A Cost-effectiveness Analysis of *Human Immunodeficiency Virus*, *Hepatitis B Virus*, and *Hepatitis C Virus* Screening in an Emergency Department in Ireland.

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

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DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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Dr Anna O'Rourke

April 2022

SUMMARY

Introduction: *Human Immunodeficiency Virus* (HIV), *Hepatitis B Virus* (HBV), and *Hepatitis C Virus* (HCV) are three bloodborne viruses (BBVs) with common modes of transmission. There are appreciable overlaps in affected population groups and high levels of dual infection (herein referred to as co-infection) and tri-infection. Integrated screening reflects existing patterns of service delivery (1). Treatment targets have been established by the World Health Organisation (WHO) and the Joint United Nations Progamme on HIV/AIDS (UNAIDS), and are aimed at eliminating these infections. A key strategy to reaching these targets is by screening for infection (2, 3).

Screening for HIV, HBV, and HCV is a well established healthcare intervention (4-6). The questions, however, of whom to screen (including general population screening versus high risk population screening), how frequently to screen, and in what setting to screen, remain debatable (4, 7, 8). In addition, while some programmes screen individuals for HIV, HBV, or HCV, screening for all three infections together is less common and less well studied. To our knowledge, there are no guidelines on general population screening for all three infections in the Emergency Department (ED) setting nationally or internationally.

A sentinel paper entitled *The principles and practice of screening for disease* by Wilson and Junger (1968) state that cost of case-finding (e.g. screening for HIV, HBV, and HCV) should be economically balanced in relation to possible expenditure on medical care as a whole (9). This founding principle has led to the requirement for data to assess cost-effectiveness of screening for HIV, HBV, and HCV amongst the general population and in an ED setting.

Cost-effective analyses (CEAs) can provide this cost-effectiveness data. CEAs can inform health care decision makers about which healthcare interventions to fund from available resources (10). Given the need for most healthcare systems to make resource allocation decisions across a whole range of disease areas, CEAs are increasingly being used. CEAs require decision modelling, and with that can come a degree of uncertainty. However, uncertainty within a model can be measured with sensitivity analysis (SA) (11).

Aims: The aim of this research was to perform a cost-effectiveness analysis (CEA) of screening for HIV, HBV, and HCV in the ED setting.

Methods: A bespoke cost-effectiveness model was developed for this CEA. This model reflected the lifetime pathways of patients attending an Irish healthcare setting. In the model, patients were either screened or not screened for HIV, HBV (Hepatitis B surface antigen/HBsAg), and HCV (Hepatitis C antibody±ribonucleic acid/Ab±RNA). The modelling approach used in this CEA was a Markov model. The model was informed by applicable and validated real-world practice in the form of the Emergency Department Viral Screen (EDVS) Programme. In addition, a targeted literature review of available national and international data was undertaken to inform the Markov model.

The EDVS Programme, established as routine practice in 2015 in a busy inner-city ED in a tertiary referral hospital in Dublin, offers opt-out screening for HIV, HBV, and HCV to all phlebotomised patients attending that ED. Data from the first five years of the EDVS Programme (July 2015 to June 2020 inclusive) was analysed and inputted into the Markov model.

The cost-effectiveness model was programmed in TreeAge Pro 2020® (TreeAge Software Inc, Williamstown, MA, USA). This model compared two interventions: the EDVS Screen strategy was compared to the No EDVS Screen strategy. *Guidelines for the Economic Evaluation of Health Technologies in Ireland* informed the CEA (12). Results were reported as incremental cost-effectiveness ratios (ICERs). Deterministic SA and probabilistic SA (PSA) were reported.

Results: The results of this CEA suggest that the ED setting in this jurisdiction was a high risk setting. Assuming payer-thresholds of €20,000/quality-adjusted life-year (QALY) and €45,000/QALY, screening for HIV, HBV, and HCV was cost-effective at our base-case combined seroprevalence of 4.8% (HIV, HBsAg, HCV Ab±RNA). The ICER was €9,130/QALY. The results were robust to SA. In addition, a one way SA (OWSA) confirmed that screening remained cost-effective when the combined seroprevalence (HIV, HBsAg, HCV Ab±RNA) ranged between 3.5% to 7.8% inclusive. Beyond these upper and lower ranges, screening was not cost-effective.

