borne viral infection were aged >65. Given the high cost of such a screening approach, it is possible that costs may have

been decreased by excluding this older population. A detailed cost analysis will be performed to assess the cost efficiency of performing panel testing for HIV, hepatitis B and C viral infections in this setting will address this question. Also, a qualitative interview should be performed for those patients who were diagnosed as positive during the study. This will inform us about the individual patient journey throughout the testing and results delivery process, so we can understand how to improve this programme and other BBV screening projects moving forward.

As part of the extension of the proposed NaTlve (National Viral Testing Initiative) project, further studies examining the sero-prevalence rates in both targeted and non-targeted settings in areas of differing demographics will be performed.

4.5 Conclusion

Within a large urban Emergency Medicine Department in a tertiary referral centre, it was possible to achieve an uptake rate of 50% in an HIV, hepatitis B and C opt-out testing pilot study. Over a 10-month period, 7 new HIV diagnoses were made, demonstrating the importance of testing in the ED to reduce onward transmission. Patients diagnosed had mainly late HIV diagnoses and were not all from high risk-groups, providing support for universal testing. This study enabled linkage to care of new individuals for early treatment in an era of early treatment for HIV and newly developed successful therapies for hepatitis C with high success rates.

The impact of this study has positive health implications both at an individual patient and at population health level. It has raised awareness about HIV, hepatitis B and C testing and its

clinical indicators. Given the opt-out nature of the test, stigma has potentially been removed from the process of testing, for both the patient and the staff member. Furthermore, those patients previously unaware of their diagnosis are at a significant health advantage by being diagnosed at an earlier stage in their illness. Once diagnosed and treated appropriately, rates of transmission will decrease. The strategy of linking testing to treatment (Test and Treat) has proved an effective public health intervention for HIV infection and may become part of the ambitious Department of Health public health intervention to eradicate hepatitis C. While current European guidelines recommend routine commencement of ART for HIV at a CD4 count of greater than 350 cells/mm³, interim results of a large-scale randomised clinical trial recently showed significant clinical benefits for those patients commenced on ART at an earlier point in their illness, thus supporting the US recommendation that all asymptomatic HIV positive patients take ART irrespective of CD4 count and the strategy of linking testing to immediate treatment. [132]

While previous studies have involved opportunistic HIV testing alone in non-traditional environments including Emergency Medicine Departments, no study to date has looked at the benefits of opt-out panel testing- where all 3 viruses are tested from a single serum sample. Particularly of note, of those who tested positive for HIV infection, our pilot study showed that almost half those patients with HIV infection had co-infection with hepatitis C, thus to screen for one virus alone runs the risk of missing other infections at the time of screening. This pilot study has not only offered patients a unique opportunity to be tested but also to be linked back to care. This study has provided us with valuable local population prevalence data that will inform blood-borne virus testing practice.

4.6 The Transition of BBV Testing to Routine Care

4.6.1 Introduction

On World Hepatitis Day, 28th July 2015, opt-out blood borne virus testing was implemented as standard of care at our Emergency Department. We again aimed to determine sero-prevalence of infections found since that time as compared with our pilot study, as the number of those tested continues to increase. A secondary aim of this programme was to compare the uptake of testing in a busy Emergency Department, as blood-borne virus testing moved from a research scenario with continued motivation to test within a routine hospital-approved programme.

All patients who were undergoing phlebotomy as part of routine clinical care were tested for HIV, Hepatitis B and C viral infection. Unlike the pilot study, the electronic test order was included in all care-set testing panels in the ED. The healthcare staff could remove the test order in the event the patient was unsuitable for testing, the patient opted-out or the patient recently had a test taken.

Like the pilot study design, posters were placed in the ED waiting room advising patients that BBV testing is part of their blood tests that are taken in that ED. Patient information leaflets were made available for the patients having blood tests taken with a contact number to phone should the patient want to do so.

To avoid excessive duplication of BBV testing for ED re-attenders, a six month “no-retest” rule was implemented at the beginning of the programme, based on the high frequency of duplicate testing during the pilot study. The healthcare staff could then choose to continue to include the test, if they felt it was necessary to do so.

As with during the pilot study, regular Question and Answer information sessions are provided for the ED staff.

The EDVS clinic began in March 2016, where a specific clinic appointment was allocated at GUIDE to allow me to see patients in a set time period each week. Rapid triage of patients could then take place, where hepatitis C genotyping, fibroscan and disease staging could take place in a timely manner and treatment assessment could be dealt with. Also, as medical lead for this programme, I ensured correct governance of effective programme delivery including appropriate test follow up, the management of laboratory and ED issues as they arose, and I devised a clinical risk register to document potential clinical risk, in conjunction with the EDVS Committee and Risk and Legal Manager at St James's Hospital.

4.6.2 Results Comparison

Results from 28th July 2015 to 6th February 2017 are presented. These data were collected over an 18-month period, in comparison with a 10-month period during the pilot study. 26,779 tests have been taken since routine testing began. Results of routine testing are described, and results of pilot study and routine testing are compared below.

4.6.2.1 HIV

Three hundred and thirty-three positive HIV tests were obtained over the 18-month testing period. Age range (years) was 19-80. Median age was 49.5. Two hundred and seventeen patients (65%) were male. Twenty-three of these patients were new diagnoses; this represents a 180% increased rate of new HIV diagnoses in comparison with the pilot study. Three hundred and nine positive samples were found who were previously known to be infected. All (100%) of patients with previously known infection were linked to care at the time of testing.

Of the twenty-three newly diagnosed patients, sixteen were male, age range was 24-67 and median (IQR) age was 45.5 (33, 51) years. Mode of acquisition included eight MSM, five heterosexuals, three from country of high prevalence and seven patients reported a history of intravenous drug use. Seven (30%) of these patients presented to the ED without any clinical indicators for HIV infection. Ten (43%) patients presented with a CD4 count of less than 350 mm³. See Table 4-4 for detailed demographics and comparison with pilot study.

Seventy-nine (55.2%) patients were co-infected with hepatitis C infection.

Emergency Department new diagnosis and prevalence rates for HIV infection were 0.85 and 12.4 per 1000 respectively.

Table 4-4 Comparison of Demographics – New HIV Cases

	Pilot (n=7)	Programme (n=23)
Age (Range, Median)	23-51, 29.5	24-67, 45.5
Gender (male)	4(57%)	16(77%)
Irish	4(57%)	13(56%)
Risk		
MSM	3(43%)	8(35%)
HS	3(43%)	5(22%)
IDU	1(14%)	7(30%)
COHP	0(0%)	3(13%)

CD4 (Range, Median)	13-743, 249	27-1297, 365
Viral Load (Range, Median)	357 – 7969977, 125357	83-3347738, 96811
HIV Clinical Indicator	4(57%)	7(30%)
Previous HIV Test	1(14%)	15(65%)
On ART	6(86%)	16(70%)
VL ND	6(86%)	15(65%)

4.6.2.2 Hepatitis B

One hundred and twenty-seven samples tested positive for hepatitis B surface antigen. Eighty-three of these were known, thirty-two were new diagnoses, eight were false reactive tests and four patients with positive samples are lost to follow up

Of the 32 newly diagnosed patients, 25(78%) were male, age range was 24-71 and median (IQR) age was 47.5 (32,48) years. Ten (31%) of these patients are from Ireland. Mode of acquisition included being from a country of high prevalence including possible vertical transmission (n=13), IVDU (n=2), MSM (n=1) heterosexual (n=1), tattoos (n=2), unknown (n=2). Eleven patients (34%) had no identifiable risk when a full clinical history was taken at subsequent out-patient assessment. See table 4-5 for detailed demographics and comparison with pilot study.

ED new diagnosis and prevalence rates for chronic hepatitis B infection were 1.2 and 4.74 per 1000 respectively.

Table 4-5 Comparison of Demographics – New HBV Cases

	Pilot (n=20)	Programme (n=32)
Median Age (Range)	44(29-78)	47.5(24-71)
Gender (male)	16(80%)	25(78%)
Irish	8(34.8%)	10(31%)
Risk		
MSM	1(5%)	1(3%)
HS	0	1(3%)
IDU	1(5%)	2(6%)
COHP	9(45%)	13(41%)
Unknown	0	2(6%)
NRI	9(45%)	11(34%)
Tattoos	0	2(6%)
Linked to care	19(95%)	31(97%)
eAg positivity	1(5%)	7(22%)
Treatment given	1(5%)	3(9%)

4.6.2.3 Hepatitis C

1487 samples tested positive for hepatitis C antibody. One hundred and five of these patients were newly diagnosed with hepatitis C infection and 1211 were previously diagnosed. A further 32 patients are currently being followed up and 139 are false positive hepatitis C antibody results, with a positive antibody assay on initial testing but a negative result on a different antibody assay.

Of the newly diagnosed group (n=105), age range for this group was 39-91, median (IQR) age was 57 (34, 52.5). 69(66%) were male. 72(68.6%) were Irish.

37% (n=39) of new cases had a positive PCR. All 39 patients have been linked to specialist care. See Table 4-6 for detailed demographics and comparison with pilot study.

ED new diagnosis and prevalence rates for hepatitis C viral infection were 3.9 and 55.5 per 1000 respectively.

Table 4-6 Comparison of Demographics – New HCV Cases

	Pilot (n=58)	Programme (n=105)
Median Age (Range)	25(18-69)	57(39-91)
Gender (male)	47(81%)	69(66%)
Irish	52(90%)	72(68.6%)
Risk		
MSM	0	4(4%)
HS	2(3%)	4(4%)
IDU	37(64%)	49(47%)
Nasal Drug Use	2(3%)	3(3%)
NRI	14(24%)	11(10%)
Tattoos	0	13(12%)
COHP	3(5%)	7(7%)
Unknown	0	10(10%)
Anti-D	0	2(2%)
Needlestick	0	1(1%)
IBTS	0	1(1%)
Linked to care (of PCR positive)	100%	100%

4.6.3 Discussion

This programme has allowed us to continue to diagnose people with BBV infections who were previously unaware of their status. Since funding has been secured, this programme continues in St James's Hospital Emergency Department as part of routine clinical care.

Uptake of BBV testing in those who are having bloods taken has remained greater than 50% (50.1% during pilot study vs 52% during routine testing).

During this programme period we have seen a higher proportion of patients presenting with IDU as risk factor for HIV acquisition as compared to during our pilot study and to nationally reported rates. This may reflect the surge in new HIV diagnoses amongst intravenous drug users in the Dublin area that has recently been reported. (141)

We continue to see high rates of HIV-HCV co-infection; this is accounted for by the patient demography attending of an inner-city cohort with a high prevalence of intravenous drug use.

Most patients with newly diagnosed chronic hepatitis B infection were born in a country of high prevalence for hepatitis B infection. No routine migrant screening programme currently exists in Ireland apart from the offer of voluntary-based opt-in testing as a person arrives in the country through a reception centre. Such migrants account for a very small percentage of overall migrants now coming to Ireland. These data highlight the need to implement the newly published Health Protection Surveillance Centre of Ireland Infectious Disease Screening Guidelines for Migrants, published in 2015. (142) However, it is worth noting that 25% of patients with newly diagnosed hepatitis B infection were Irish and would not have been considered for testing on risk-based assessment alone.

We continue to find high rates of Hepatitis C infection in our ED cohort; a significant proportion of these are newly diagnosed. Of note, 10% of those with newly diagnosed HCV infection had no risk identifiable on assessment, so would not have been diagnosed with current risk-based strategies in place in Ireland.

This is the first programme of its kind based on literature search that we are aware of internationally, where opt-out panel testing for all three BBV infections has been implemented as part of routine care. Given common risk demography for acquisition of all three infections, and the high rate of HIV/HCV co-infection we continue to find, this programme demonstrates the ongoing need for panel testing of all three infections in the population attending our ED.

4.6.4 Conclusion

The introduction of routine BBV testing in St James's Hospital ED has been shown to be a valuable addition to patient care at our centre. Anecdotally it has continued to decrease the stigma associated with HIV testing in St James's Hospital. Point of care testing and the inclusion of molecular point of care testing now need to be evaluated in our ED on a pilot basis, to ensure all patients are screened, to ensure we capture HCV positive patients with viremia rather than antibody positivity alone and to overcome the challenge associated with notification of patients with results when they have left the ED.

Because only 50% of ED attendees have bloods taken, it can be hypothesised that those patients who are not having bloods taken also carry a high rate of BBV infection. Further data from the evaluation of patient demographics of those who attend ED who don't have bloods taken compared to those who do will be informative and is planned.

4.6.4.1 Recommendations

In the interests of patient safety and effective patient care, the need for future testing strategies include blood-borne virus point-of-care testing and the use of hepatitis C molecular point of care testing in a busy ED now arises. We now propose to evaluate mechanisms to test patients attending the ED who do not undergo routine phlebotomy.

Chapter 5

Chapter 5: Hepatitis C Attendance to Care – A Quality Improvement Programme

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5.1.1 Introduction

With the widespread introduction of newer successful DAA therapies and the goal of the National Hepatitis C treatment programme, a greater emphasis has been placed on improving the hepatitis C diagnosis and retention in care rates in recent times.

5.1.2 EDVS Linkage to Care

To understand the outcomes of patients who were newly diagnosed or disengaged from care who had been re-referred, during the EDVS pilot study and routine programme, I sought to gain a better understanding of the cascade of care for individuals referred to the GUIDE clinic. We defined linkage to care as patient notification that BBV infection was present and an appointment given to attend clinic; attendance rates were then recorded. Retrospective analysis was performed on PCR positive hepatitis C mono-infected patients who were referred to the Viral Hepatitis Clinic during both the pilot EDVS study from March 2014 to January 2015 and the subsequent roll-out programme from July 2015 to February 2017.

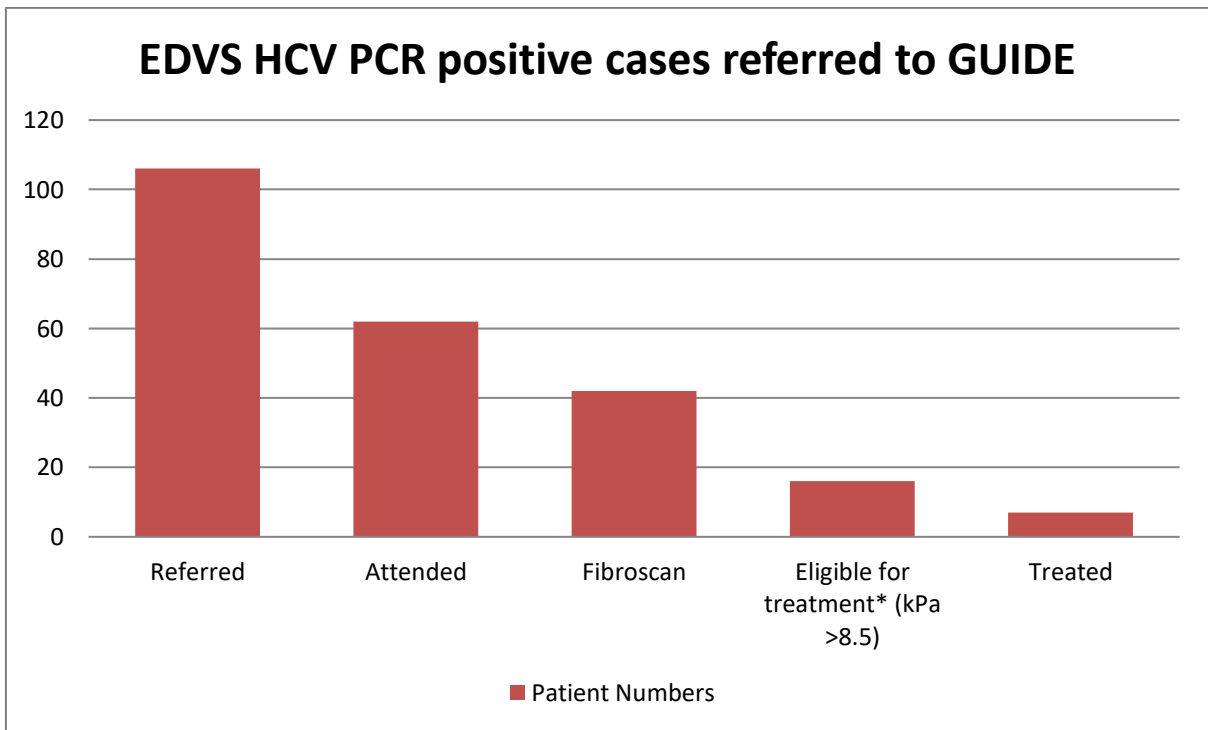
Of the 106 new or re-linked patients with active hepatitis C infection, all patients were linked to the Viral Hepatitis Clinic, 62 (58.5%) of whom attended. See Table 5-1 for further details.

Table 5-1: Characteristics of Active Hepatitis C Cohort and Cascades of Care

HCV PCR +VE (n=)	106
Age - Median (IQR)	39 (35, 49)
Sex - Female - Male	26 (24.5%) 80 (75.5%)
Ethnicity	Caucasian = 104 (98.2%) African =1 (0.9%) Asian = 1 (0.9%) Other = 0
Risk group	IVDU = 85 (80.2%) Heterosexual = 1 (1%) MSM = 1 (1%) Transfusion = 6 (5.7%) Other = 3 (2.8%) Unknown = 10 (9.4%)
GUIDE referral	106(100%)
No. who attended	62 (58.5% of referrals)
Genotype tested (n=)	66 (62.3%) G2 = 2 (3%)

	<p>G3 = 33 (50%)</p> <p>G4 = 2 (3%)</p> <p>G1 = 29 (43.9%)</p>
<p>Patients who had fibroscan (n=)</p> <p>- Number of fibroscans above threshold for treatment (>8.5kPa)</p> <p>- Median score (IQR)</p>	<p>42 (39.6%)</p> <p>16 (38.1%)</p> <p>7.7 (5.98, 11.3)</p>
<p>Treatment commenced</p> <p>- SOF/DAC/RBV</p> <p>- SOF/LDV/RBV</p> <p>- IFN/RBV</p>	<p>7(43.8% of those eligible)</p> <p>2</p> <p>2</p> <p>3</p>
<p>Treatment outcomes</p> <p>- SVR 12</p> <p> ○ SOF/DAC/RBV</p> <p> ○ SOF/LDV/RBV</p> <p>- Failures</p> <p> ○ IFN/RBV</p> <p>- Ongoing</p> <p> ○ SOF/DAC/RBV</p> <p> ○ IFN/RBV</p>	<p>3 (42.9%)</p> <p>1</p> <p>2</p> <p>2 (28.6%)</p> <p>2</p> <p>2(28.6%)</p> <p>1</p> <p>1</p>

Figure 5-1: New Referrals from EDVS to GUIDE – Cascade of Care



*According to current national criteria

5.1.3 Barriers Associated with Non-Engagement in Hepatitis C Care

The continuum of hepatitis C testing and care involves the process of antibody screening, confirmation with hepatitis C polymerase chain reaction testing (PCR), engagement in a specialist clinic and treatment. A recent study in the United States shows that patients often do not follow this pathway, with reported rates of retention in hepatitis C care in the United States as low as 27%. (133) Many barriers for poor engagement in hepatitis C care are recognised including homelessness and intravenous drug use. (135)

In recent years, hepatitis C therapy has been delivered at a community level internationally, to try to overcome barriers to hepatitis C treatment delivery in challenging cohorts. The ECHO™ model of care has been shown to be successful in New Mexico, where improved access to hepatitis C care has been provided in the community. (136) Results of the project ECHO™ pilot for hepatitis C care in Ireland suggest the need to extend a similar community-based project in the Irish healthcare system. (139)

In 2015 a retrospective review of patients with previously known hepatitis C who underwent screening during the EDVS pilot study was carried out. Those who had disengaged from hepatitis C care were identified. Barriers associated with non-engagement in care were examined.