Conclusion: Cost-effectiveness model-based evaluations are a valuable resource for health care decision makers. The results of this CEA suggest that ED screening for HIV, HBV, and HCV was cost-effective at our base-case combined seroprevalence of 4.8%. Moreover, the SA highlighted that there is an upper and lower threshold at which ED screening for HIV, HBV, and HCV is cost-effective. The results suggest the benefit of screening for tri-infections. By performing this CEA, we can better reflect medical practice and provide better quality evidence for decision makers who are required to make difficult trade-offs between funding screening interventions or other health technologies.

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This thesis is dedicated to Kieran and Fionn.

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ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome

ALT: Alanine transaminase

Anti-HBe: Anti-Hepatitis B e antibody

AST: Aspartate transaminase

ART: Antiretroviral therapy

AASLD: American Association for the Study of Liver Diseases

BASHH: British Association of Sexual Health and HIV

BBV: Bloodborne virus

BHIVA: British HIV Association

CC: Compensated cirrhosis

cccDNA: Covalently closed circular DNA

CDC: Centre for Disease Control and Prevention

CEA: Cost-effectiveness analysis

CHI: Pearson's chi-squared test

CI: Confidence interval

CI: Contraindicated

COHP: Country of high prevalence

COVID-19: Coronavirus disease of 2019

CSO: Central Statistics Office

CUA: Cost utility analysis

DC: Decompensated cirrhosis

DAA: Direct-acting antivirals

DNA: Deoxyribonucleic acid

DNA: Did-not-attend

EACS: European AIDS Clinical Society

EASL: European Association for the Study of the Liver

ECDC: European Centre for Disease Prevention and Control

ED: Emergency Department

EDVS: Emergency Department Viral Screen

EE: Economic evaluation

EEA: European Economic Area

ETV: Entecavir

EU: European Union

EQ-5D: EuroQoL 5 dimensions

FISCHER: Fischer's exact test

HBeAg: Hepatitis B e antigen

HBsAb: Hepatitis B surface antibody

HBsAg: Hepatitis B surface antigen

HBV: Hepatitis B Virus

HCC: Hepatocellular carcinoma

HCV: Hepatitis C Virus

HCV Ab±RNA: Hepatitis C antibody±ribonucleic acid

HIQA: Health Information and Quality Authority

HIV: Human Immunodeficiency Virus

HPSC: Health Protection Surveillance Centre

HPTN: HIV Prevention Trials Network

HRQOL: Health-related quality of life

HSE: Health Service Executive

HTA: Health technology assessment

ICER: Incremental cost-effectiveness ratio

IDU: Injection drug use

IPHA: Irish Pharmaceutical Healthcare Association

IQR: Interquartile range

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

LT: Liver transplantation

LTC: Linkage to care

LTFU: Lost to follow up

MMP: Medical Monitoring Project

MSc: Master of Science

MSM: Men who have sex with men

MWU: Mann-Whitney U test

NA: Nucleos(t)ide analogue

NCPE: National Centre for Pharmacoeconomics

NHCTR: National Hepatitis C Treatment Registry

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NTCP: Sodium taurocholate co-transporting polypeptide

PCR: Polymerase chain reaction

PegIFN: Pegylated interferon

PEP: Post-exposure prophylaxis

PHE: Public Health England

PJP: Pneumocystis Jirovecii Pneumonia

PLD: Patient-level data

PLHIV: People who live with HIV

PrEP: Pre-exposure prophylaxis

PSA: Probabilistic sensitivity analysis

PWID: People who inject drugs

QALY: Quality-adjusted life-year

RAI: Receptive anal intercourse

rcDNA: Relaxed circular DNA

RCT: Randomised control trial

RNA: Ribonucleic acid

SA: Sensitivity analysis

SD: Standard deviation

SF-12: Short form 12

SF-36: Short form 36

SMDM: Society for Medical Decision Making

SVR: Sustained virologic response

TACE: Transarterial chemoembolisation

TDF: Tenofovir disoproxil fumarate

UK: United Kingdom

ULN: Upper limit of normal

UNAIDS: Joint United Nations Programme on HIV/AIDS

US: United States

WHO: World Health Organisation

RESEARCH OUTPUTS

Oral presentation

Cost-effectiveness analysis of screening for HIV, HBV, and HCV in an inner-city Emergency Department (ED).