373 patients with previously known hepatitis C infection were identified during the pilot ED testing project. Of those with a history of IDU, 135(36.2%) were actively using drugs at the time of testing and 255(77.7%) were receiving methadone replacement therapy. Forty-seven

(32%) patients who were engaged in care had no fixed abode and 24(39%) of disengaged patients had no fixed abode (p=0.227).

One hundred and twenty-nine (88%) patients who were engaged in care had a history of intravenous drug use as compared with 59(95%) of disengaged patients (p=0.197).

On multivariate analysis for those with active hepatitis C infection, active IDU was more likely in the disengaged from care cohort (OR 0.272, CI: 0.11-0.64, p: 0.003). Those with HIV co-infection were much more likely to be engaged in care (OR: 22.2, CI: 2.95-166.7, p: 0.003)

See Table 5-2 for characteristics of those with active hepatitis C infection in the engaged and disengaged cohort, including univariate and multivariate analysis.

Table 5-2 Patient Demographics: Active Hepatitis C Infection

N(%)	Engaged in Care n=146	Disengaged from Care n=62	p value	Odds Ratio	p value
Age Mean (SD)	146(40.4)	62(39.9)	0.714(-3.1 - 2.1)	0.976(0.92-1.03)	0.424
Gender n (%) male	97(66%)	45(73%)	0.39	0.591(0.25-1.39)	0.230
IDU n(%)	129(88%)	59(95%)	0.197	0.386(0.1 – 1.36)	0.140
Active IDU n(%)	49(36%)	32(52%)	0.04	0.272(0.11-0.64)	0.003
Housing Status					

No Fixed Abode n(%)	47(32%)	24(39%)	0.227	1.39(0.63-3.1)	0.408
Risk					
PWID	129	59	0.522	0.386(0.1-1.36)	0.140
HS	2	1			
Blood Transfusion	3	0			
Anti D	2	0			
No risk identified					
Nasal Drug Use	7	1			
	0	1			
Haemophilia					
MSM	1	0			
Unknown	1	0			
	1	0			
HIV co-infection	37(25%)	1(2%)	<0.001	22.2(2.95-166.7)	0.003
IDU (n=188)					
Active DU	49(36%)	32(52%)	0.033	0.272(0.11-0.64)	0.003
On MRT	102	46	0.846	0.774(0.34-1.73)	0.535
Attending MC	87	37	0.476	1.67(0.61-4.95)	0.315

Table 5- 2 Legend: IDU: Intravenous Drug User, PWID: People who inject drugs, HS: Heterosexual, MSM: Men who have sex with men, COHP: Country of high prevalence, MRT: Methadone replacement therapy, MC: Methadone Clinic.

5.1.4 Discussion

During the EDVS pilot study and routine testing programme, 106 newly diagnosed or patients not currently engaged in care with active chronic hepatitis C were linked to GUIDE Viral Hepatitis Clinic services. To date 7 patients were treated who otherwise would not have been. Despite best efforts to follow-up on patients with active hepatitis C, subsequent clinic attendance rate is 58%. However, once engaged, 44% were deemed eligible by current national criteria received treatment.

During the EDVS pilot, high rates of active intravenous drug use were seen in patients who were previously diagnosed with HCV. Also, 33.5% of these patients had no fixed abode. This is much higher than the national rate of 0.08%. National reports show a steadily increasing rate of homelessness in Dublin. (138) These data represent areas of concern for the delivery of hepatitis C care, given that it has been well documented in the literature that homelessness is associated with poor health outcomes (140)

Factors associated with disengagement from hepatitis C care including active intravenous drug use and hepatitis C mono-infection were identified in the EDVS cohort.

Conclusion

Considering the barriers that already exist for patients, strategies to improve attendance to hepatitis C services are required to improve the hepatitis C care continuum and optimize outcomes from the screening programmes and from routine clinical care pathways. I then developed and led a quality improvement programme at GUIDE to explore ways to possibly improve these attendance rates. (Section 5.2)

5.2 Hepatitis C Attendance to Care Rates: A Quality Improvement Programme

5.2.1 Service Description and Driver for Patient Safety

As previously described, during the Emergency Department Blood Borne Viral Screening programme, high sero-prevalence rates were found for all three infections. While linkage to care rates for HIV, hepatitis B and C infection were obtained (100%, 95% and 87% respectively) by the end of the study, attendance to care rates for those with hepatitis C were found to be low after 1 year of follow up (67%) and continues to be low at 2 years of combined pilot and programme delivery (58.5%).

Hepatitis C therapies have improved considerably in recent years. A goal of screening is to offer access to this treatment to patients, not possible unless patients engage in care.

As part of the St James's Hospital and Dartmouth Institute Microsystem Academy Quality Improvement programme, I decided to form the Infectious Disease Quality Improvement team to address the problem of poor hepatitis C attendance rates seen during EDVS. I formed the Department of Genito-Urinary Medicine and Infectious Diseases QI team in May 2016. The team was coached by coaches-in-training, and consisted of a Team Leader, Viral Liaison Nurse, Hepatitis C Clinical Nurse Specialists (CNS), a Hepatitis C Pharmacist and a departmental Senior Administrator.

5.2.2 Patient Safety Initiative

We used the Clinical Microsystem structure as a tool to guide the process of quality improvement. A process map for the service was created, and areas within this process were identified as potential areas for improvement:

1. The did-not- attend (DNA) rate for patients requiring follow up for blood test results suggestive of hepatitis C infection, fibroscan procedure and for follow up to clinic for care was suspected to be high. We then developed several run charts to quantify these DNA rates. A run chart is a run-sequenced plot that describes observed data over a set time sequence. Median DNA rate for the fibroscan procedure was 1 per week and for blood result follow up was 2 per week. (Appendix 5, 6) We aimed to decrease both these DNA rates by a median of 1 per week with the interventions listed below.

2. A necessary administrative role for the process was clearly defined as a deficiency in the process, while a large amount of Clinical Nurse Specialist Time was spent performing non-clinical administrative duties. Data collated from both the EDVS programme and the Viral Hepatitis Clinic to measure attendance rates, treatment rates and treatment outcomes. This was then presented and submitted to the National Hepatitis C Treatment Programme to gain long term funding for this administrative role.

Other tools such as fishbone analysis were utilised, to explore other ways to improve parts of the clinical service pathway. (Appendix 7) A fishbone analysis, otherwise known as an Ishikawa diagram, is a cause and effect analysis. The diagram, shaped like a fishbone, examines many areas, some that may have previously been unidentified, as potential causes for a problem. This can be used before deciding how to appropriately resolve a problem.

5.2.3 Interventions

Multiple PDSA (Plan, Do, Study, Act) cycles were created, as part of the Quality Improvement Programme. (Figure 5.2) A PDSA cycle is a systematic series of steps for gaining valuable learning and knowledge for the continual improvement of a product or process. Firstly, a plan is put in place to identify a purpose. Then an intervention is made to improve that plan.

Outcomes are then monitored to measure the validity of the plan. The act step then closes the cycle, by learning from the process that can be used to adjust the plan.

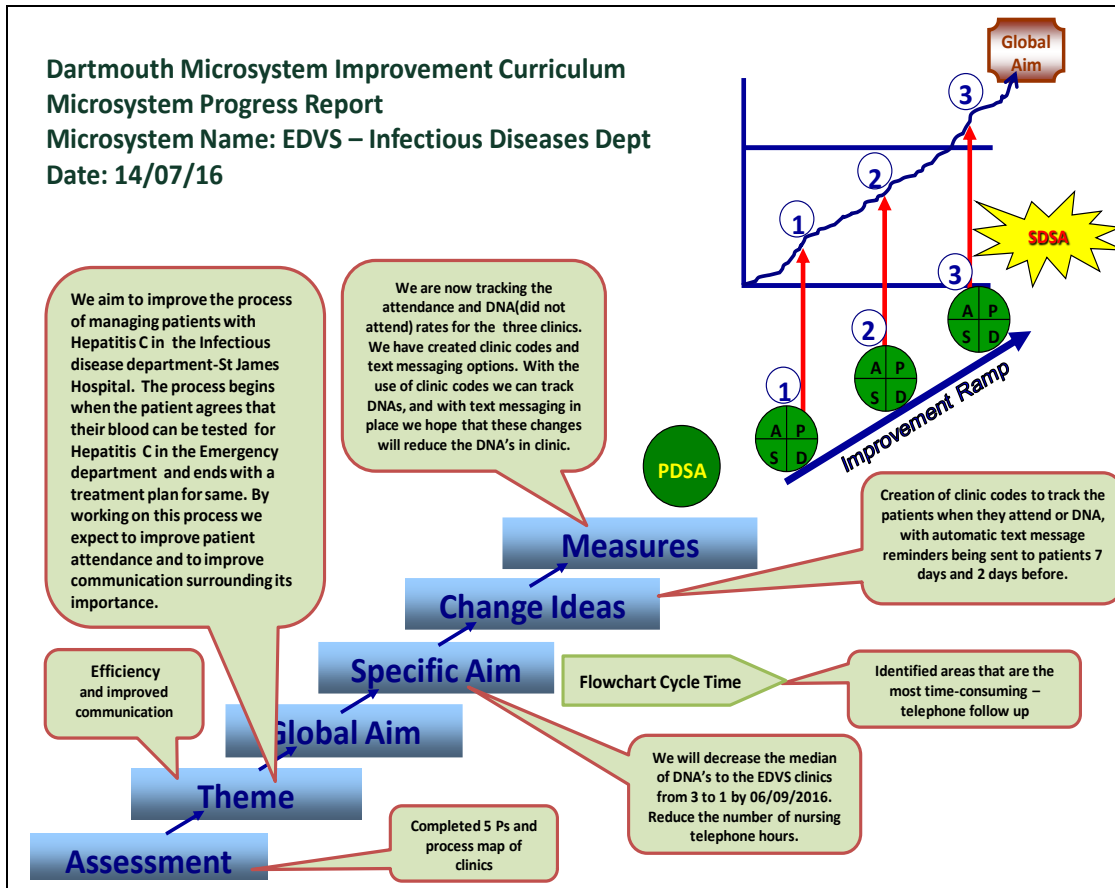
To improve attendance rate, automated text messaging that had not previously been used for this clinical service was implemented for EDVS patients from initial follow up visit, in July 2016, to remind patients of appointment times on 3 different occasions prior to their attendance.

Despite potential bias, a hospital approved patient satisfaction questionnaire was given to those patients recalled for hepatitis C care, to gain a better understanding of how service improvement could be delivered. (Appendix 8)

A new clinic code was introduced, so that all fibroscan procedures could be electronically ordered, tracked and arranged by administrative staff instead of clinical nurse specialists. Introduction of this clinic code has also allowed the fibroscan service to become more streamlined, with the ability to check DNA rates on a regular basis and to accurately measure fibroscan rates.

A tick and tally exercise was performed by the clinical nurse specialists in early September 2016, where hours spent on administrative duties were recorded over a 1 week period. Tick and tally exercises involve simply recording how often an event happens and then comparing the number of times that intervention happens after an intervention has taken place. A senior administrator then took over certain administrative roles as agreed. While no financial support for this QI programme was required, results of this programme then allowed us to argue the need for further administration support. The administrative role was then successfully endorsed and funded by the National Hepatitis C Treatment Programme and this role is now incorporated as standard of care in the GUIDE Viral Hepatitis Clinic.

Figure 5-2: Microsystem Quality Improvement Ramp: Infectious Diseases Team



5.2.4. Challenges and Supports

Attendance at weekly meetings was a challenge for all staff involved, as all staff involved are working in a busy clinical service.

The team were enthusiastic and willing for change. No financial support has been granted for this, and all improvements have been done as part of working day duties.

5.2.5. Benefits and Outcomes

Median DNA rates for fibroscan attendance remained unchanged at a median rate of 1 per week. Median DNA rates for those attending for follow up blood tests and clinical follow up increased despite interventions used. (Appendix 5,6)

Patient satisfaction survey results showed a very high patient satisfaction rate with the service delivered for follow up in the GUIDE clinic. This only reflects the opinion of those patients who attended, however. (Appendix 8)

Clinical Nurse Specialist tick and tally results showed a significant increase in time liberated by administrative duties being carried out by a senior administrator recently allocated to the role. This increase in time for clinical nurse specialist clinical activity will ensure better patient education, support and overall care. However, more CNS time will not improve outcomes for those patients who continue to disengage, and outreach supports are needed for these patients.

This work has shown that using an appropriate clinical microsystem structure and a willing team, small improvements can be made to any service within a short time period, with limited availability of resources. Despite maximal intervention employed to encourage attendance for clinical review; attendance rates were not improved. Other ways to encourage attendance at clinic should include offsite triage and treatment to allow safe and streamlined treatment delivery for patients. These data have argued for the provision of resources to develop an outreach programme, and as a result plans for this strategy are in place for 2017, with the recent appointment of a further hepatitis C Nurse Specialist in GUIDE. This programme has equipped me, as team leader, with the necessary skills required to lead teams in the future to continue to improve quality in healthcare service delivery.

Chapter 6

Chapter 6: Summary, Conclusion and Recommendations

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6.1 Summary

Despite HIV prevention strategies in place both nationally and internationally, rates of HIV infection acquisition remained static for the past 9 years, with recent rises in HIV notifications over the past 2 years in Ireland in certain risk groups. Rates of late HIV presentation continue to be excessively high almost 50% of total diagnoses reported to the HPSC every year, suggesting that a significant proportion of those with HIV infection continue to be undiagnosed and are not accessing testing. However, it is important to note that late HIV presentation needs to be redefined, as it is likely that a high proportion of those with CD4 of less than 350 have recently acquired the infection. The addition of the RITA algorithm outlined in chapter 2 as part of routine HIV surveillance in Ireland will help us gain a better understanding of timing of HIV acquisition and true late HIV presentation. The risk demography for HIV acquisition continues to change as demography in Ireland changes over the past 10 years, with a decrease in those from the migrant populations being diagnosed and a sharp rise in MSM acquisition, PWID and migrant MSM acquisition in more recent times. Our late presentation retrospective cohort study has also identified that those who continue to present late are those that are often not perceived to be at risk of HIV infection, with a subsequent negative impact on morbidity, mortality and public health perspective. In line with the UNAIDS 90-90-90 target, where 90% of those with HIV infection need to be diagnosed in an effort to retain and treat 90%, widespread screening protocols to address the problems outlined above were needed. This call led us to develop the pilot Blood Borne Virus Screening Study outlined in chapter 4, which confirms the feasibility and acceptability of such a screening protocol.

Rates of hepatitis B notifications with the HPSC continue to be static, and every year the majority of those with newly diagnosed chronic hepatitis B infection are from a migrant population. No screening protocol exists in Ireland currently, where those from a migrant

population are being screened as routine practice, despite HPSC Infectious Disease Assessment for Migrants Guidelines, 2015. Equally, screening for hepatitis B exists only in STI clinics, at blood donation sites and antenatal clinics, thus a need arises for more widespread hepatitis b infection testing.

Overall rates of Hepatitis C infection notifications are unchanged, and it is estimated that over 50% of those with hepatitis C infection in Ireland are unaware of their infection. The landscape of hepatitis C infection has changed in recent times, with the advent of newer, successful hepatitis C therapies. It is our responsibility as clinicians to now address the need to diagnose and link patients to care, which can often be challenging given the historic poor rates of retention in care for many patients with hepatitis C infection.

In our nested case-control study, we have shown adequate rates of retention in care for patients with HIV infection in our cohort; we have also identified factors associated with non-engagement in care in our HIV cohort. Rates of effective ART treatment are also acceptable compared with international standards. These factors will continue to help clinical staff identify those at highest risk of disengaging from care in our cohort, so extra intervention can be put in place to prevent this happening.

Rates of hepatitis B and C retention in care rates for our cohort are low. These are however comparable with international rates, but much work needs to be done to develop a healthcare structure that allows these individuals to access treatment. Recent evidence shows that intravenous drug users have similar treatment outcomes to other individuals, so this group should no longer be precluded from treatment. Our retrospective cohort study of those with previously diagnosed hepatitis C had helped us identify factors including active intravenous drug use associated with non-engagement in care. This informs us that what is required in the

first instance is to provide an optimum care package where this cohort, often associated with social deprivation can access hepatitis C care with ease and to ensure adequate follow up, facilitating safe access to effective hepatitis C therapy.

In an effort to understand the feasibility and acceptability of BBV testing in an Emergency Department, to increase the number of BBV diagnoses, to prevent late diagnosis of BBV infection and to prevent onward transmission of infection, a pilot opt-out blood borne virus screening study took place at St James's Hospital over a ten month period. 10,000 patient samples were tested for HIV, hepatitis B and C infection with a testing uptake rate of 50.1% obtained. This showed that this type of screening approach is both feasible and acceptable to patients and healthcare staff in the ED setting. Unexpectedly high prevalence rates were found for all 3 infections. The linkage to care rates was high for HIV and Hepatitis B infection. Only 58% of those with known hepatitis C infection (the majority of those found to be hepatitis C positive during screening) were engaged in care at the time of screening.

Following on from this successful pilot study, testing for BBV infections in the ED transitioned to routine practice, in July 2015. This programme has continued to diagnose those who previously would not have undergone BBV testing as part of routine care, and patients with HIV and hepatitis B infection have successfully been linked to care. This programme has also helped inform the practice of occupational health at St James's Hospital, with the recording of a source patient's recent HIV and Hepatitis B and C results, in the event that needlestick injury occurs.

However, despite extensive intervention involved in linking those with both new and known hepatitis C infection to care, with one on one nurse specialist contact, frequent phone calls, flexible clinic times and assessment of those individuals who "walk-in" to clinic, we found that

attendance rates for hepatitis C care continued to be low. This is the case whether the patient was diagnosed and assessed through EDVS programme or via normal clinic referral pathways, most frequently from GPs. We embarked on a quality improvement programme in our department, to explore ways retention in care rates could be improved. We found that despite the introduction of frequent automated text messaging and development of clinic codes to electronically record attendance, rates of attendance did not improve. Tracking of these patients however by clinic DNA rates and fibroscan DNA rates has helped us to avoid pitfalls in their care. With the monitoring of CNS time by way of tick-and-tally measures, and the introduction of administrative staff to take over non-essential clinical nurse specialist activities, a significant amount of time was given back to the clinical nurse specialists, which will be used to educate and treat a further number of patients and develop nurse-led HCV treatment clinics. This intervention does not help those patients who were contacted but have failed to attend the clinic for follow up. Outreach hepatitis C care plans have been developed for 2017.

Results of this pilot study and routine testing programme in a high prevalence area has informed us and confirmed that we should be screening for these infections in an area of high prevalence for BBV infections. The question now arises whether such a screening strategy is feasible and acceptable and required in an area of perceived low prevalence. A screening study in Galway Medical Assessment Unit that has just recently completed has again shown a high feasibility and acceptability rate for BBV testing in an Acute Medical Unit. (Personal Communication, Dr Helen Tuite). Results of this study have confirmed a very low prevalence for BBV infections.