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CHAPTER 1 BLOODBORNE VIRAL DISEASES AND THE EMERGENCY DEPARTMENT VIRAL SCREEN PROGRAMME

1.1 Introduction to thesis

HIV, HBV, and HCV are BBVs with common modes of transmission. There are appreciable overlaps in affected population groups and high levels of co-infection, and tri-infection. Integrated screening reflects existing patterns of service delivery (1). Treatment targets have been established by the WHO and the Joint United Nations Progamme on HIV/AIDS, and are aimed at eliminating these infections. A key strategy to reaching these targets is by screening for infection (2, 3).

Screening for HIV, HBV, and HCV is a well established healthcare intervention (4-6). The questions, however, of whom to screen (including general population screening versus high risk population screening), how frequently to screen, and in what setting to screen, remain debatable (4, 7, 8). In addition, while some programmes screen individuals for HIV, HBV, or HCV, screening for all three infections together is less common and less well studied.

In 1968, Wilson and Junger descsribed criteria for a screening programme, in a sentinel paper entitled *The principles and practice of screening for disease*. These criteria have been used for over 50 years to guided decisions regarding the establishment of screening programmes (13). The authors emphasised the important features of any screening programme. The authors state that cost of case-finding (e.g. screening for HIV, HBV, and HCV) should be economically balanced in relation to possible expenditure on medical care as a whole (9). This thesis is a study of the economic benefit of screening for HIV, HBV, and HCV.

In the paper by Wilson and Junger described above, the authors also state that the natural history and condition of a health problem should be understood (9). For this reason, in this thesis, Chapter 1 introduces the reader to each infection individually, and includes epidemiology, natural history, disease progression, and treatment options for each infection. An understanding of the natural hoistory and disease states of each infection will also allow the reader of this thesis understand the CEA model design and input parameters, including, for example, transition probabilities of each infection, and disease states. Chapter 2 of this thesis summarises current

screening recommendations at national, European, and international levels. Chapter 2 also introduces the reader to CEAs. Chapter 3 includes a description of the model structure used in this CEA. Chapter 4 describes the input parameters used in the model. Chapter 5 includes the results of this CEA.

1.2 Human Immunodeficiency Virus

1.2.1 Epidemiology

HIV was first identified as the infection that caused acquired immune deficiency syndrome (AIDS) in 1983, two years after AIDS was first identified as a syndrome (14-17). In 2020, according to WHO/UNAIDS estimates, there are 37.7 million people who live with HIV (PLHIV) globally (18).

Since the HIV epidemic began, an estimated 75.7 million people have become infected worldwide (19). The WHO African region remains the most severely affected region worldwide, with nearly one in every 25 adults in that region (3.6%) living with HIV, accounting for more than two-thirds of PLHIV globally. While the numbers of new infections have decreased since 2010, there were 1.5 million people newly infected with HIV in 2020, and 680,000 deaths from HIV-related causes globally in 2020 (20) (Figure 1.1).

Figure 1.1: Summary of the global HIV epidemic 2020.