Whilst these are non-targeted testing strategies, a targeted testing strategy, examining the feasibility and acceptability of testing those from a migrant population in GP practices in the Dublin area has begun. High rates of hepatitis C infection were found in those from a migrant

population during the EDVS pilot study and routine testing programme both of which informed the extension of screening to GP practices with migrant populations attending. Screening of migrant populations is also envisaged to be a key recommendation of the national HCV screening guidelines presently being prepared for NCEC approval.

These results have already informed national testing guidelines as I am now a committee member of the HSE National HIV Testing Working Group at which results of this research and programme has been presented. We now confirm that BBV testing in acute healthcare settings in both high and low prevalence areas is both feasible and acceptable to patients and staff.

6.2 Conclusion

High new diagnosis rates of HIV, hepatitis B and C infection continue to be reported to the HPSC yearly. Despite current HIV prevention strategies in place, our findings show that a significant proportion of those presenting with newly diagnosed HIV-1 infection continue to present at a late point in their illness, with a subsequent negative impact on overall morbidity and mortality.

We have also shown that several patients presented to a range of healthcare facilities for investigation of HIV clinical indicator illness, without having a HIV test done. Notably a significantly smaller proportion of those with advanced HIV had previously undergone HIV testing and the definition of LPS needs to be re-defined. It is possible that our patients were not tested for reasons including physician barriers to testing, poor understanding of HIV clinical indicant conditions and stigma. Research conducted in St James's Hospital previously reported a low level of junior doctor-initiated HIV testing at this institution. This suggests that physicians

are a barrier to testing and advocates that a better approach is to extend testing to all and make HIV testing routine. (143) A need still exists for further education of healthcare providers, to re-emphasise the need for HIV clinical suspicion in all risk and age groups when presenting for care and to further examine the role for widespread HIV testing in areas of different prevalence and demography.

While all risk groups are less likely to present as LPS over time, similar proportions of those with advanced HIV are presenting over the past decade. Potential targets for future HIV testing in areas of perceived lower HIV prevalence include increased HIV testing at other hospitals and GP practices, where a large proportion of those presenting late were first tested. Within the MSM risk group, patients are overall less likely to present at a late point in their illness, likely due to higher rates of screening and HIV awareness in this group. However, a better understanding of those who recently acquired infection within the MSM risk group needs to be sought, so those who are true late presenters can be targeted in future screening programmes. Furthermore, people are likely to be older when presenting as LPS. Thus other risk groups apart from MSM also need to be targeted, and given that patients are now older with late HIV presentation, when considering HIV testing in patients any age group should be considered. Individual recent HIV infections have occurred despite evidence of recent HIV testing and patient awareness of the need for HIV testing. Also, a high proportion of those newly diagnosed in perceived high risk groups had never tested for HIV. These data highlight the need to evaluate why certain people do not access testing and also highlight the need for enhanced behavioural interventions, to prevent onward HIV transmission.

HIV retention in care rates at our centre compare favourably with international figures and changing rates occur where patient demography in Ireland is changing over time.

An intervention undertaken in our department to contact these patients who were lost to follow up was successful, but only for the limited number who were contactable; 81.2% of patients who disengaged from care were not contactable, where registered phone numbers were out of service or the person could not be reached. This information suggests that a better way of maintaining patient demographics at each clinic appointment needs to be employed, including the use of self-service kiosks and the use of new methods for patients to update contact details including phone numbers at each clinic visit. This method of patient registration has now been put in place in the Department of Genito-Urinary Medicine and Infectious Diseases, St James's Hospital.

While we have identified specific characteristics of this disengaged HIV-1 infected patient group, including the younger, non-Irish heterosexual risk group, anecdotal evidence suggests that perhaps this cohort have been re-located to another part of the country or have travelled abroad. Furthermore, 56% of patients were on ART at the time of disengagement; 12% of these were females who had stopped ART post-partum, and did not return for care after cessation of ART. With HIV treatment guidelines change, ART is now to be continued throughout both pregnancy and the post-partum period. This information highlights the previously made call for a national HIV disease registry, so we can fully understand the dynamic nature of our HIV cohort as it changes over time.

While these data provide us with some information around those who disengage from care, we do not have a real understanding of why patients disengage. A semi-structured interview

has now been completed, where reasons for disengaging from HIV care were explored in depth with patients who have since re-engaged in care.

On evaluation of the care of patients with Hepatitis B mono-infection at the Department of Genito-Urinary Medicine and Infectious Diseases, St James's Hospital, we have identified multiple ways that patient care can be improved upon. Patients require more frequent liver ultrasound monitoring, measurement of alpha-fetoprotein at baseline and rates of hepatitis B eAg recording needs to improve also. A small proportion of patients still require screening for hepatitis A immunity and possible vaccination. These recommendations have been disseminated to all clinical staff at departmental level and a further audit is planned for 2017. Further intervention including electronic health record prompts for vaccine reminders and automatic 6-month liver ultrasound recall are planned.

Rates of hepatitis B related disengagement are higher than those for HIV infection but lower than those for hepatitis C infection. Most of these patients were living in a fixed abode, were employed and did not have a history of intravenous drug use. Notably, most of our hepatitis B mono-infected patient population are from a migrant population. It is possible that these people have either moved abroad or to another part of Ireland, and thus have not truly disengaged from care. Factors such as age, gender, region of origin and mode of acquisition were not significantly associated with disengagement from care. A National Unique Patient Identifier may help with tracing these patients, to adequately differentiate patients who have disengaged from care from those who are attending a clinical service elsewhere.

All patients with hepatitis B mono-infection who require treatment according to EASL guidelines are being treated accordingly. The treatment cascade for patients with hepatitis B mono-infection requires clinical surveillance on at least a six-monthly basis, and for many no

treatment is ever given. While clinical surveillance is still necessary in this cohort, it is possible that many stop attending due to perceived lack of clinical input. We do not truly understand the reasons for hepatitis B disengagement from care. A detailed semi-structured interview is necessary to further understand reasons for hepatitis B disengagement from care.

Rates of retention in care in our hepatitis C cohort continue to be lower than the National HSE DNA rate, albeit this rate is inclusive of all types of illness. This is a commonly observed phenomenon in the hepatitis C cohort nationally. However, of those patients who were engaged in care, a high proportion of these patients were triaged appropriately for treatment, and the majority were treated where approval was in place to do so. Of those patients who were treated, high SVR rates were observed. These rates are higher than those that have been seen in recent clinical trials internationally. Furthermore, no significant difference of SVR 12 between the HIV/hepatitis C co-infected and hepatitis C mono-infected groups was observed.

Valuable experience has been gained in the hepatitis C DAA era about effective treatment delivery to both mono-infected and co-infected hepatitis C patients. These data demonstrate that when a patient attends for care, and fulfils the criteria for access to DAA therapy, optimum patient outcomes are seen. However, much work remains to improve retention in care rates for those with active hepatitis C infection, so the infection can be successfully treated, and eradication of hepatitis C is seen nationally, in line with targets outlined in the 2015 Department of Health Multiannual Hepatitis C Pharmaceutical Plan.

The use of panel testing as a method of screening for blood-borne viruses including HIV, hepatitis B and hepatitis C viral infection in a busy urban ED has been shown to be a novel and effective blood borne screening approach. At the time of the pilot study initiation, no previous studies had been conducted examining this method as a screening strategy.

A high uptake rate was seen from an early point in the study, with 50.1% of all bloods in the ED taken over the study period containing an extra sample for viral screening. The approach was found to be acceptable to patients and feasible to ED and medical staff.

HIV prevalence rate is much higher than the results of previous work that determined the rate of those living with HIV in the greater Dublin area to be at least 0.2% and suggests that HIV screening should be performed as routine in those undergoing venepunctures or accessing secondary care. Furthermore, 5% of all attendees undergoing study bloods had a positive hepatitis C antibody test and a significant number of HIV/Hepatitis C co-infection was noted. Both these rates reflect our inner-city attending cohort and high prevalence of intravenous drug use in this group.

On the basis of these results, to advocate patient safety and to reduce the risk of onward transmission, we recommended and subsequently secured resources to implement this screening practice as a standard of care in St James's Hospital Emergency Department, in collaboration with the Department of GU Medicine and Infectious Diseases (GUIDE), St James's Hospital, the HSE Acute Hospitals Division, the HSE Social Inclusion Unit and the HSE Wellness Directorate, on 28th July 2015.

It should be noted that the HIV new diagnosis rate found was lower than those found in previous studies. A different study design is responsible for this, the EDVS study outlined in chapter 4 incorporated an opt-out approach. In previous studies, an "opt-in" approach has been utilised, where patients are approached and offered the tests, and different testing

methods have been used including salivary point of care tests in these studies. It is possible that due to the exclusion of greater than 50% of ED attendees over the study period who did not have bloods taken, the HIV new diagnosis rate found was lower than if this cohort had also undergone testing.

A very small proportion of those patients testing positive for blood borne viral infection were aged >65. Given the high cost of such a screening approach, it is possible that costs may have been decreased by excluding this older population. A detailed cost analysis should be performed to assess the cost efficiency of performing panel testing for HIV, hepatitis B and C viral infections in this setting.

Of those who tested positive for HIV infection, our pilot study showed that almost half those patients with HIV infection had co-infection with hepatitis C, thus to screen for one virus alone runs the risk of missing other infections at the time of screening. This study has provided us with valuable local population prevalence data that will inform blood-borne virus testing practice soon. Testing for BBV infection should be done as a panel in high prevalence areas.

At the time patients underwent blood-borne virus testing in the Emergency Department, most patients with previously diagnosed hepatitis C infection were Irish males with a history of intravenous drug use. Our findings are comparable with those found in national reports. High rates of homelessness were observed in the hepatitis C cohort from the EDVS study. These data represent areas of concern for the delivery of hepatitis C care, given that it has been well documented in the literature that homelessness is associated with poor health outcomes.

Rates of active intravenous drug use in this cohort were high, representing over 50% of those patients with known hepatitis C who had disengaged from care. Furthermore, active intravenous drug use was more likely in those who had disengaged from care as compared to those who remained engaged in care since initial diagnosis. A further public health emphasis needs to be made on factors associated with intravenous drug use and enhanced awareness of the existence of needle exchange services available nationally to decrease the rate of acquisition of hepatitis C infection.

A significantly large proportion of patients in the EDVS pilot study with known HCV infection were disengaged from care at the time of testing. Efforts now need to be made to re-engage this population to care, in an era of effective DAA therapy.

When comparison was made between demographics of those who were newly diagnosed with hepatitis C through the EDVS pilot study, the benefits of non-risk-based testing becomes apparent. A significantly higher proportion of those from a migrant population, those with no risk identifiable and less people with history of intravenous drug use were found in those who were newly diagnosed; this suggests that risk-based testing has previously failed to identify these individuals with hepatitis C who require treatment. Given common risk demography for BBV infection, a panel-based testing approach is required to identify those individuals with any or some of all three infections.

Significant barriers to hepatitis C engagement in care remain. Much work is required to further understand individual patient reasons for poor engagement in care. A qualitative semi-structured interview is required to further explore these factors associated with non-engagement in care.

The need to explore how to effectively deliver hepatitis C care in the community has been highlighted by this research. High rates of disengagement in hepatitis C care in the St James's patient cohort are evident and significant barriers exist for patients to attend regular hospital appointments. We need to better understand how to deliver an improved hepatitis C model of care within our current healthcare infrastructure to a designated subgroup of patients. This model of care will serve as an example of how to address other healthcare needs to individuals whom mostly remain at an economic, educational and social disadvantage. This will need to be re-evaluated in the DAA era and compared with rates found during the interferon era of hepatitis C therapy.

The Extension of Community Healthcare Outcomes (ECHO) project is a novel educational intervention designed in New Mexico to transfer subspecialty knowledge about hepatitis C to primary care providers, thereby increasing patient access to hepatitis C care. The ECHO model has been shown to deliver educational benefits and to result in good treatment outcomes for hepatitis C-infected individuals in the US; however, this approach has not been assessed in a European setting. The Irish ECHO Pilot Study sought to evaluate the feasibility, acceptability and implementation of the ECHO model in Ireland. In the original Project ECHO in New Mexico, geographical distance posed the greatest barrier to accessing hepatitis C care. In Ireland, people who inject drugs were identified by interviewees as the main group facing barriers to accessing specialist hepatitis C care. State-employed doctors and nurses caring for large numbers of hepatitis C-infected PWID in opiate substitution treatment centres and homeless hostels were successfully recruited to participate in the project. Self-employed general practitioners did not participate, due mainly to a lack of time and the absence of reimbursement for participation. Practitioners who participated in the pilot reported benefits to themselves and their patients and would like to continue to participate in similar multi-disciplinary, multi-site educational

interventions in the future. An ECHO Complex Care Network is planned for 2017, to address the medical, psychological and social needs of PWID in South Dublin. (144)

High rates of active intravenous drug use were seen in the EDVS hepatitis C cohort. These numbers represent the high numbers of active drug users attending the Emergency Department at St James's Hospital. A smaller proportion of patients who were newly diagnosed were receiving methadone replacement therapy. As healthcare workers, we need to continue to place emphasis on the need for linkage to addiction services where patients are not linked.

Through the pilot study and routine EDVS testing programme, 106 newly diagnosed or patients not currently engaged in care with active chronic Hepatitis C were linked to the GUIDE Infectious Diseases services. Despite best efforts to follow-up patients with active Hepatitis C, only 58% of patients attended. However, once engaged, 44% were deemed eligible by current national criteria to receive treatment. In the future, as national access threshold for treatment is removed all viraemic patients will be treated as part of a test and treat strategy. Strategies to improve engagement in Hepatitis C services are required to improve the Hepatitis C care continuum and optimize outcomes from the screening programmes and from routine clinical care pathways.

A Quality Improvement programme to improve hepatitis C engagement in care rates began at St James's Hospital in April 2016. Coached by two coaches in training, Dr O'Connell, team leader, led a multi-disciplinary team through a learning and innovative process. With the use of PDSA cycles, process mapping and other quality improvement tools, ways to improve the EDVS

follow up service were explored. Despite interventions, median DNA rates for first EDVS hepatitis C follow-up blood testing at GUIDE have not improved. Fibroscan DNA rates were unchanged but tick and tally measures have shown with improved administrative assistance that more CNS time can be released to offer more direct patient care interventions including nurse-led treatment clinics and outreach work.

Success of such a project is due to the successful collaboration of a multi-disciplinary team, who were eager to be involved and to see the project to the finish. The team have been equipped with valuable tools which they now will use to explore other measures of service delivery in the Viral Hepatitis Clinic at GUIDE. Quality Improvement tools used in this programme can be used in other aspects of screening programmes and service delivery to overcome barriers that any programme, either new or established, deals with on a day-to-day basis.

To conclude, we have shown that an adequate, effective and holistic HIV, Hepatitis B and C service is in place that allows us to explore blood borne virus screening strategies in the safe knowledge that patients will be cared for.

We have demonstrated that many problems still exist in the current disease epidemiology of HIV, hepatitis B and C infection, from 1) lack of prevention, 2) failure to test and 3) retention in care.

We have shown that a pilot opt-out Emergency Department blood borne viral screening programme is both feasible and acceptable to patients and staff and adds another positive dimension to the care of patients attending St James's Hospital Emergency Department.

Routine BBV testing is now implemented as standard of care in the ED.

It has also recently been demonstrated that in low prevalence areas, such routine BBV screening practice is acceptable to patients and healthcare staff. Prevalence of these infections is low, however, and a detailed cost analysis of such studies is required to understand the true cost efficiency of this screening approach, in both high and low prevalence areas.

This information has already contributed to National Guidelines on HIV testing as results have been submitted to the National HSE HIV testing working group and will contribute to further national testing guidelines in due course.

6.3 Recommendations

6.3.1 Healthcare Policy Recommendations

1. Education of healthcare providers needs to begin during third-level education. Blood-borne virus prevalence, the need for testing for all three infections as part of clinical practice and a competent working knowledge of HIV clinical indicant conditions needs to be taught to students at an early stage and incorporated as part of initial clinical investigation.
2. BBV screening should routinely be performed by healthcare providers on hospital admission or in GP practices in the Dublin area, where HIV prevalence is greater than 2 per 1000.
3. Given common risk demography, a panel based testing approach is required, where testing of HIV, hepatitis B and C infection is done as one panel, to identify those individuals with any or some of all three infections.

4. If targeted consideration of HIV testing in any individual is taking place, older and heterosexual risk groups need to be considered as a risk cohort, as well as all those recognised high-risk groups already recognised by physicians.
5. Quality Improvement tools should be used in future screening programmes from the outset to optimise service delivery.
6. Outreach Hepatitis C services need to be piloted and then delivered in the community, to deliver safe, effective and easy to access care for those number of difficult to reach individuals.
7. A National Irish HIV Disease Registry is necessary to understand the nature of our dynamic HIV cohort in Ireland, to understand migration patterns affecting care utilisation to evaluate, patterns of attendance nationwide and to report on the uptake and outcome of ART in an era of widespread ART use.

6.3.2 Research Related Recommendations

1. Further studies examining feasibility and acceptability of BBV testing in both targeted and non-targeted settings in areas of differing demographics should be performed.
2. A detailed semi-structured interview is necessary to further understand reasons for hepatitis B and hepatitis C disengagement from care. A semi-structured interview for HIV and HCV patients is planned to commence at GUIDE in mid-2017.
3. A cost-efficiency analysis should be performed to assess the cost efficiency of performing panel testing for HIV, hepatitis B and C viral infections in high and low prevalence acute medicine settings.
4. A pilot of molecular-based point-of-care testing project should be performed in the ED.

6.3.3 Public Health Policy Recommendations

1. Factors associated with increasing rates of intravenous drug use need to be explored and ways to improve access and resources to current addiction services and needle exchange programmes already in place need to be made available.
2. A National Unique Patient Identifier is required to trace patients with BBV infection, to avoid duplication, to track patient care provision to monitor patient outcomes and to adequately differentiate patients who have disengaged from care from those who are attending a clinical service elsewhere. Data from this registry will be a valuable resource to inform policy and to generate funding in required areas.

Related Presentations:

- 1) **National Patient Safety Conference, Dublin Castle. 7th December 2016. Hepatitis C Retention in Care Rates: A Quality Improvement Programme.**
S O'Connell, G Farrell, C Murray, A Moriarty, M Coghlan, C Murray, M Kelly, A Gorgan, C Bergin
- 2) **ID Week 2016. October 26th – 31st, New Orleans. Infectious Disease Society of America.** Factors Associated with Non-Retention in HIV Care.
S O'Connell, A Lynam, A O'Rourke, E Sweeney, C Sadlier, C Bergin
- 3) **20th Annual Antiviral Therapy and Drug Resistance Meeting, 15th September, London.** BBV Screening in the Emergency Department – from study to implementation.
S O'Connell.
- 4) **Infectious Disease Society of Ireland (IDSi) Croke Park, Dublin, Ireland, 9th May 2016.** Late HIV presentation - factors associated with a changing pattern over time.
S O'Connell, J Enkelmann, C Sadlier, C Bergin.
- 5) **Infectious Disease Society of Ireland (IDSi) Dublin, Ireland, 9th May 2016.** Retention in HIV Care in the era of highly active anti-retroviral therapy (ART) for all HIV-1 infected individuals.
S O'Connell, A Lynam, A O'Rourke, E Sweeney, C Sadlier, C Bergin
- 6) **22nd Annual Conference of the British HIV Association (BHIVA), Manchester Central, 19 - 22 April 2016**
Late HIV presentation - factors associated with a changing pattern over time. S O'Connell, J Enkelmann, C Sadlier, C Bergin.
- 7) **22nd Annual Conference of the British HIV Association (BHIVA), Manchester, 19 -22 April 2016**
Retention in HIV Care in the era of highly active anti-retroviral therapy (ART) for all HIV-1 infected individuals. S O'Connell, A Lynam, A O'Rourke, E Sweeney, C Sadlier, C Bergin
- 8) **The International Liver Congress, (EASL) Barcelona, 13-17th April 2016.** Hepatitis C (HCV) Diagnosis and Linkage to Care Rates in an Urban Emergency Department Blood Borne Virus Screening Programme. S O'Connell, D Lillis, A Cotter et al.
- 9) **Invited Speaker: Liverpool Institute of Infection and Global Health 21st Century Research Seminar Series. Liverpool University. 5th April 2016.** Opt-out Panel Blood-Borne Virus Testing – a Unique Screening Approach. Dr Sarah O'Connell

- 10) European Aids Clinical Society International Conference, Barcelona, October 2015.** A Universal Testing Programme for Blood Borne Viruses in an Urban Emergency Department – a call for widespread testing in Ireland. S O’Connell, D Lillis, S O’Dea, H Tuite, C Fleming, H Barry, L Dalby, D Shields, S Norris, B Crowley, P Plunkett, C Bergin
- 11) Infectious Disease Society of Ireland Annual Scientific Meeting May 2015.** Patient Characteristics associated with Non-Engagement in Hepatitis C Care – Data emerging from an opt-out Emergency Department Blood-Borne Virus Screening Programme. S O’Connell, D Lillis, S O’Dea, H Tuite, C Fleming, H Barry, L Dalby, D Shields, S Norris, B Crowley, P Plunkett, C Bergin.
- 12) The Liver Meeting - American Association for the Study of Liver Diseases November 2014, Boston.** A Universal Testing Programme for Blood Borne Viruses in an Urban Emergency Department – a call for widespread ED testing in Ireland. S O’Connell, D Lillis, S O’Dea, H Tuite, C Fleming, H Barry, L Dalby, D Shields, S Norris, B Crowley, P Plunkett, C Bergin

Appendices

Appendix 1: Ethical Approval for EDBBVi Study



**THE ADELAIDE & MEATH
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SJH/AMNCH Research Ethics Committee
David Willow david.willow@amnch.ie
Secretariat Phone: (01) 414 2342

Prof. Colm Bergin
Consultant in Infectious Diseases
GUIDE Clinic
St. James's Hospital
Dublin 8

13th February 2014

RE: EDeBVI Study
Reference REC: 2014/01/List 1 / 2014/02/List 6

(please quote references above on all correspondence)

Dear Prof. Bergin,

With thanks for your letter and amended Patient Information Sheet sent on 3rd February, 2014.

Dr. Paul Crotty on behalf of the Research Ethics Committee has reviewed and approved the amended document.

I hope all goes well in the Study.

Yours sincerely,



David Willow
Secretary
SJH/AMNCH Research Ethics Committee

Appendix 2: Ethical Approval for HIV Qualitative Semi-Structured Interview



SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

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Dr. Sarah O'Connell
Infectious Disease Clinical Research Fellow
St James's Hospital
James's Gate
Dublin 8

8th April 2016

Re: Understanding barriers and facilitators to patient retention in HIV care

REC Reference: 2016 - 04 Chairman's action (3)
(Please quote reference on all correspondence)

Dear Dr. O'Connell,

Thank you for your recent application to SJH/AMNCH Research Ethics Committee in which you requested ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this application and grants ethical approval for it to proceed.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix 3: In House Ethical Approval for Late HIV Presentation Study

ST. JAMES'S HOSPITAL

PROPOSED INTERNAL AUDIT / RESEARCH ACTIVITY

HOSPITAL APPROVAL FORM

PREAMBLE

This form should be completed in respect of all proposed internal research / audit projects and Submitted to the Legal/Insurance Manager for approval prior to the research being undertaken. Internal audit/research means research that does not involve patient contact, but does involve the use of hospital information, or information systems.

The research may proceed subject to approval being forthcoming from the relevant Department/s, and where hospital resource usage applies, that related requirements can be met from within the relevant departmental/line item budgetary allocation. Such research is also governed by ethical and data protection principles.

1. TYPE OF RESEARCH ACTIVITY (please tick)

- Clinical Research
- Non-Clinical Research
- Clinical Audit
- Non-Clinical Audit

2. PROJECT TITLE (PRINT)

Late HIV presentation - missed opportunities and factors associated with a changing pattern over time: A stimulus to Review Screening Strategie

3. BRIEF DESCRIPTION OF THE PROPOSED RESEARCH/AUDIT ACTIVITY:

we plan to review demographics of those diagnosed with late HIV infection who present for care to our clinic in GUIGE. This will be done with electronic chart record review at GUIGE, for all these patients who presented for care over 2014, who had a CD4 count of less than 350 cells/mm³.

➤ Liaison Person and Contact Number/Bleep Sarah O'Connell 087 2833350

Please Note: Where Charts are required to be pulled by chart room staff, a list of MRNs should be furnished to the Medical Records Officer along with a copy of this form once approved. Chart pulling arrangements should be agreed with the Medical Records Officer. Removal of charts or other patient related information from St James's Hospital premises is forbidden.

7. FINANCIAL ARRANGEMENTS

Will there be funding available for this research activity?

YES NO

If YES, Please state

Amount and source of funding _____

8. DATA CONTROL AND PROTECTION

In what form will data be collected and held?

Patient age/gender/mode of acquisition/previous HIV test/previous clinical investigations /nre of HIV diagnosis.

How long is collected data intended to be retained?

7 years - as per hospital guidelines

What physical or computerised protections will be in place in relation to data collected?

Data will be recorded and cleaned/analysed on the excel database that is stored in the research folder on the confidential G-drive - access only given to BUOE clinical staff.

Will a memory stick or removable memory storage device be used?

NO

Will collected data be transferred outside of the Hospital computer system?

NO

If Yes:

What transfers are envisaged?

What agreements are in place/planned?

Appendix 4: In House Ethical Approval for Hepatitis B Retention in Care Cohort Study

ST. JAMES'S HOSPITAL

PROPOSED INTERNAL AUDIT / RESEARCH ACTIVITY

HOSPITAL APPROVAL FORM

PREAMBLE

This form should be completed in respect of all proposed internal research / audit projects and Submitted to the Legal/Insurance Manager for approval prior to the research being undertaken. Internal audit/research means research that does not involve patient contact, but does involve the use of hospital information, or information systems.

The research may proceed subject to approval being forthcoming from the relevant Department/s, and where hospital resource usage applies, that related requirements can be met from within the relevant departmental/line item budgetary allocation. Such research is also governed by ethical and data protection principles.

1. TYPE OF RESEARCH ACTIVITY (please tick)

- Clinical Research
- Non-Clinical Research
- Clinical Audit
- Non-Clinical Audit

2. PROJECT TITLE (PRINT)

A RETROSPECTIVE REVIEW OF PATIENT ATTENDANCES ^{FOR HEPATITIS B INFECTION} ✓ AT THE VIRAL
HEPATITIS CLINIC AND CHARACTERISTICS OF THOSE RETAINED IN CARE.

3. BRIEF DESCRIPTION OF THE PROPOSED RESEARCH/AUDIT ACTIVITY:

WE PLAN TO REVIEW DEMOGRAPHICS AND RECORD ATTENDANCE RATE,
DISEASE STAGE AND TREATMENT OUTCOMES IN OUR NEWLY
DIAGNOSED HEPATITIS B COHORT FROM 1ST JANUARY 2010 TO
AUGUST 2015.

WE WILL THEN COMPARE THESE PARAMETERS WITH EUROPEAN
ASSOCIATION OF LIVER DISEASES GUIDELINES AND STANDARDS FOR
HEPATITIS B CARE.

> Liaison Person and Contact Number/Bleep DR EGENIA DAVENPORT #987/989/982

Please Note: Where Charts are required to be pulled by chart room staff, a list of MRNs should be furnished to the Medical Records Officer along with a copy of this form once approved. Chart pulling arrangements should be agreed with the Medical Records Officer. Removal of charts or other patient related information from St James's Hospital premises is forbidden.

7. FINANCIAL ARRANGEMENTS

Will there be funding available for this research activity?

YES NO

If YES, Please state

Amount and source of funding _____

8. DATA CONTROL AND PROTECTION

In what form will data be collected and held?

Data will be collected on an excel database that is stored in an encrypted file on the G-drive.

How long is collected data intended to be retained?

Data will be retained until analysed and then will be destroyed (March 2016)

What physical or computerised protections will be in place in relation to data collected?

Data will be stored on an encrypted excel data sheet, on the Guide G-drive, (access only to research team)

Will a memory stick or removable memory storage device be used? *and analysed using SPS on research computer at Guide only.*

NO

Will collected data be transferred outside of the Hospital computer system?

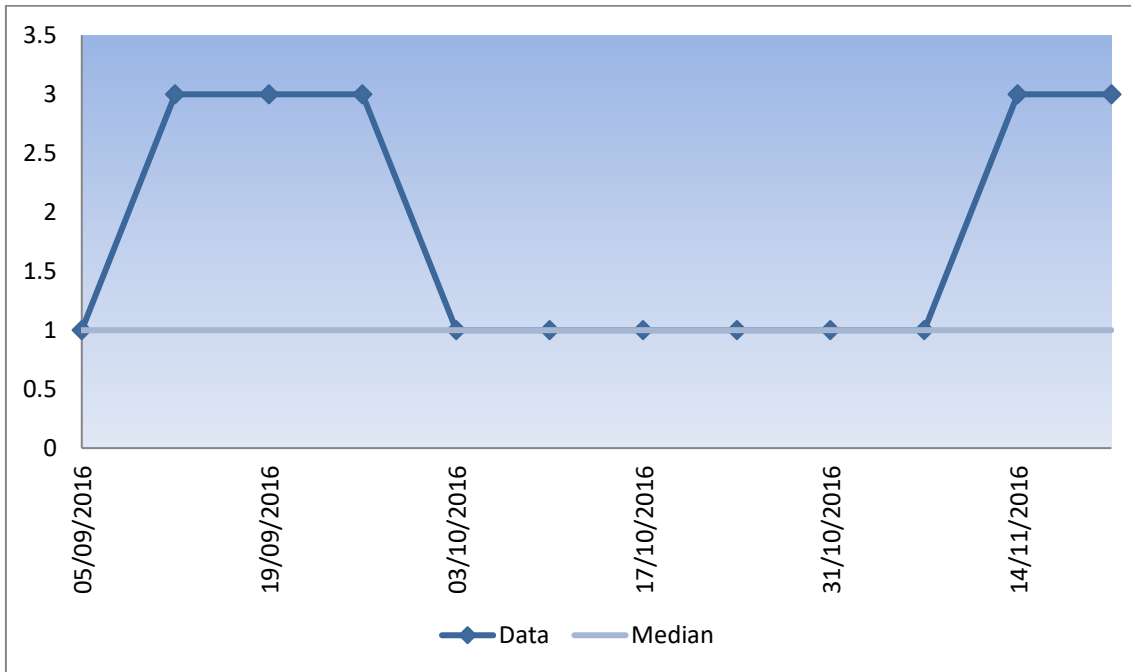
NO

If Yes:

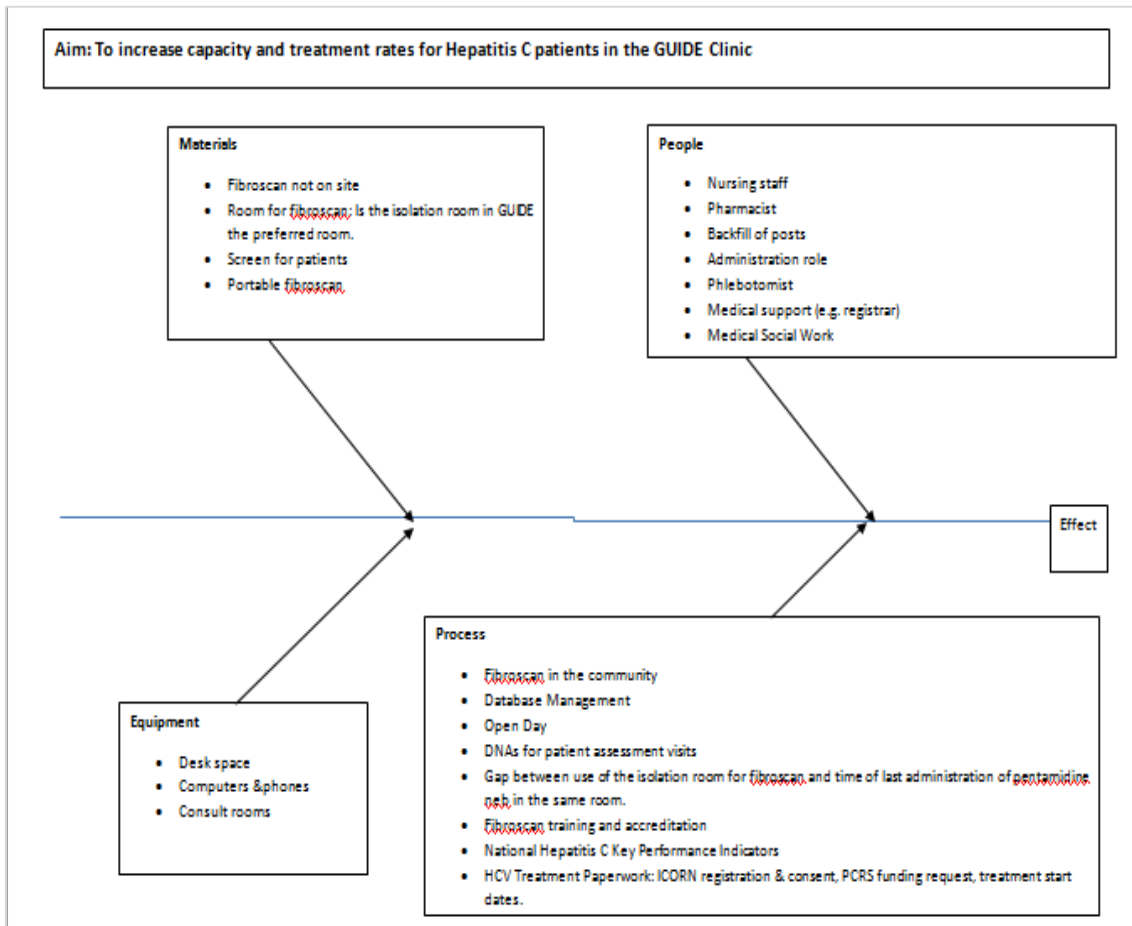
What transfers are envisaged?

What agreements are in place/planned?

Appendix 6: Median DNA Rates for Fibrosan Procedure



Appendix 7: Fishbone Analysis of EDVS Follow up Service



Appendix 8: Patient Experience Survey

Patient Experience Survey	
1. Did someone speak to you and provide help as soon as you arrived in the Ward or Department? Initial contact was:	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
2. How would you rate your experience with the length of time you waited today?	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
3. Was your privacy respected at all times during this visit? Respect for privacy was:	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
4. Were your comfort needs met? (e.g. were you given a suitable place to lie down, sit, access to toilets, drinks, food etc.) The team's management of your comfort needs was:	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
5. Did all the people you met here treat you with courtesy and have a friendly, helpful attitude? How would you rate their attitude to you:	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
6. How would you rate your overall experience today?	<input type="checkbox"/> Excellent <input type="checkbox"/> Very Good <input type="checkbox"/> Good <input type="checkbox"/> Fair <input type="checkbox"/> Poor
7. What would make this unit better in your opinion?	
8. Time/date arrived at Ward/Unit _____	
Thank-you for completing this survey. Please feel free to provide additional comments overleaf or to talk to a member of staff about any issues you may wish to discuss.	

Appendix 9: Patient Experience Survey Results

There were **18** respondents to the questionnaire.

- 1) When asked about the quality of initial contact ie patient provided with help/direction when he/she first entered the department: 14 (78%) felt this was excellent, 3 (17%) felt this was very good and 1 (6%) felt it was good
- 2) Regarding patient waiting time experience: 10 (56%) Excellent, 7 (39%) very good, 1 (6%) fair
- 3) Respect for privacy was: 15 (83%) Excellent, 2 (11%) Very good, 1(6%) good
- 4) Comfort needs were managed? : 13 (72%) Excellent, 3 (17%) Very good, 1 (6%) good. 1 did not answer
- 5) Staff attitude to patient: 16 (89%) Excellent, 2 (11%) Very good.
- 6) Overall experience rate: 14 (78%) Excellent, Very good 3 (6%), Good 1 (6%)
- 7) What would make experience better? : 8 responses (64%)
 - 2 people found the clinic hard to find and needs more signage
 - 1 person reports more pay needed for nurses and doctors
 - 1 person reports a tea/coffee machine would make the experience better
 - 4 people reported the clinic “couldn’t be better”.

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RESEARCH ARTICLE

Opt-Out Panel Testing for HIV, Hepatitis B and Hepatitis C in an Urban Emergency Department: A Pilot Study

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Abstract

Objectives

Studies suggest 2 per 1000 people in Dublin are living with HIV, the level above which universal screening is advised. We aimed to assess the feasibility and acceptability of a universal opt-out HIV, Hepatitis B and Hepatitis C testing programme for Emergency Department patients and to describe the incidence and prevalence of blood-borne viruses in this population.

Methods

An opt-out ED blood borne virus screening programme was piloted from March 2014 to January 2015. Patients undergoing blood sampling during routine clinical care were offered HIV 1&2 antibody/antigen assay, HBV surface antigen and HCV antibody tests. Linkage to care where necessary was co-ordinated by the study team. New diagnosis and prevalence rates were defined as the new cases per 1000 tested and number of positive tests per 1000 tested respectively.

Results

Over 45 weeks of testing, of 10,000 patient visits, 8,839 individual patient samples were available for analysis following removal of duplicates. A sustained target uptake of >50% was obtained after week 3. 97(1.09%), 44(0.49%) and 447(5.05%) HIV, Hepatitis B and Hepatitis C tests were positive respectively. Of these, 7(0.08%), 20(0.22%) and 58(0.66%) were new diagnoses of HIV, Hepatitis B and Hepatitis C respectively. The new diagnosis rate for HIV, Hepatitis B and Hepatitis C was 0.8, 2.26 and 6.5 per 1000 and study prevalence for HIV, Hepatitis B and Hepatitis C was 11.0, 5.0 and 50.5 per 1000 respectively.

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Conclusions

Opt-out blood borne viral screening was feasible and acceptable in an inner-city ED. Blood borne viral infections were prevalent in this population and newly diagnosed cases were diagnosed and linked to care. These results suggest widespread blood borne viral testing in differing clinical locations with differing population demographic risks may be warranted.

Introduction

Screening for infectious diseases including HIV, Hepatitis B (HBV) and Hepatitis C (HCV) offers a health benefit to the individual and prevents onward transmission. These viruses are world-wide public health problems resulting in a significant impact on healthcare resource utilisation and costs. [1,2] Furthermore these infections disproportionately affect socially marginalised groups.