	PLHIV IN 2020	PEOPLE ACQUIRING HIV IN 2020	PEOPLE DYING FROM HIV-RELATED CAUSES IN 2020
TOTAL	**37.7 million (30.2 – 45.1 million)**	**1.5 million (1.0 – 2.0 million)**	**680,000 (480,000 – 1.0 million)**
ADULTS (15+ YEARS)	36.0 million (28.9 – 43.2 million)	1.3 million (910,000 – 1.8 million)	580,000 (400,000 – 850,000)
WOMEN (15+ YEARS)	19.3 million (15.5 – 23.1 million)	660,000 (450,000 – 920,000)	240,000 (170,000 – 360,000)
MEN (15+ YEARS)	16.7 million (13.3 – 20.1 million)	640,000 (460,000 – 890,000)	340,000 (230,000 – 490,000)
CHILDREN (< 15 YEARS)	1.7 million (1.2 – 2.2 million)	150,000 (100,000 – 240,000)	99,000 (68,000 – 160,000)

HIV indicates Human Immunodeficiency Virus; **PLHIV**: people who live with HIV.

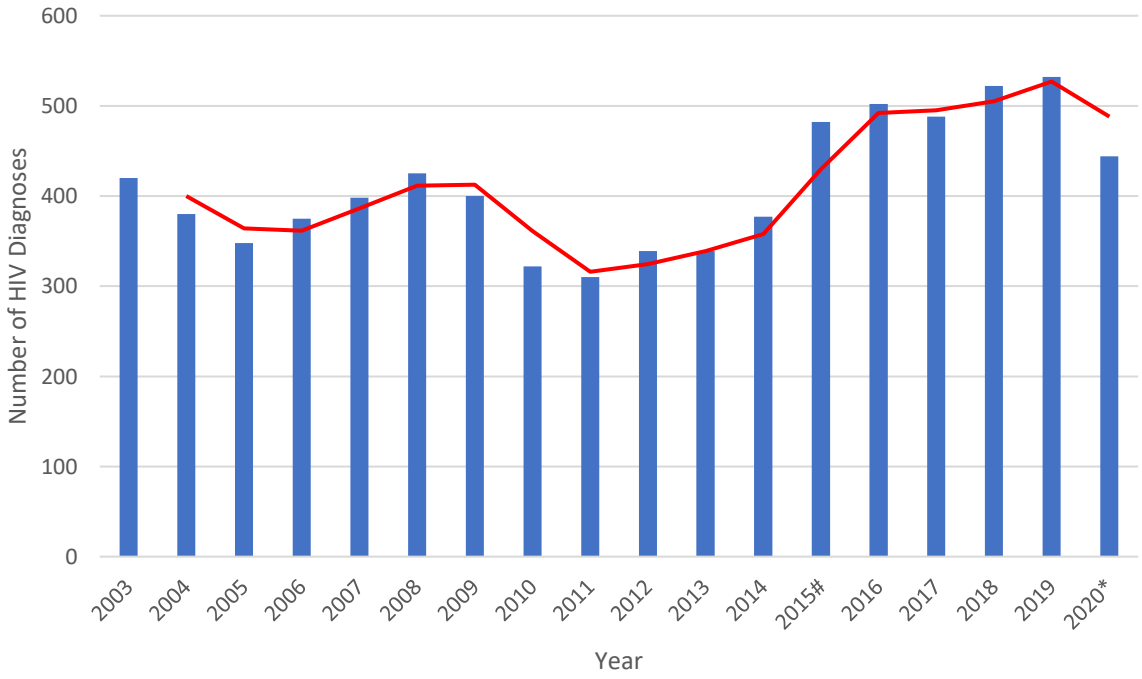
Source: Adapted from WHO/UNAIDS Global HIV/AIDS Statistics (19).

In 2014, UNAIDS and partners launched the 90-90-90 programme. This was a treatment target aimed at ending the AIDS epidemic by 2020 (2). The treatment targets were to have 30 million people globally on HIV treatment by 2020, with 90% of PLHIV aware of their diagnosis, 90% on antiretroviral therapy (ART), and 90% virally suppressed. In reality, in 2020, globally, 84% of PLHIV knew their HIV status, 87% of these people were accessing ART, and 90% of people on ART were virally suppressed (19).

In Ireland, the Health Protection Surveillance Centre (HPSC) provisionally reported 444 new HIV diagnoses in 2020 (9.3 per 100,000 population) (21). This was a 17% decrease nationally compared to 2019 (Figure 1.2). The HPSC assumed that the number of new HIV diagnoses in 2020 was likely impacted by the Coronavirus disease of 2019 (COVID-19) pandemic. The number of new HIV diagnoses in 2020 was lower than the previous five years.