In 2014, 377 people were newly diagnosed with HIV-1 infection in Ireland, representing an 11% increase from 2013. [3] A HIV prevalence rate of over 2 per 1000 among 15–59 year olds in the Dublin area has previously been reported. [4] In 2013 there were 429 new diagnoses of HBV reported in Ireland, where the HBV prevalence rate is thought likely to be <0.5%. [5, 6] 786 cases of HCV were reported in 2013 in Ireland and the HCV prevalence rate is estimated to be between 0.5 and 1.2%. [7] According to ECDC data, despite falling rates in recent years, Ireland has one of the highest rates of new hepatitis B and C notifications in Europe. [8] Furthermore, it is estimated that the majority of patients infected with HCV in Ireland remain undiagnosed. [9]

There continues to be significant morbidity and mortality related to late diagnosis of HIV. In Ireland, 49.5% of new HIV cases in 2013 presented late, with 28% having a CD4 cell count of less than 200/mm³. [10] Associated with late diagnoses are significant costs; the direct medical costs for HIV care in the first year after diagnosis are twice as high as those with a CD4 count < 350. [11] The benefits of an earlier diagnosis of HIV include earlier access to treatment, reduced mortality, reduced risk of cardiovascular diseases and malignancies and overall improved outcomes. Furthermore, in 2006 it was estimated that 50% of new HIV infections in the US were transmitted by the 25% of HIV-positive individuals unaware of their status and more recently the CDC estimate 12.8% of those in the US with HIV infection are unaware of their HIV status. [12, 13]

Complications of chronic HBV and HCV infection include cirrhosis, decompensated liver disease, hepatocellular carcinoma and death. In an era of newly developed successful HCV therapies and the introduction of the Irish Health Service Executive (HSE) Service Plan for 2015 that provides a financial commitment to treat those with HCV infection, the requirement to test and diagnose those with unknown HCV infection has vastly increased in recent times. The role of anti-viral therapies to suppress HBV infection has also clearly been demonstrated. [14] Early treatment of HBV and HCV infection can prevent disease progression, the complications of which represent a significant burden of care to the Irish healthcare system.

CDC guidelines in the USA recommend an opt-out HIV screening approach. In the UK it is recommended that HIV testing is considered where HIV prevalence rates exceed 2/1000. [15] In the US, the CDC recently recommended one-time HCV screening of all persons born between 1945 and 1965, in addition to risk factor based screening already in place. [16] CDC HBV testing guidelines suggest testing those with exposure risk factors to HBV. [17]

In Ireland risk-based testing for HIV, HBV and HCV is most commonly offered. Despite the known prevalence in Dublin, universal HIV and HBV screening is performed on an opt-out basis only in antenatal care, sexual health clinics and for blood donors. Common risk

demography exists for HCV acquisition in migrants, men who have sex with men and persons who inject drugs (PWID). Significant rates of HCV have been reported amongst PWID in the Dublin maternity hospitals also. [18,19] Despite these factors, only risk based targeted HCV screening strategies are operational in Ireland and in most maternity hospitals. The universal screening of migrants has not yet been undertaken and overall there has been no integrated programme to screen patients for multiple blood-borne viral (BBV) infections with panel testing in a healthcare setting.

The offer of HIV testing in healthcare settings that do not routinely test for BBV infections including Out-Patient Clinics, General Practice, Acute Care Units and Emergency Departments has been shown to be acceptable and feasible. [20] Similar screening strategies include a universal point of care testing approach in an acute admission unit; this appeared to be an effective, feasible, acceptable and low cost approach to HIV screening. [21] The emergency department (ED) is a desirable target for HIV testing within hospitals as it serves a high-throughput population of diverse attendees. Our ED serves a population with a very high diagnosed prevalence of HIV (2.25 per 1000) and this busy ED has 46,000 attendances per year.

Methods

This was a cross-sectional study conducted at a large urban Emergency Department in Dublin, Ireland. Collaboration between the Departments of Genito-Urinary and Infectious Diseases, Emergency Medicine, Hepatology and Microbiology allowed for the opt-out screening of all suitable patients who had bloods taken as part of routine clinical care. Nursing and Medical staff in the ED attended didactic teaching sessions and workshops provided by the Infectious Disease and Emergency Department study team to provide background information for the pilot study and to explain the testing protocol.

All patients over the age of 18 with the capacity to consent were included, as outlined in ethical approval granted by our local ethics committee. Posters were placed in the waiting room and patient information leaflets were made available at various care stages throughout the Emergency Department, including at reception and at triage. Patient information leaflets were translated into the 7 most common languages. A contact number for the responsible study team member was provided on these and on separate slips for those patients who had further questions for the study team or to find out their results.

Patients were advised that an extra serum sample would be taken when undergoing phlebotomy as part of routine clinical care at no extra cost, and this sample would be tested for HIV, Hepatitis B and Hepatitis C viral infection. The patient was given the option to opt-out following a set time period of 20 minutes to consider his/her options. (Fig 1) Verbal consent was obtained in all cases in line with good clinical practice and current international clinical guidelines [22]. Written consent was deemed unnecessary as stated in these guidelines and is no longer part of routine clinical practice. When a study blood sample was taken this was recorded in the Emergency Department patient case notes.

Patients were informed that they would be contacted 3 working days after their initial ED visit, if the blood test taken was reactive. Patients were also informed that they would not be contacted if results were negative.

Appropriate ethical approval was obtained from the St James's Hospital/Adelaide and Meath, National Children's Hospital (SJH/AMNCH) Research Ethics Committee. (REC reference 2014/01) The consent process was approved by this committee.

Given potential common risk demography for all three infections, panel testing for all three infections was performed in the possible scenario that a patient disclosed one blood borne viral

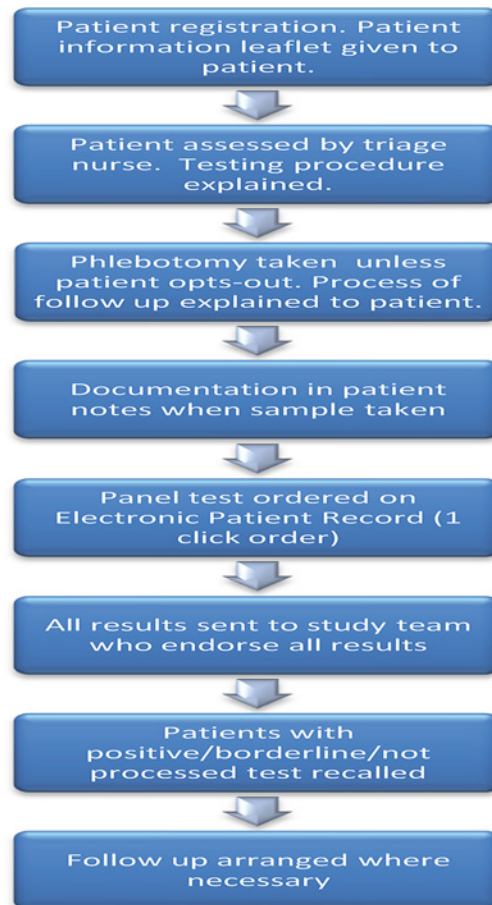


Fig 1. Patient Testing and Results Process.

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infection to the healthcare staff member at the time of screening, or where the patient had study bloods taken at an earlier point in the study.

Weekly progress updates were sent by the study team the ED staff to inform them of study blood uptake and details of positive tests found. Furthermore, information and Q and A sessions were provided for the ED staff throughout the project.

Results governance and delivery was managed by the study team and patients requiring follow up bloods or with a reactive blood test were contacted using contact details provided at ED reception. Follow up bloods were taken at the study facility and appropriate patients were linked to care. Those who had previously disengaged from care were also identified in the study and linkage back to care was co-ordinated by the study team. Patient demographics for those who had a positive test were subsequently captured on electronic and paper chart review.

Taking into account a range of previous opt-in rates (23% - 66%) reported for HIV testing in Emergency Departments [23,24, 25], and a previous study which showed a higher patient offer rate with an opt-out approach,[26] target uptake rate was set at greater than 50%. Uptake rate was defined as the number of study bloods taken when the patient was undergoing phlebotomy as part of routine clinical care, proportional to the total number of bloods taken in the Emergency Department over the study period.

New diagnosis rate and study prevalence were defined as the number of new cases per 1000 tested and number of positive tests per 1000 tested for BBV respectively.

The primary aim of this study was to assess the feasibility and acceptability of this approach of panel testing for HIV, HBV and HCV in a busy urban ED where opt-out testing was performed on patients having bloods done as part of routine clinical care.

The secondary aim of this study was to determine the sero-prevalence of these three viral infections in this ED and to determine the new diagnosis rate of new viral infections. New and previously known and disengaged patients were linked back to care for early treatment to prevent morbidity/mortality and to prevent onward transmission.

Results

10,000 serum samples were tested for HIV antibody/antigen, hepatitis B surface antigen and hepatitis C antibody from March 2014 to January 2015. A sustained cumulative target testing uptake rate of 50.1% was obtained. Of all ED blood samples taken, the proportion of study bloods taken was greater than 80% on specific days selected, where uptake of study bloods was examined using Emergency Department patient notes.

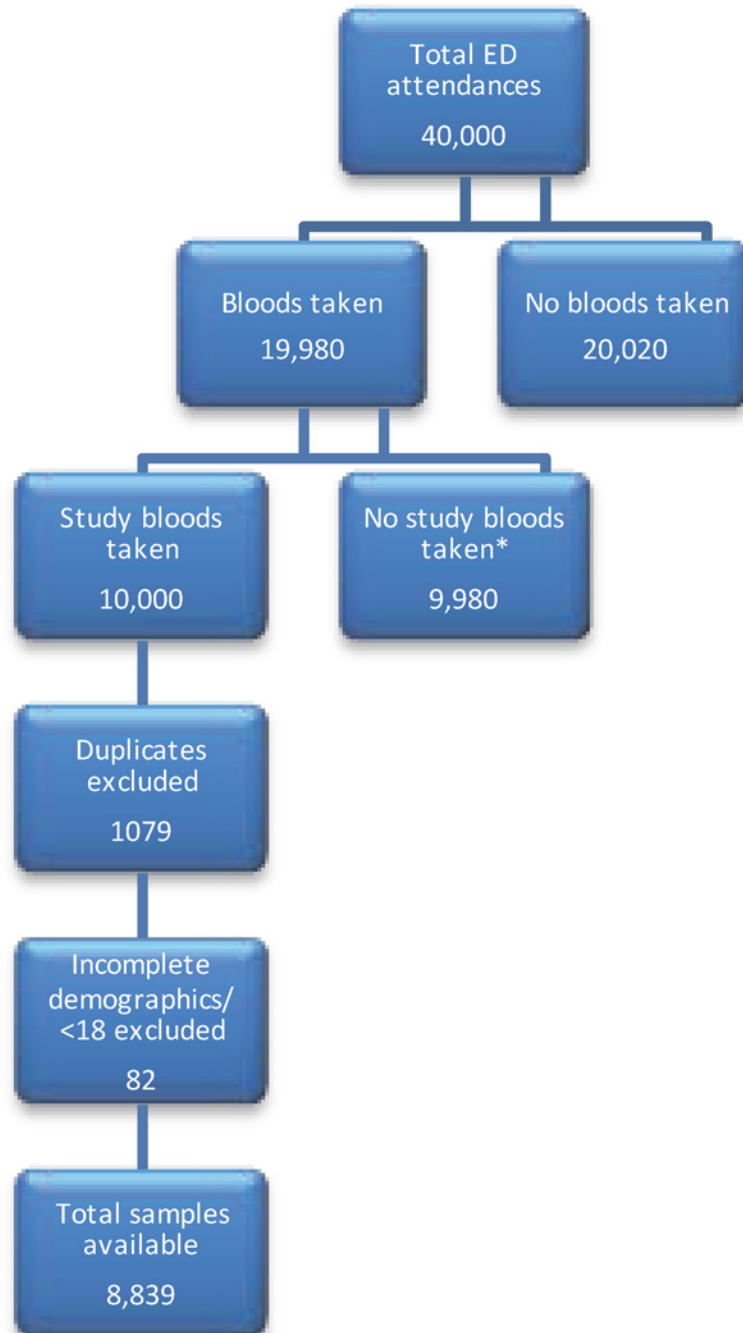
1079 subjects had a sample tested greater than once during the study period. 74 subjects under the age of 18 and 8 subjects with incomplete demographics were excluded from analysis. Following exclusion of these patients and removal of duplicates, a total of 8,839 individual patient test results were available for analysis. (Fig 2) Median age (IQR) for this group tested was 45 (32,66). Age range was 18–102 years. 4463 (50.4%) were male subjects.

HIV

97 subjects who underwent testing had a positive HIV test. Age range (years) was 20–60. Median (IQR) years was 39(33,43). 68 patients (61.8%) were male. 7 of these patients were new diagnoses and 90 of these patients were previously known. 89 (98.8%) of patients with previously known infection were linked to care at the time of testing, and one further patient was re-linked to care as result of study team intervention.

Of the 7 newly diagnosed patients, 4 were male, age range was 23–51 and median (IQR) age was 29.5(38,43.5). (Fig 3) Mode of acquisition included 3 MSM, 3 Irish female patients with heterosexual contact with a person from a country of high prevalence and 1 male with a history of previous intra-venous drug use. 4 (57.1%) of these patients presented to the ED with no clinical indicators for HIV infection. 3 (42.9%) presented with clinical indicators including *Pneumocystis Jirovecii* pneumonia (n = 2) and pyrexia of unknown origin (n = 1), with a subsequent diagnosis of Multicentric Castleman's disease. Five of these patients presented at a late point in their illness, with a Cd4 count of less than 350 cells/mm³. Two of these patients had a CD4 count of less than 50 cells/mm³ at presentation, one of less than 200 cells/mm³ and the remaining two had a CD4 count of less than 350 cells/mm³. One patient was experiencing HIV seroconversion at the time of testing based on viral load result, avidity and HIV antibody results. HIV -1 viral load measured for this patient was greater than 10 million copies/mL, posing a very high risk of onward transmission. 1 patient (MSM) had previously tested for HIV; this was negative 1 year prior to diagnosis. 5 patients have been successfully commenced on ART; a further 2 patients have plans to start in the near future, in the setting of interim results of a large-scale randomised clinical trial that recently showed significant clinical benefits for those patients commenced on ART at an earlier point in their illness, thus supporting the US recommendation that all asymptomatic HIV positive patients take ART irrespective of CD4 count. [27] (Table 1)

Of those with previously diagnosed HIV infection, 70 (77.6%) were Irish. Other countries of origin included United Kingdom (n = 1), Brazil (n = 5), Greece (n = 1), Latvia (n = 1), Lithuania (n = 1), Russia (n = 1), Sub-saharan Africa (n = 7), Poland (n = 2) and Pakistan (n = 1).



*patient opted-out, staff member did not perform test, patient did not fulfil inclusion criteria (ie unable to give verbal consent for testing)

Fig 2. Description of Patient Numbers Tested.

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49 (50.5%) and 2 (2%) patients were co-infected with hepatitis C and B viral infection respectively. All these patients were aware of their co-infection status.

Emergency Department new diagnosis and prevalence rates for HIV infection were 0.8 and 11 per 1000 respectively. Patients were recalled and linked to care where appropriate. (Table 2)

Hepatitis B

A total of 44 patients had a positive blood test for hepatitis B surface antigen. 23 of these patients were known and 20 were new diagnoses. One further patient is currently lost to follow up. Of the 20 newly diagnosed patients, with chronic hepatitis B infection, 16 were male, age range was 29–78 and median (IQR) age was 44(34–57). (Fig 3) 6(30%) of these patients are from Ireland, other countries of origin included Afghanistan (n = 1), China (n = 3), Romania (n = 3) and Brazil (n = 1), Eastern Europe (n = 2), Pakistan (n = 1), Phillipines (n = 1) and sub-saharan Africa (n = 2). Mode of acquisition included vertical transmission (n = 9), MSM (n = 1), IVDU (n = 1) and a further 9 patients (45%) had no identifiable risk when a full clinical history was taken at subsequent out-patient assessment. (Table 1)

8 (34.8%) of those with previously diagnosed HBV infection were Irish. Other countries of origin included Italy (n = 1), Brazil (n = 1), Latvia (n = 1), Sub-Saharan Africa (n = 8), Thailand (n = 1) and Pakistan (n = 3).

ED new diagnosis and prevalence rates for chronic hepatitis B infection were 2.26 and 5 per 1000 respectively. Patients were recalled and linked to care where appropriate. (Table 2)

Hepatitis C

447 patients had a positive blood test for hepatitis C antibody. 58 of these tests were newly diagnosed infection and 373 were previously diagnosed. A further 16 are currently lost to follow

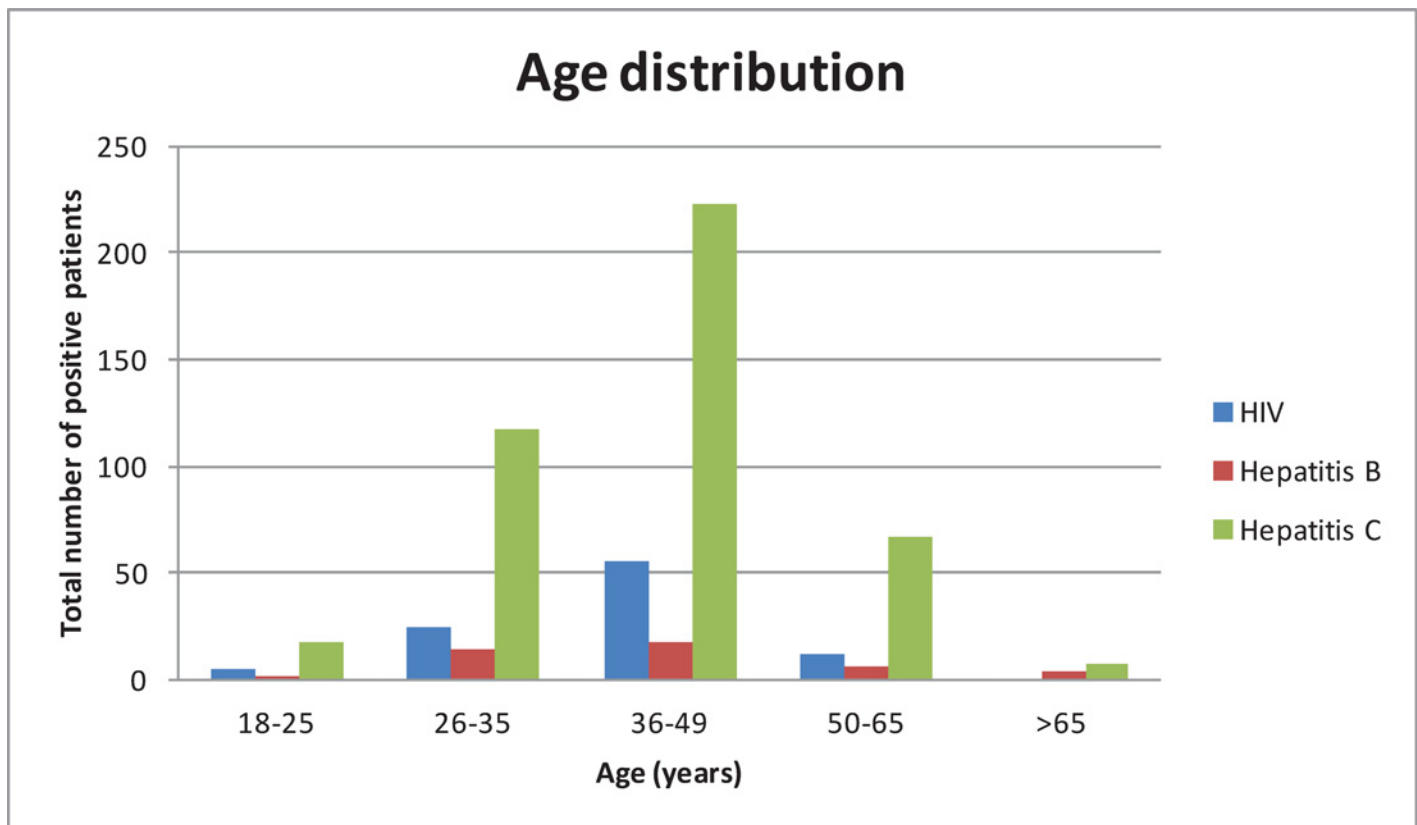


Fig 3. Positive Patient Age Distribution.

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Table 1. Demographics of Positive Patients.

	HIV	Hepatitis B	Hepatitis C
	N (%)	N (%)	N (%)
Age			
New	7	20	58
<i>Range</i>	23–51	29–78	18–69
<i>Median (IQR)</i>	29.5 (38,43.5)	44 (34,57)	25 (36,49)
Known	90	23	373
<i>Range</i>	20–60	21–72	18–81
<i>Median (IQR)</i>	47.5 (33,44.5)	42 (33.5,45)	39 (34,46)
Gender			
New	7	20	58
<i>Male</i>	4 (57.1)	16 (80)	47 (81)
<i>Female</i>	3 (42.9)	4 (20)	11 (19)
Known	90	23	373
<i>Male</i>	57 (63.3)	16 (69.6)	235 (63)
<i>Female</i>	33 (36.7)	7 (30.4)	138 (37)
Mode of Acquisition			
New	7	20	58
<i>MSM^a</i>	3 (42.8)	1 (5)	0
<i>IVDU^b</i>	1 (14.3)	1 (5)	37 (63.8)
<i>HS^c</i>	3 (42.8)	0	2 (3.4)
<i>NRI^d</i>	0	9 (45)	14 (24.1)
<i>Vertical/COHP^e</i>	0	9 (45)	3 (5.1)
<i>Nasal DU^f</i>	0	0	2 (3.4)
Known	90	23	373
<i>IVDU^b</i>	48 (53.3)	5 (21.8)	333 (89.3)
<i>HS^c</i>	12 (13.3)	13 (56.5)	5 (1.3)
<i>Blood Transfusion</i>	0	1 (4.3)	4 (1)
<i>Anti D</i>	0	0	5 (1.3)
<i>NRI^d</i>	0	2 (8.7)	21 (5.6)
<i>Nasal DU^f</i>	0	0	1 (0.3)
<i>Vertical^e</i>	0	1 (4.3)	2 (0.5)
<i>Haemophilia</i>	0	0	1 (0.3)
<i>MSM^a</i>	30 (33.3)	1 (4.3)	1 (0.3)
Active IVDU			
New	7	20	58
<i>Active IVDU^b</i>	1 (14.3)	1 (5)	37 (63.8)
Known	90	23	373
<i>Active IVDU^b</i>	17 (18.8)	0 (0)	135 (40.5)
High Risk Postal Codes			
New	7	20	58
<i>Dublin area</i>	7 (100)	18 (90)	54 (93.1)
Known	90	23	373
<i>Dublin area</i>	63 (70)	19 (82.6)	221 (59.2)
Homelessness			
New	7	20	58
<i>No fixed abode</i>	2 (28.5)	1 (5)	19 (32.7)
Known	90	23	373

(Continued)

Table 1. (Continued)

	HIV	Hepatitis B	Hepatitis C
	N (%)	N (%)	N (%)
No fixed abode	20 (22.2)	3 (13)	125 (33.5)

^aMSM: Men who have sex with men

^bIVDU: Intravenous drug users

^cHS: Heterosexual

^dNRI: No risk identified

^eCOHP: Country of high prevalence

^fNasal DU: Nasal drug use

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up, have not received their results and attempts to actively contact these patients are being pursued.

Of the newly diagnosed group (n = 58), 15% (n = 12) had a negative PCR during study follow up. Age range for this group was 18–69, median (IQR) age was 25(36,49). (Fig 3) 47(81%) were male. Country of origin included 52 Irish, Morocco (n = 1), Pakistan (n = 1), China (n = 1), Asian (n = 1) and Latvian (n = 2).

Of the 43 patients with newly diagnosed hepatitis C linked to care, 32 had a history of intravenous drug use, 1 with a history of nasal cocaine use, 6 had no risk identified on assessment,

Table 2. Description of Linkage to Care.

	N (%)
N = 8,839	
Total HIV+ cases	97
New HIV+ cases	7
Now linked	7 (100)
Unlinked	0 (0)
Known HIV+ cases	90
Linked	90 (100)
Unlinked	0 (0)
Total hepatitis B sAg+ cases	44
New hepatitis B sAg+ cases	20
Now linked	19 (95.0)
Linkage ongoing	1 (5.0)
Known hepatitis B sAg+ cases	23
Linked	23 (100)
Undetermined new/known hepatitis B sAg+ve	1 (2.27)
Total hepatitis C Ab+ cases	447
New hepatitis C Ab+ cases	58
Now linked	43 (74.1)
Linkage not required (PCR–ve)	11 (18.9)
Unlinked	4 (6.89)
Known hepatitis C Ab+ cases	373
Linked	202 (54.1)
Relinked	80 (21.4)
Relinkage not required (PCR–ve)	64 (17.1)
Unlinked	27 (7.2)
Undetermined new/known hepatitis C Ab+ve	16 (3.5)

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1 reported due to blood transfusion, 1 nosocomial acquisition, 2 heterosexual risk and 39 (93%) were Irish. Of those 32 patients who had a history of intravenous drug use, 12 were actively injecting drugs, 18 previously injected drugs and 2 had unknown active injection drug use status. 16 (50%) of these patients with a history of intravenous drug use were receiving methadone replacement therapy. ([Table 1](#))

364 (97.6%) of those with previously diagnosed HCV infection were Irish. Other countries of origin included United Kingdom (n = 1), Afghanistan (n = 1), Latvia (n = 1), Poland (n = 2), Ukraine (n = 1), Congo (n = 1), China (n = 1) and country of origin for one patient is unknown.

3 newly diagnosed patients seroconverted to hepatitis C viral infection during the study duration, with an initial negative hepatitis C antibody test followed by newly diagnosed positive during the study period on re-attendance to the Emergency Department. 2 of these patients carried risk of intravenous drug use for acquisition and 1 patient has no identifiable risk for acquisition. 1 newly diagnosed patient was treated for HCV 10 years previously and after a subsequent positive PCR was diagnosed with re-infection as a result of ongoing intravenous drug use.

ED new diagnosis and prevalence rates for hepatitis C viral infection were 6.5 and 50.5 per 1000 respectively. Patients were recalled and linked to care where appropriate. ([Table 2](#))

Discussion

This study demonstrates the novel use of panel testing as a method of screening for blood-borne viruses including HIV, hepatitis B and hepatitis C viral infection in a busy urban ED. No previous studies have been conducted examining this method as a screening strategy.

A high uptake rate was seen from an early point in the study, with 50.1% of all bloods in the ED taken over the study period containing an extra sample for viral screening. ED staff members reported it was easier to take the bloods on a regular basis instead of consideration of risk before the patient underwent phlebotomy. The medical teams at our hospital gave feedback that with the process of blood-borne viral screening being performed at the stage of presentation to the hospital and this allowed for a faster assessment process and formulation of differential diagnosis by including immunosuppression or hepatitis as a factor in clinical decision making.

A broad range of ages were tested and as testing was undertaken on an opt-out basis, patient risk was not considered prior to screening, thus the assumption is held that all risk groups were possibly screened.

A high Emergency Department study prevalence was seen for all three viral infections, with a positive HIV blood test in 1.1% of attendees having study bloods taken. This prevalence rate is much higher than the results of previous work that determined the rate of those living with HIV in the greater Dublin area to be at least 0.2% and suggests that HIV screening should be performed as routine in those undergoing venepuncture or accessing secondary care. Furthermore, 5% of all attendees undergoing study bloods had a positive hepatitis C antibody test and a significant number of HIV/Hepatitis C co-infection was noted. Both these rates reflect our inner-city attending cohort and high prevalence of intravenous drug use in this group.

On the basis of these results, to advocate patient safety and to reduce the risk of onward transmission, we have implemented this practice as standard of care, in partnership with the HSE Acute Hospitals Division, National Social Inclusion Unit and the Population Health and Wellbeing Directorate.

This study had some limitations. Due to the study design of opt-out testing as part of routine clinical care in a busy ED and limitations with our electronic medical record system, we

were unable to ascertain a refusal rate of HIV tests offered, or to obtain patient feedback to establish acceptability of patients at the time of routine screening. Furthermore, risk demography of patients was not routinely collected at the time of testing, thus electronic patient records were relied upon to collect this risk demography subsequent to screening. ED prevalence and new diagnosis rates reflect those who had study bloods done only, thus these reported figures may be an over-representation of viral infection prevalence in the ED attendees. Conversely, the HIV new diagnosis rate found was lower than those found in previous studies [28,29]. This study design incorporated an opt-out approach, where patients having phlebotomy done as part of clinical care were given the option to opt out of BBV testing. In previous studies, an “opt-in” approach has been utilised, where patients are approached and offered the tests, and different testing methods have been used including salivary point of care tests in these studies. It is possible that due to the exclusion of greater than 50% of ED attendees over the study period who did not have bloods taken, the HIV new diagnosis rate found was lower than if this cohort had undergone testing.

A very small proportion of those patients testing positive for blood borne viral infection were aged >65. Given the high cost of such a screening approach, it is possible that costs may have been decreased by excluding this older population. A detailed cost analysis will be performed to assess the cost efficiency of performing panel testing for HIV, hepatitis B and C viral infections in this setting will address this question.

As part of the extension of the proposed NaTIVE (National Viral Testing Initiative) project, further studies examining the sero-prevalence rates in both targeted and non-targeted settings in areas of differing demographics will be performed. Following this, a detailed cost-efficiency study will be performed to examine these testing approaches.

Conclusion

Within a large urban Emergency Medicine Department in a tertiary referral centre, it was possible to achieve an uptake rate of 50% in an HIV, hepatitis B and C opt-out testing pilot study. Over a 10 month period, 7 new HIV diagnoses were made, demonstrating the importance of testing in the ED to reduce onward transmission. Patients diagnosed had mainly late HIV diagnoses and were not all from high risk-groups, suggesting scope for further universal testing. This study enabled linkage to care of new individuals for early treatment in an era of early treatment for HIV and newly developed successful therapies for HCV with high success rates.

The impact of this study has positive public health implications both at an individual patient and at population health level. It has raised awareness about HIV, HBV and HCV testing and its clinical indicators. Given the opt-out nature of the test, stigma has potentially been removed from the process of testing, for both the patient and also the staff member. Furthermore, those patients unaware of their diagnosis are at a significant health advantage by being diagnosed at an earlier stage in their illness. Once diagnosed and treated appropriately, rates of transmission will decrease. The strategy of linking treatment to testing (Test and Treat) has proved an effective public health intervention for HIV infection and may become part of the ambitious Department of Health public health intervention to eradicate HCV. While current European guidelines recommend routine commencement of ART for HIV at a CD4 count of greater than 350 cells/mm³, interim results of a large-scale randomised clinical trial recently showed significant clinical benefits for those patients commenced on ART at an earlier point in their illness, thus supporting the US recommendation that all asymptomatic HIV positive patients take ART irrespective of CD4 count and the strategy of linking treatment to testing. [30]

While previous studies have involved opportunistic HIV testing alone in non-traditional environments including Emergency Medicine Departments, no study to date has looked at the

benefits of opt-out panel testing- where all 3 viruses are tested from a single serum sample. Particularly of note, of those who tested positive for HIV infection, our pilot study showed that almost half those patients with HIV infection had co-infection with Hepatitis C, thus to screen for one virus alone runs the risk of missing other infections at the time of screening.

This pilot study has not only offered patients a unique opportunity to be tested but also to be linked back to care. This study has provided us with valuable local population prevalence data that will inform blood-borne virus testing practice in the near future.

Author Contributions

Conceived and designed the experiments: SOC HT CF CB SOD SN PKP. Performed the experiments: DL DS LD IF HB BC. Analyzed the data: SOC AC. Contributed reagents/materials/analysis tools: LD HB IF. Wrote the paper: SOC. Reported results to the study team: BC.

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Factors associated with non-retention in HIV care in an era of widespread antiretroviral therapy

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Abstract

In an era of antiretroviral therapy (ART) for all HIV-1-infected patients, our primary aim was to describe prevalence and characteristics of patients disengaged from care at an urban ambulatory HIV clinic. We conducted a nested case-control study. All patients who disengaged from care (defined as being lost to follow-up for at least one year) from 2007 to 2014 inclusive were identified. Cases were matched to controls in a 1:4 ratio. A total of 1250 cases were included; 250/2289 (10.9%) of patients attending our HIV clinic disengaged from 2007 to 2014. One hundred and twenty-six (50.4%) were heterosexual, 81 (32.4%) were men who have sex with men and 40 (16%) were intravenous drug users. On univariate analysis only, patients with heterosexual risk were more likely to disengage from care (50.4% vs. 33.7%, $p < 0.001$). Those who disengaged were younger, mean age of 39 ($p < 0.001$). A higher proportion of patients who disengaged from care was not receiving ART and did not have a suppressed HIV-1 viral load ($p < 0.001$). On multivariable analysis, Irish patients were less likely to disengage from HIV care (odds ratio: 0.567, $p = 0.002$). Factors associated with non-retention in HIV care have been identified. A semi-structured interview of those patients who re-engaged will take place to further examine reasons for disengagement from care.

Keywords

Human immunodeficiency virus, retention in care, antiretroviral therapy, lost to follow-up

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Background

Retention to human immunodeficiency virus (HIV) care is crucial for patient survival, to prevent onward transmission and avoid emergence of drug resistance. Continuous retention in HIV care has been associated with prevalent HIV-1 viral suppression.¹ The UNAIDS global HIV targets of 90% diagnosed, 90% on antiretroviral therapy (ART) and 90% suppressed suggest that testing and ART are the tools necessary to reach these targets. Without an adequate rate of retention in HIV care, reaching these targets will not be possible.

ART is now thought to have a clinical benefit to all individuals with HIV infection, including those with asymptomatic HIV; thus, international HIV treatment guidelines now recommend ART for all HIV-1-infected individuals who are ready to start.² ART also has a public health benefit beyond that of the individual, with reduction in transmission at both individual and

population levels with ART now established – Treatment as Prevention.^{3,4} Retention in care for the HIV-infected individual is therefore vitally important to allow for adherence to ART and optimal treatment outcomes.

In Ireland, in 2014, 377 new HIV diagnoses were made. This was an increase of 11% as compared to 2013 with an increasing number of men who have sex with men (MSM) and people who inject drugs being diagnosed.⁵ It was estimated that 3254 people were attending specialist services for HIV care in 2010 in Ireland. For the 3202, where data were available, 2574 (80%) were on ART. HIV ribonucleic acid

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(RNA) values were available on 2528 (98%) of patients on ART; 2208 (87%) of these had HIV viral load responses of less than 50 copies per ml.⁶ With the lack of an Irish National HIV Disease Registry, a recent and accurate number of those currently diagnosed and living with HIV in Ireland is not available.

Numerous factors that negatively affect HIV retention in care have been reported. These factors can be both patient related and disease related. Patient-related factors previously identified include stigma^{9,10} associated with a positive infection status, logistic and financial difficulties in transportation to an ambulatory clinic,⁹ younger age⁹ and lack of education and social support.^{11,12} In less developed countries, patient-related factors such as those who have not yet started ART,^{13,14} travelling long distances to receive care,¹³ tuberculosis co-infection¹³ and competing life activities¹⁰ all negatively affect retention in HIV care. Disease-related factors associated with poor retention in HIV care that have been previously identified include feeling too sick to attend clinic, depression and mental illness.¹⁰

In the United States, the Center for Disease Control (CDC) estimate that more than 1.2 million people are living with HIV infection, and almost one in eight (12.8%) are unaware of their infection.⁷ The CDC also estimates that less than 50% of persons diagnosed with HIV receive regular HIV care.⁸ Similarly, in the United Kingdom, it has been reported that 19% of adults seen for HIV care between 1998 and 2006 were lost to follow-up by the end of 2007.¹⁷

The primary aim of our study was to describe the prevalence of retention in HIV care at the Department of Genito-Urinary Medicine and Infectious Diseases, St James's Hospital, Dublin, Ireland from 2007 to 2014 inclusively. A secondary aim was to examine patient factors associated with non-retention in HIV care over this time period.

Methods

Study sample and data collection

For the purpose of this study, retention in care was defined as at least one HIV clinic attendance every year. One year was chosen as the time interval based on the recommendation by Medland et al.,¹⁵ following a systematic review of data sources recording the HIV care cascade in the United States. All patients who disengaged from HIV care for greater than a one year time period, from 2007 to 2014 were identified with a departmental database. Appropriate institutional ethical approval was obtained. Retrospective electronic patient chart review was undertaken, and demographics were recorded on a confidential departmental Excel

database. Patients who were disengaged from care for greater than one year but subsequently re-attended over the eight-year time period of follow-up were categorised as 'poor-attenders' but were included in study analysis.

Definitions of variables

For each patient, variables including age, gender, mode of acquisition, geographic origin, use of ART, CD4 cell count and HIV viral load at the time of disengagement were recorded. Variables including missing values were then coded and exported to SPSS version 23. SPSS was then used to describe and compare patient demographics in both retained and non-retained groups.

Statistical analysis

A nested case-control study was performed. Controls were randomly selected from the active attending HIV cohort during the same year that the case was identified as disengaging from care. Controls were matched to cases at a 4:1 ratio. Demographics for both cases and controls were retrospectively recorded from electronic chart review. Variables including missing values were then coded and exported to SPSS version 23. SPSS was used to describe patient demographics in both retained and non-retained groups. Univariate and multivariable analyses for this dataset were then carried out. T-test independent samples of means, Mann-Whitney U and Chi-square tests were used for continuous and categorical variables, respectively. Re-coded variables were then used to perform binary logistic and multivariable logistic regression. Weighted odds-ratio was then interpreted for independent variables, using a 95% confidence interval and a p value of less than 0.05 to determine statistical significance.

Results

Description of total cohort

A total of 1250 patients were included in this study. Two hundred and fifty patients had disengaged from HIV care from 2007 to 2014, and the remaining 1000 patients were randomly selected as controls, matched on a 4:1 ratio for same year of attendance and HIV-1 infection. Age range was 19–78, median age (interquartile range [IQR]): 42 (36,50). Six hundred and forty-one (51%) patients were Irish and 842 (67%) were male. Four hundred and sixty-three (37%) were heterosexual, 471 (38%) were MSM and 291 (23%) had a history of intravenous drug use (IDU) as mode of acquisition. Three hundred and seventeen (25%) of patients had a CD4 cell count below 350 cells/mm³. The majority of patients (n=930, 75%) had a CD4 cell count of

>350 cells/mm³ and 612 (66%) of these had a CD4 cell count of >500 cells/mm³. Nine hundred and fifty (76%) patients were taking ART and 769 (62%) patients had a suppressed HIV-1 viral load at the time of attendance or disengagement.