The HPSC does not cite any studies to support this assumption regarding the COVID-19 pandemic and lower rates of new HIV diagnoses rates during 2020 (21). This assumption is possibly due to lower rates of migration during the COVID-19 pandemic, and is supported by anecdotal evidence from the Department of Genitourinary Medicine and Infectious Diseases in St James's Hospital, Dublin. This department has noted that the number of new HIV diagnoses, in particular new diagnoses amongst MSM from South America attending for ambulatory HIV care, has dropped significantly during the COVID-19 pandemic. Further study is needed in this area however.

Figure 1.2: Trend in new HIV notifications in Ireland, 2003 – 2020.



HIV indicates Human Immunodeficiency Virus.

Case definition changed in 2015.
* Number of new notifications impacted by COVID-19 pandemic.
Red line represents trendline of notifications year-on-year.

Source: Adapted from *HIV in Ireland: Latest trends including 2019 and 2020 provisional data report* (2021), HPSC (21).

HIV has multiple modes of transmission, and is predominantly transmitted through sexual intercourse or exposure to contaminated blood (22). In 2020, 79% of new diagnoses of HIV in Ireland were amongst men. The most common route of transmission in 2020 was amongst men who have sex with men (MSM) (21).

HIV is more prevalent in patients with HBV or HCV (23, 24). In the most up-to-date data available from the HPSC, of all the new HIV diagnoses in 2018, 3.3% of people with newly diagnosed HIV were co-infected with HBV and 4.6% were co-infected with HCV (25).

1.2.2 Virology

HIV is a single-stranded ribonucleic acid (RNA) retrovirus. It distinguishes itself from other RNA viruses by its ability to replicate through a deoxyribonucleic acid (DNA) intermediate using a unique enzyme called reverse transcriptase.

HIV infects human $CD4^+$ cells, for example T-lymphocytes. The HIV surface protein gp-120 binds to cellular $CD4^+$ co-receptors (predominantly CCR5 or CXCR4) on susceptible cells in the host. Enzymes including reverse transcriptase and RNAase enzymes convert HIV viral RNA to double-stranded DNA. This process is called reverse transcription. This newly formed viral DNA is then inserted by another HIV enzyme, viral integrase enzyme, into the genetic material of the infected cell in the host. This process is called integration. After integration, the new genetic material in the infected cell of the host is transcribed into new RNA, sometimes called messenger RNA, when the cell is appropriately stimulated. This process is under the control of viral regulatory proteins. This process is called transcription. Some of these proteins along with other RNA molecules are incorporated into the newly formed viral proteins. This process is called translation (26).

Viral assembly is the next stage in HIV viral replication. During this process, HIV protease enzyme cleaves these newly formed precursor viral proteins. The new mature viral proteins are incorporated into a new virion and assemble, and bud from the plasma membrane. This process is called budding. As the virions bud, the viral protease enzyme cleaves HIV polyproteins into individual subunits. These subunits are then free to infect more helper T-lymphocytes and other cells containing $CD4^+$ proteins, to include macrophages and dendritic cells. This process is called maturation (26). Many of the enzymes involved in the viral replication of HIV are the target of ART. The life cycle of HIV is summarised in Appendix 1.

There are two main types of HIV: HIV-1 and HIV-2. HIV-1 is the most common worldwide, with HIV-2 more common in West Africa. Each type can be further broken down into groups which themselves can be further divided into clades or subgroups.

1.2.3 Natural History

The clinical course of HIV (HIV-1) infection can vary widely amongst individuals. The Centre for Disease Control and Prevention (CDC) in the United States (US) and WHO both have case definitions based on $CD4^+$ count and clinical stage of HIV (27, 28). These definitions are used for surveillance purposes. The four stages of HIV infection defined by the CDC are:

1) Acute Retroviral Syndrome: This is an illness with flu-like symptoms, like infectious mononucleosis. It can occur a few days and up to several weeks after the person is infected with HIV. Symptoms of acute retroviral syndrome can range from mild to severe and usually resolve after two to three weeks. Most people may develop mild symptoms or no symptoms at all.