Description of non-engaged group (cases)

Of 2289 patients attending our ambulatory HIV clinic, 250 (11%) patients had disengaged from HIV care from 2007 to 2014; 21 (8%) of these 250 patients subsequently re-engaged in HIV care. From retrospective review, we found that seven (3%) patients died over the study period, after disengaging from care, and figures may be higher. See Figure 1 for description of the cohort lost to follow-up. One hundred and fifty-three (61%) were male; 126 (50%) were heterosexual, 81 (32%) were MSM and 40 (16%) were IDU. Eighty-seven (35%) patients who disengaged were Irish and 90 (36%) were from Sub-Saharan Africa; 88% of the heterosexual risk group were non-Irish.

Four (2%) patients had a CD4 cell count of <50 and 59 (24%) patients had a CD4 cell count of <350 at the time of disengagement from HIV care. One hundred and forty (56%) patients were taking ART at the time of disengaging from care, and only 59 (42%) of these patients had a suppressed HIV-1 viral load at the time of disengagement from care.

Telephone follow-up of 243/250 (97%) patients was undertaken. No contact details were available for 7/250 (3%) of patients. Successful contact was made with 47/243 (19%) of patients. Contact was unsuccessful for the remaining 196 (81%) patients as contact details were no longer up-to-date, and the person could not be reached. It is not known how many of these had migrated out of Ireland to explain lack of up-to-date contact details. When interviewed over the phone, 34 (72%) stated they were willing to return and 17 (50%) of these 34 patients have re-engaged in care at our centre to date.

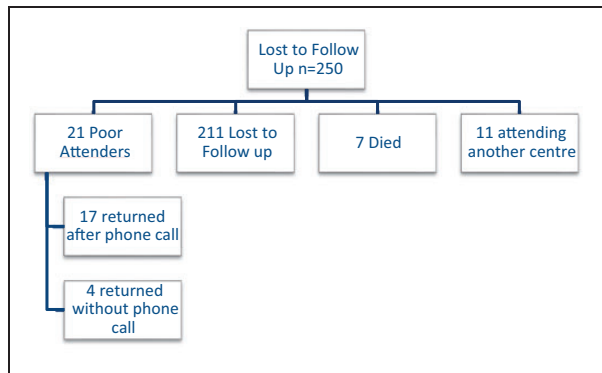


Figure 1. Patients Lost to Follow Up.

A further 11 (23%) patients are now attending another centre, and two (4%) have not disclosed why they will not follow up for care. See Figure 2 for description of the phone call intervention.

Univariate analysis between groups

As shown in Table 1, the mean age of patients who were retained in care was higher than that for those patients who had disengaged (p: <0.001, 95% CI: 2.24–4.95). A higher proportion of patients who had disengaged from care had not been receiving ART, and a higher proportion of patients who had disengaged from care did not have a suppressed HIV-1 viral load (p: <0.001). No significant gender difference was found between cases and controls (p: 0.056).

The majority of patients who had disengaged from care were non-Irish (65%); 45% of those who retained in care were non-Irish and this difference was statistically significant (p: <0.001). No difference in distribution of CD4 cell counts was observed between cases and controls (p: 0.181).

A significantly higher proportion of patients who disengaged from care were heterosexual (50%) as compared to those who retained in care (34%); (p: <0.001, 95% CI: 0.378–0.662). Conversely, a significantly lower proportion of those with IDU as mode of acquisition (16%) had disengaged from care, as compared with 25% of those in the retained in care group (p: 0.002). Thirty-two per cent of those who disengaged from care were MSM, as compared to 39% of those who were retained in care. This difference was not found to be

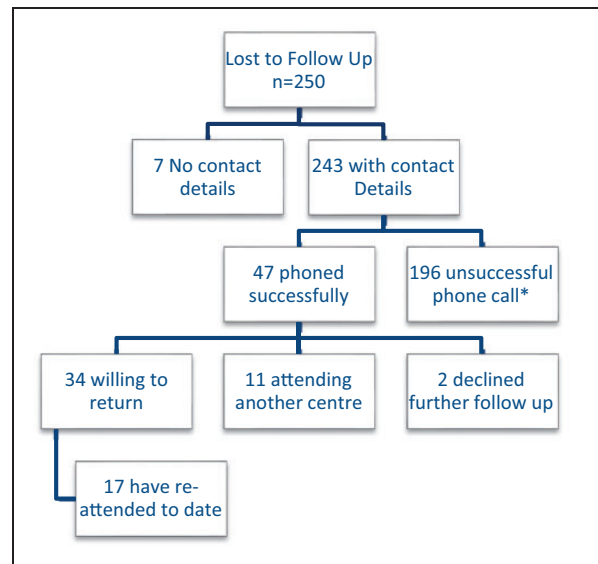


Figure 2. Phone Call Intervention.

Table 1. Description of patient characteristics/univariate analysis.

	Retained in care N = 1000	Disengaged from care N = 250	P
Age	Mean age: 43.38	Mean age: 39.88	<0.001, CI: 2.24–4.95
Geographic origin			
Ireland	554 (55)	87 (35)	<0.001
SSA	243 (24)	90 (36)	
South America	34 (3)	21 (8)	
SE Asia	23 (2)	6 (2)	
Other	146 (15)	46 (18)	
Gender			
Male	689 (69)	153 (61)	0.056
Female	310 (31)	97 (39)	
Risk			
HS	337 (34)	126 (50)	<0.001
MSM	390 (39)	81 (32)	0.058
IDU	251 (25)	40 (16)	<0.001
Other	22 (2)	2 (0.80)	
CD4 cell count			
<50	17 (2)	4 (2)	0.181
50–200	74 (7)	14 (6)	
200–350	167 (17)	41 (16)	
350–500	260 (26)	58 (23)	
>500	482 (48)	130 (52)	
Viral load			
Suppressed	710 (71)	78 (31)	<0.001
Not suppressed	224 (22)	164 (66)	
Just started (six months)	42	0	
New diagnosis	16	0	
ART			
On ART	810 (81)	140 (56)	<0.001
Not on ART	187 (19)	110 (44)	

SSA: Sub-Saharan Africa; SE Asia: South East Asia; HS: heterosexual; IDU: intravenous drug use; MSM: men who have sex with men; ART: antiretroviral therapy.

statistically significant (p : 0.058). See Table 1 for description of patient characteristics.

Multivariable analysis of predictors for disengagement in care

Patients from Ireland were less likely to disengage from HIV care (OR: 0.567, CI: 0.397–0.811, p : 0.002). Those with a suppressed HIV-1 viral load were also less likely to disengage from HIV care (OR: 0.191, CI: 0.128–0.284, p : <0.001). Patients on ART were less likely to disengage from care, but results were not found to be statistically significant (OR: 0.914, CI: 0.611–1.368, p : 0.663).

Taking into account other independent predictors including age, gender, ethnicity and immune status, heterosexual mode-of-acquisition, IDU and MSM were all

associated with a higher risk of disengagement from care. These results were not found to be statistically significant. Male gender was associated with disengagement from HIV care, but results were not statistically significant (OR: 1.14, CI: 0.782–1.664, p : 0.495). See Table 2 for description of logistic multivariable regression model.

Discussion

HIV retention in care rates at our centre is overall comparable with international figures,^{16,17} and rates occur over a time where patient demography in Ireland is changing over time.¹⁸

As a possible explanation for the slightly higher proportion of those who disengaged being from

Table 2. Multivariable regression model.

	Retained	Non-retained	B	OR	95% CI	p
Age (median, IQR)	43 (28,58)	39.5 (27.5,51.5)	0.252	1.286	0.937–1.765	0.119
Gender	689 (69)	153 (61)	0.131	1.140	0.782–1.664	0.495
Irish	554 (55)	87 (35)	–0.567	0.567	0.397–0.811	0.002
CD4 cell count < 200	91 (9)	18 (7)	–0.407	0.666	0.372–1.192	0.171
HS	337 (34)	126 (50)	0.616	1.852	0.507–6.761	0.351
MSM	390 (39)	81 (32)	0.032	1.032	0.281–3.789	0.962
IDU	251 (25)	126 (50)	0.056	1.057	0.3281–3.983	0.934
ART	810 (81)	140 (56)	–0.090	0.914	0.611–1.368	0.663
VL	710 (71)	59 (24)	–1.658	0.191	0.128–0.284	0.000

IQR: interquartile range; HS: heterosexual; MSM: men who have sex with men; IDU: intravenous drug use; ART: antiretroviral therapy; VL: viral load.

Sub-Saharan Africa as compared to other areas of geographic origin, from 2000 to 2011 in Ireland, as seen throughout Europe, a large proportion of those attending for HIV care with newly diagnosed HIV were from the asylum seeker population.¹⁹ It is possible that some of these patients have either relocated to another HIV centre with further provision of accommodation elsewhere in the country or it is also possible that these patients moved abroad.

Fifty-six per cent of patients were on ART at the time of disengagement; 12% of these were females who had stopped ART post-partum, and did not return for care after cessation of ART. With HIV treatment guidelines change, this is no longer part of normal practice, as ART is continued throughout both pregnancy and the post-partum period.

An intervention undertaken in our department to contact these patients who were lost to follow-up was successful, but only for a limited number who were contactable; 81% of patients who disengaged from care were not contactable, where registered phone numbers were out of service or the person could not be reached. This information suggests that a better way of maintaining patient demographics at each clinic appointment needs to be employed, including the use of self-service kiosks and the use of new methods for patients to update contact details including phone numbers at each clinic visit.

While on univariate analysis, gender does not appear to be a factor associated with disengagement from HIV care, on multivariable analysis, males were more likely to disengage from HIV care. Also, patients who had disengaged from care were younger than those who retained in care. Literature has previously described this as a factor associated with poor retention in care.⁹

Thirty-two per cent of patients who had disengaged from care were taking ART but did not have a suppressed viral load at the time of disengagement. This suggests a history of erratic ART use and possible

intermittent clinic attendance. Overall, patients who disengaged from care were less likely to have received ART and to have a suppressed HIV viral load, over this eight-year period.

The heterosexual risk group was most likely to disengage from care, with significantly higher rates of retention seen in the MSM and IDU risk groups. We have previously understood from the literature that those with a history of IDU can have poor rates of healthcare attendance, but we also know that people who inject drugs frequently attend hospital services. It is possible that these patients engage in a more frequent manner due to such attendances and higher rates of points of contact with the healthcare provider.

Multivariable analysis shows that when confounding for other independent predictors of non-retention in HIV care, non-Irish patients are more likely to disengage from care. Those with a suppressed HIV-1 viral load were more likely to engage in care, but those on ART alone were not found to be significantly more likely to engage in care. This logistic regression model with multiple co-variables shows that when other independent predictors are taken into account, few predictors are significantly associated with non-retention in HIV care.

These results have been presented to staff at our department, including to doctors and clinical nurse specialists who regularly review the patients attending the ambulatory care clinic. Factors associated with non-retention in care have been highlighted to the staff, to raise awareness of the problem and to address the possibility of disengagement when people with these predictors attend for care, to prevent future disengagement.

Limitations

This study has some limitations including those that are inherent in a retrospective study. We do not have accurate numbers of those who may have passed away since

disengaging. Individual patient reasons for defaulting from care were not elicited. To further understand reasons for disengagement from care, a semi-structured interview is planned where these reasons will be explored in depth with patients who have since re-engaged in care. Patients were matched for year of attendance but not for other demographic factors. This decision was made to allow examination of other demographics as possible predictors for disengagement from care.

Conclusion

While we have identified specific characteristics of this patient group, including that the younger, non-Irish heterosexual risk group is at the highest risk of disengaging from care, anecdotal evidence suggests that perhaps this cohort have been re-located to another part of the country or have travelled abroad. This information highlights the importance of the previously made call for a national HIV disease registry, so we can gain a better understanding of the dynamic nature of our HIV cohort as it changes over time.

Declaration of Conflicting Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Late HIV presentation – missed opportunities and factors associated with a changing pattern over time

Sarah O’Connell, Julia Enkelmann, Corinna Sadlier and Colm Bergin

Abstract

Delayed diagnosis of HIV infection has negative clinical, economic and public health implications. The study primary aim was to identify factors associated with late HIV presentation (Late Presenters [LPS], CD4 cell count < 350 cells/mm³). A secondary aim was to identify changing trends of late HIV presentation from 2002 to 2014 at our centre. A retrospective cohort study was performed. Demographic data and CD4 cell count of new HIV diagnoses presenting to our ambulatory HIV service over four time-periods from 2002 to 2014 were recorded. Proportion of LPS and factors associated with late presentation were compared using Graphpad Instat. In 2014, of 231 new patients attending for HIV care, 75 (32.6%) were late presenters versus 146 (66.4%) in 2002. This indicates a decreasing proportion of LPS from 2002 to 2014. However, the proportion of those with CD4 cell counts <200 on presentation at these two time intervals remain unchanged. The overall proportion of male LPS has increased over time and the proportion of LPS in the men who have sex with men (MSM) cohort has decreased over time, reflecting increased frequency of both HIV testing and diagnoses in MSM in recent years. The proportion of heterosexual LPS has not changed significantly in the same time period and LPS were older in 2014 versus 2002. The proportion of LPS defined by CD4 cell count remains higher than is justifiable in an era of increased HIV testing and awareness. Further targets for HIV testing to decrease rates of LPS include non-traditional risk groups including heterosexual and older patient cohorts. LPS rates are lower than rates found internationally, and it is possible that consensus definition of LPS needs to be revised.

Keywords

AIDS, HIV, prevention, screening

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The WHO estimates that worldwide, 37 million people are living with HIV, and now recommend anti-retroviral therapy for all those with HIV infection. It is estimated that currently worldwide, only 54% of people are aware of their infection status.¹

Late HIV presentation can be defined as those presenting for HIV care with a CD4 cell count of less than 350 cells/mm³.² Late presentation with HIV infection has a negative impact on outcome for the individual. Those who are unaware of their positive HIV status cannot benefit from widely available treatment options. As a result, late presentation for HIV care is associated with higher morbidity and mortality, even after treatment with antiretroviral therapy.^{3,4} Late presenters also carry a lower chance of recovery of CD4⁺ T lymphocytes (CD4)⁵ following treatment, and without

treatment carry a risk of HIV transmission while unaware of their HIV status. Furthermore, costly inpatient hospital admissions may be avoided with appropriate management of HIV at an earlier point.

In 2014, 377 new HIV diagnoses were notified in Ireland, giving a crude notification rate of 8.2 per 100,000 population. This is an increase of 11% compared with 2013 and can be accounted for by an increasing number of HIV notifications among men

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who have sex with men (MSM) and people who inject drugs (PWID). Between 2010 and 2013, the annual rate of new HIV diagnoses had been relatively stable in Ireland, ranging from 7.0 to 7.5 per 100,000 population.

The highest number of new diagnoses ever reported in MSM was in 2014, comprising 49% of new HIV diagnoses in Ireland. In the 10 years since 2005, the number of new diagnoses among MSM has increased threefold (from 60 to 183) and the median age at diagnosis has dropped from 37 to 31 years. Furthermore, in 2014, there were 27 (7%) new diagnoses among PWID, the highest number reported in this risk group since 2009.

In Ireland, the Health Protection and Surveillance Centre (HPSC) report that 49% of new HIV diagnoses in 2014 were late presenters, with CD4 less than 350 cells/ μ l or an AIDS defining illness at diagnosis. This number reflects similar proportions over recent years. Late presentation was less common among MSM (38%) and PWID (44%) than among heterosexuals (56% in females and 71% in males). Regular testing among MSM and PWID is likely to be a major reason for this as both groups had a much higher proportion reporting ever having had a previous negative test (58% in MSM and 66% in PWID versus 20% in heterosexuals). However, the lower proportion of late diagnoses among MSM and PWID may also be a result of more recently acquired infections in these population groups. Based on previous HIV testing history, 27% of infections in MSM, and 41% in PWID were acquired in the previous 2 years.⁶

The primary aim of this study was to identify factors associated with late HIV presentation (LPS, CD4 cell count < 350 cells/mm³) and to further examine differences between those with moderate immunodeficiency (MI, CD4 200–350 cells/mm³) and advanced immunodeficiency (CD4 < 200 cells/mm³). We sought to determine opportunities missed to diagnose HIV earlier in this patient cohort. A secondary aim was to identify changing trends of late HIV presentation from 2002 to 2014 at our centre.

Methods

Study design and population

This was a retrospective cohort study. Appropriate in-hospital approval for research activity was obtained (ref 2015/109). Retrospective electronic chart review was undertaken. Patients with a new diagnosis of HIV infection who presented for care at our HIV centre over 2014, 2012, 2007 and 2002 with newly diagnosed HIV infection were included. Time intervals were chosen to reflect the possible changing demographics of our cohort over time. Data collection had previously taken place at our department for 2002, 2007 and 2012.

Following on from this, data were then collected for the most recent year that had passed (2014). Patients who had already received care for their HIV infection at another centre were excluded from the study.

Variable of interest

The primary variable of interest was CD4 cell count (cells/mm³) at presentation. Patients were identified by a departmental patient database; these were new attenders for HIV care over defined time-points (2014, 2012, 2007 and 2002). By electronic chart review, various demographic data including age, gender, risk group, geographic origin, previous HIV testing status, previous investigation of unexplained symptoms prior to HIV diagnosis, clinical indicator condition at time of diagnosis and CD4 cell count at presentation of new HIV diagnoses over 2014 were collected on Excel Database. HIV transmission risk group was categorised as MSM, IDU, heterosexual and other/unknown. Using data available, further comparison was then made between variables of this group and those of late presenters from three previous time-points over the past decade. (2002, 2007 and 2012). These variables included age, gender, mode of acquisition, country of origin and CD4 cell count at presentation. Data were coded anonymously and statistical analysis was performed using Graphpad Instat. Wilcoxon, ANOVA and χ^2 tests were used to compare variables. Late presentation (LPS) was defined as those who presented with a CD4 cell count of <350 cells/mm³. Moderate immunodeficiency (MI) was defined with an initial CD4 cell count between 200 and 350 cells/mm³ and advanced immunodeficiency (AI) was defined as an initial CD4 cell count of <200 cells/mm³.

Results

In 2014, a total number of 231 patients were referred for management of newly diagnosed HIV infection. Seventy-five (32.6%) patients presented with a CD4 cell count of <350 cells/mm³ (LPS). Of these, 55 (73.3%) were male and 20 (26.7%) were female. Mean (SD) age at presentation was 39.7 (11) years. The majority of patients (n=33, 44%) were Irish. Mean (SD) CD4 cell count was 166 (109) cells/mm³. See Figure 1 for information on probable route of transmission and geographic origin and see Table 1 for detailed demographic information for each presentation stage.

Moderate immunodeficiency in 2014 (n = 32)

The majority of patients (n=23, 72%) were tested in healthcare settings outside our hospital. Seventeen

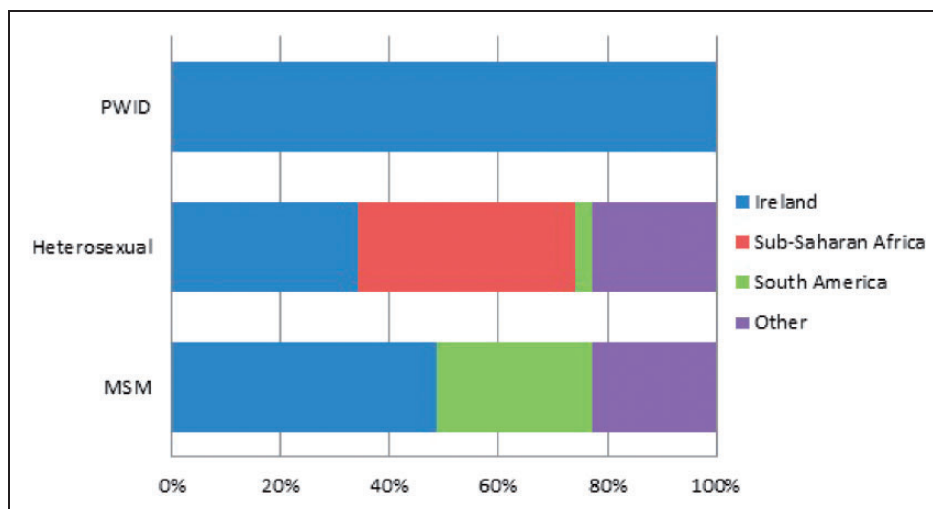


Figure 1. LPS by mode of acquisition and country of origin.

(53.1%) patients had previously been tested for HIV infection. Eight (50%) of these patients had a HIV test within 2 years prior to HIV diagnosis and 7 (88%) of these were MSM.

Advanced immunodeficiency in 2014 (n = 43)

Eighteen (42%) patients were tested in healthcare settings outside our hospital. Seventeen (39.5%) had previously been tested for HIV infection. Eleven (65%) of these had a HIV test within 2 years of diagnosis and 6 (54.5%) of these were MSM. See Table 2 for a detailed description of factors associated with moderate and advanced immunodeficiency presentation.

Comparison of groups over time

Proportions of male LPS compared with female LPS have increased over time ($p \leq 0.001$). With this, proportions of MSM compared with other risk groups diagnosed over time have increased ($p \leq 0.001$) (Figure 1). A decreased proportion of those with heterosexual risk in the LPS group was seen over time, however in 2014, the risk group most likely to present as LPS was heterosexual: HS (58%) vs. MSM (22.8%). Proportions of LPS from Sub-Saharan Africa in comparison with other geographic origins have decreased from 2002 to 2014 ($p \leq 0.0001$). In contrast to this, proportions of LPS attending from South America have increased significantly from 2002 to 2014 ($p \leq 0.001$). As rates of those from Sub-Saharan Africa have fallen, another significant proportion (44%) of LPS with heterosexual mode of acquisition in 2014 was from Ireland. No overall significant age difference was seen amongst LPS over time ($p = 0.593$). However, a direct comparison

between 2002 and 2014 shows a significant difference in age, where LPS are presenting at an older age in 2014 than in 2002 ($p \leq 0.001$) (Table 1).

The overall proportion of LPS newly diagnosed with HIV attending our centre for care has decreased over time ($p \leq 0.001$). However, the proportion of those who presented with advanced immunodeficiency (AI) over time has not significantly changed ($p = 0.69$) (Figure 3).

Within risk category analysis shows that the percentage of MSM LPS has decreased, as has the percentage of males, females and those from Sub-Saharan Africa. No significant decrease in proportions of LPS in the heterosexual risk group was seen, with 100% of the heterosexual risk group diagnosed in 2012 presenting with a CD4 cell count of less than 350 cells/mm³. These findings reflect the overall decreased proportion of those presenting late since 2002. See Table 3 for percentage rate change over time amongst each category.

Discussion

Over time, proportions of those with newly diagnosed HIV-1 infection presenting at a late stage in their illness are decreasing. Proportions of those with very late presentation presenting over the past 12 years, with a CD4 cell count of <200 cells/mm³, remain unchanged. The demographics of those with late HIV presentation are changing over time. Those with heterosexual mode of acquisition, older patients and those from South America are more likely to present with late HIV infection in recent years.

Despite current HIV prevention strategies in place, including earlier introduction of ART, the widespread availability of post-exposure prophylaxis and ED screening interventions, our findings show that a

Table 1. Characteristics of First HIV Presenters to an Ambulatory HIV service from 2002–2014.

	2002			2007			2012			2014		
	n	MI	AI	n	MI	AI	n	MI	AI	n	MI	AI
Total no. patients (n)	220	99 (45)	47 (21.36)	215	92 (42.79)	45 (20.93)	200	78 (39)	40 (20)	231	32 (13.8)	43 (18.5)
Gender												
Male (%)	112 (50.9)	46 (46.46)	24 (51.06)	140 (65.12)	49 (53.26)	26 (57.78)	159 (79.5)	58 (74.36)	23 (57.5)	187 (81)	26 (81.2)	29 (67.4)
Female (%)	108 (49.1)	53 (53.53)	23 (48.94)	75 (35.88)	43 (46.74)	19 (42.22)	41 (20.5)	20 (25.64)	17 (22.5)	44 (19)	6 (18.8)	14 (32.5)
Mean age at presentation (SD)	31.73 (8.6)	32.56 (8.78)	35.27 (9.8)	34 (9)	33.03 (9.15)	34.86 (9.15)	35.32 (9.59)	36.96 (10.03)	36.32 (10.2)	35.8 (9.8)	38 (12)	40.8 (9.8)
Region of origin												
Ireland	89 (40.45)	39 (39.39)	19 (40.42)	117 (54.42)	45 (48.91)	25 (55.56)	98 (49)	39 (50)	19 (47.5)	91 (39.4)	15 (46.8)	18 (41.8)
SSA	113 (51.36)	51 (51.51)	20 (42.55)	64 (29.77)	39 (42.39)	17 (37.78)	33 (16.5)	18 (23.08)	13 (32.5)	29 (12.5)	5 (15.6)	8 (18.6)
South America	2 (0.9)	1 (1.01)	0	2 (0.93)	0	0	20 (10)	2 (2.56)	0	47 (20.3)	6 (18.75)	5 (11.6)
Other	15 (6.8)	9 (9.09)	8 (17.02)	32 (14.88)	8 (8.69)	3 (6.67)	49 (24.5)	19 (24.36)	8 (10)	64 (27.7)	5 (15.6)	12 (28)
Acquisition risk group												
HS	137 (62.27)	68 (68.68)	35 (74.47)	92 (42.79)	48 (52.17)	23 (51.1)	71 (35.5)	47 (60.26)	24 (60)	61 (26.4)	11 (34.3)	24 (55.8)
MSM	40 (18.18)	14 (14.14)	6 (12.76)	65 (30.23)	14 (15.22)	4 (8.89)	119 (59.5)	25 (32.05)	12 (30)	153 (66.2)	19 (59.3)	16 (37.2)
PWID	40 (18.18)	15 (15.15)	5 (10.64)	55 (25.58)	29 (31.52)	17 (37.78)	9 (4.5)	6 (7.69)	4 (10)	14 (6)	2 (6.25)	2 (4.65)
Other	3 (1.36)	2 (2)	1 (2.13)	3 (1.39)	1 (1.08)	1 (2.22)	1 (0.5)	0 (0)	0 (0)	3 (1.29)	0	1 (2.3)
Mean CD4 (SD)	428.2 (279.1)	189.4 (104.41)	95.4 (62.37)	427.4 (310.99)	186.1 (105.61)	94.3 (65.93)	415 (239.66)	187.82 (111.26)	94.6 (66.83)	463 (281.2)	275 (38.3)	84.8 (64.6)

Table 2. Late diagnosis 2014 demographics.

	Moderate immunodeficiency n = 32 n (%)	Advanced immunodeficiency n = 43 n (%)	p value	
Previous HIV test				
Yes	17 (53.1)	17 (39.5)	0.0071, OR: 2.25	
No	15 (46.9)	26 (60.5)		
Site of HIV diagnosis				
Gay Men's Health Service	9 (28.1)	4 (9.3)	0.0009, OR: 3.93	
Women's Health Project	0 (0)	1 (2.3)		
Abroad	0 (0)	1 (2.3)		
Medical inpatient	0 (0)	5 (11.6)		
Respiratory OPD	0 (0)	1 (2.3)		
Oncology OPD	0 (0)	1 (2.3)		
GP	8 (25)	9 (21)		0.61
ED viral screening	2 (6.3)	3 (7)		
Other hospital	5 (15.6)	10 (23.2)		0.28
STI clinic	6 (18.8)	8 (18.6)		1.00
Colorectal service other hospital	1 (3.1)	0 (0)		
Entrance to country	1 (3.1)	0 (0)		
Previous investigations				
Yes	2 (6.3)	9 (21)	0.0032, OR: 0.24	
No	30 (93.7)	34 (79)		
Nature of previous investigations				
None	30 (93.7)	34 (79)		
CXR (GP)	2 (6.3)	4 (9.3)		
CT, Mantoux, CXR	0 (0)	1 (2.3)		
ED visits for viral infection	0 (0)	2 (4.6)		
Bronchoscopy	0 (0)	1 (2.3)		
PUO investigated at other hospital	0 (0)	1 (2.3)		
Clinical indicator illness				
No	18 (56.3)	11 (25.6)	0.22	
Weight loss	2 (6.3)	8 (18.6)		
Blood dyscrasias	1 (3.1)	2 (4.6)		
Diarrhoea	1 (3.1)	1 (2.3)		
Oropharyngeal candidiasis	0 (0)	1 (2.3)		
TB	0 (0)	2 (4.6)		
HPV	1 (3.1)	2 (4.6)		
VZV	0 (0)	1 (2.3)		
HSV 2	2 (6.3)	1 (2.3)		
Non-specific myalgia	0 (0)	1 (2.3)		
Myositis	0 (0)	3 (7)		
PCP	0 (0)	5 (11.6)		
Cerebral toxoplasmosis	1 (3.1)	1 (2.3)		
Burkitts lymphoma	0 (0)	1 (2.3)		
Recurrent LRTI	0 (0)	1 (2.3)		
Septic arthritis	0 (0)	1 (2.3)		
HIV seroconversion illness	3 (9.4)	1 (2.3)		
Cervical lymphadenopathy	1 (3.1)	0 (0)		
Anal carcinoma	1 (3.1)	0 (0)		
Abnormal CXR	1 (3.1)	0 (0)		

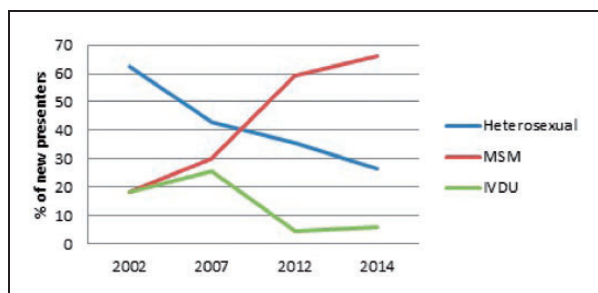


Figure 2. Risk of acquisition of HIV.

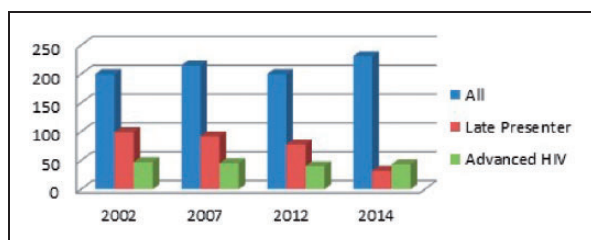


Figure 3. Stages of first presenters to HIV service.

Table 3. Rate of change over time (% of each category who presented with CD4 cell count <350).

	2002	2007	2012	2014	p value
Males	63	53.6	51	29.4	<0.001
Male MSM	50	28	31	23	<0.003
Male non-MSM	28	37	57	26	<0.001
Females	70	83	58	45	<0.001
MSM	50	28	31	23	<0.003
HS	75	77	100	57	<0.098
SSA	63	87	93	45	<0.016

significant portion of those presenting with HIV continue to present at a late point in their illness, with a subsequent negative impact on overall morbidity and mortality. These data have shown that in 2014, a number of patients presented to a range of healthcare facilities for investigation of unexplained symptoms that later were diagnosed as HIV clinical indicator illness, without having a HIV test done, including medical and surgical outpatients, general practitioners and Emergency Departments. High rates of missed opportunities for HIV diagnosis have previously been reported; one US study reports 35% of individuals newly diagnosed with HIV infection had previously attended a healthcare provider over the preceding 1

year with HIV associated signs and symptoms.⁷ The missed opportunities identified in this study further highlights the ongoing need for appropriate physician education on HIV clinical indicator illness, the need for HIV testing and the removal of barriers to performing a HIV test for patients.

Comparison between those presenting with moderate and advanced immunodeficiency in 2014 shows a significantly smaller number of those with advanced immunodeficiency had previously undergone HIV testing. At least 50% of patients in both groups had previously tested for HIV in the 2-year period prior to testing positive; the majority (69%) of these were MSM, reflecting high rates of HIV testing in this risk group. Early HIV infection with low CD4 cell count needs to be considered as a possible explanation for higher rates of LPS MSM diagnoses with higher testing rates, and suggests the definition for late HIV presentation needs to be revised. It also highlights the role for newer laboratory techniques to be developed and evaluated to distinguish recent and established HIV infection.

When comparison was made between patterns of demographics of those presenting in 2014 and over three other time points since 2002, it is clear that currently the rate of LPS in all risk groups is decreasing, however similar proportions of those with advanced immunodeficiency continue to present. Furthermore, people are likely to be older when presenting as LPS. These findings reflect those that have been found at a national level.⁸

Rates of LPS in our cohort are lower than that found internationally. The Cohere Observational Cross-European study of LPS from 34 countries showed a LPS rate of 48.7% in 2013, with overall highest rates of LPS from 2010 to 2013 in heterosexual males and females.⁹ While risk factors for late HIV presentation seen in this study are similar to our cohort, rates of LPS are higher than seen in our cohort. A possible explanation for this is that AIDS defining illness was not included as a definition for LPS in our cohort. Furthermore, a 2015 meta-analysis of gender differences at risk of late HIV presentation showed male gender to be at higher odds of late HIV presentation, similar to our cohort.¹⁰ A review of HIV presentations in the United States over a 10-year time period, with LPS defined as CD4 cell count of <350 only, showed rates of LPS decreased over this time period, with LPS rates of 53% seen most recently in 2007. The effect of the use of earlier ART in the US cohort in more recent times remains to be seen.¹¹

Various intervention strategies have been employed in recent years to reduce the rates of late HIV diagnosis, missed opportunities for HIV testing and the

detrimental sequelae of such an outcome. In the United States, to accelerate progress toward reducing undiagnosed HIV infection, the CDC and its partners have pursued an approach that includes expanding HIV testing in communities with high HIV infection rates.¹² It has previously been shown that barriers amongst healthcare providers exist, including lack of time to conduct testing and staff feeling ill-prepared to answer patient queries.^{13,14} It is possible that our patients did not have a HIV test previously for these reasons.

Limitations

This study has a number of limitations that are inherent with a retrospective cohort study. We were unable to ascertain the true timing of HIV acquisition in our patients. As late presenters were categorised on the basis of CD4 cell count only, it is likely that a proportion of these patients included in the data analysis had recently acquired infection. Because of limitations with retrospective chart review, the authors did not use the LP consensus definition,¹⁵ where AIDS defining illness was not included in our definition of LPS. As a result of this, it is possible that rates of LPS are lower in our cohort than seen internationally.

Conclusions

Potential targets for future HIV testing include testing initiatives at other healthcare settings and GP practices, where a large proportion of those LPS were diagnosed. In line with higher rates of HIV diagnosis in MSM, the proportion of MSM LPS as compared with other risk groups is increasing. A significantly smaller number of MSM were diagnosed with advanced immunodeficiency, representing the higher frequency of HIV tests performed for this risk group. With this in mind, our knowledge that the heterosexual risk group now most likely to present as LPS in 2014 and high rates of recent previous testing in the MSM group, it is now evident that other risk groups need to be targeted for HIV testing. Given the increasing age of patients who are presenting with late HIV, all age and risk groups should be considered for a HIV test. To employ these interventions effectively, widespread HIV testing in all healthcare facilities including GP practices needs to be implemented. Furthermore, the need to re-structure the education of healthcare providers, to re-emphasise the need for HIV clinical suspicion in all risk and age groups when presenting for care and to increase the awareness of the role for widespread HIV testing in areas of different prevalence and demography has been highlighted. While blood borne virus screening is now standard of care at the emergency medicine

department at our centre, further strategies needs to be employed to diagnose and treat HIV early, to prevent onward HIV transmission and avoid adverse healthcare consequence.

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482. Retention in Human Immunodeficiency Virus (HIV) Care in an Era of Highly Active Anti-Retroviral Therapy for All HIV-1-Infected Individuals

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Background. Retention in HIV care is essential to meet targets outlined in the UNAIDS 90-90-90 plan. In an era of ART for all HIV-1 infected patients, our primary aim was to describe prevalence and characteristics of patients disengaged from care at an urban ambulatory HIV clinic. A secondary aim was to determine factors associated with non-engagement in care.

Methods. We conducted a nested case-control study. All patients who disengaged from care (defined as loss to follow up for at least one year) from 2007 to 2014 inclusive were identified. Patient records were reviewed to collect demographics. Cases were matched for most recent year of attendance and HIV-1 positive status to controls in a 1:4 ratio. Statistical analysis was performed using SPSS version 23.

Results. Two hundred fifty cases were matched to 1000 controls in a 1:4 ratio. A total of 250 of 2289 (10.9%) of patients attending our HIV clinic disengaged from care from 2007 to 2014. Seven (2.8%) patients died over this period. One hundred fifty-three (61.2%) were male. One hundred twenty-six (50.4%) were heterosexual, 81 (32.4%) were MSM and 40 (16%) were IDU. Eighty-seven (34.8%) were Irish and 90 (36%) were from sub-Saharan Africa. A total of 88.4% of the heterosexual risk group were non-Irish. Fifty-nine (23.6%) patients had a CD4 count of <350 at the time of disengagement. One hundred forty (56%) patients were taking ART and only 59 (42%) of these patients had a suppressed HIV-1 viral load at time of disengagement.

On univariate analysis, those with heterosexual risk were more likely to disengage from care (50.4% versus, 33.7%, $p < 0.001$). Those who disengaged were younger with a mean age of 39 ($p < 0.001$). Non-Irish were more likely to disengage from care (65.2% versus 44.6%, $p < 0.001$). A higher proportion of patients who disengaged from care had not been receiving ART and did not have a suppressed HIV-1 viral load ($p < 0.001$).

On multivariable analysis, Irish patients were less likely to disengage from HIV care (OR, 0.567; CI, 0.397–0.811; $p = 0.002$). Those with a suppressed HIV-1 viral load were less likely to disengage from HIV care (OR, 0.191; CI, 0.128–0.284; $p < 0.001$).

Conclusion. From 2007 to 2014, 89% of those who attended our HIV clinic have retained in care. We have identified patients factors associated with non-engagement in HIV care in our cohort. A semi-structured patient interview will soon take place to gain a better understanding of patient factors associated with failure to retain in care.

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