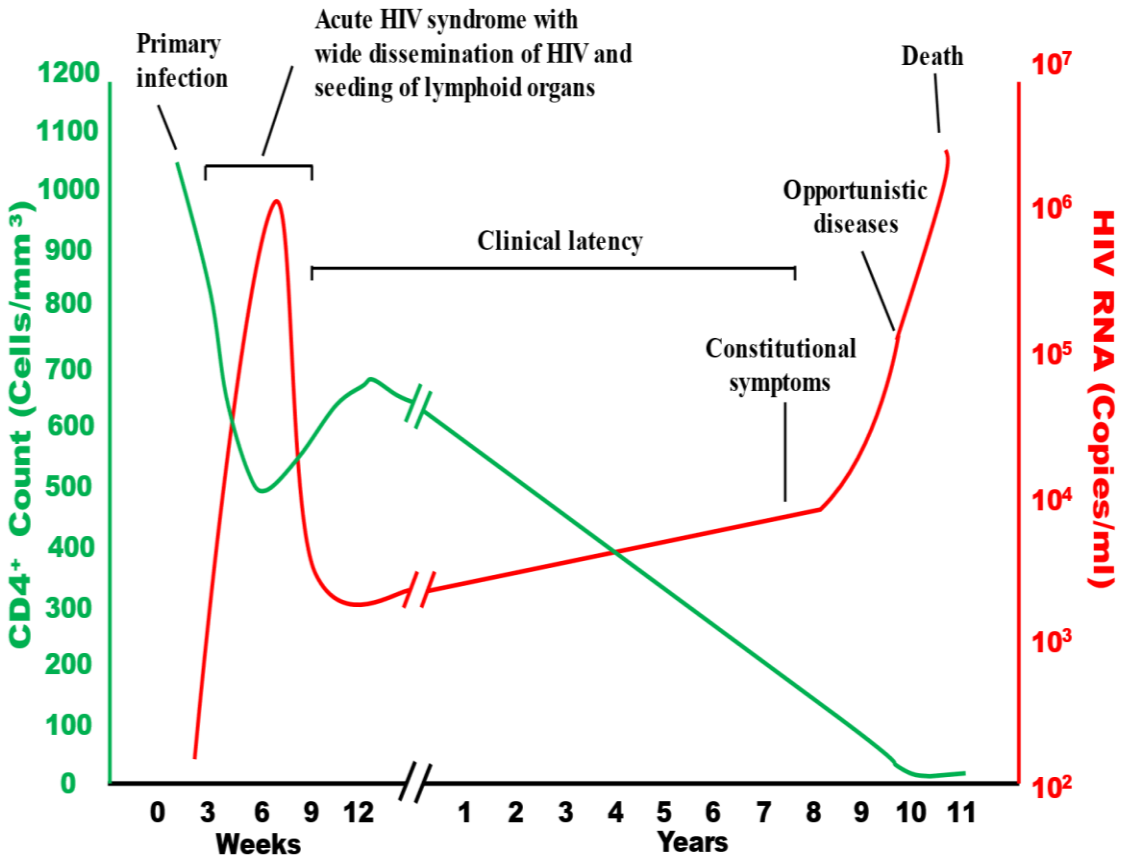
2) Stage 1 (HIV infection): At this stage of HIV infection, the $CD4^+$ cell count is at least 500 cells/mm^3 or the percent of $CD4^+$ cells is at least 29% of all lymphocytes. There are no AIDS-related clinical conditions present.

3) Stage 2 (HIV infection): At this stage of HIV infection, the $CD4^+$ cell count is between 200 cells/mm^3 to 499 cells/mm^3 or the percent of $CD4^+$ cells is 14% to 28% of all lymphocytes. There are no AIDS-related clinical conditions present.

4) Stage 3 (AIDS): At this stage of HIV infection, the $CD4^+$ cell count is less than 200 cells/mm^3 or the percent of $CD4^+$ cells is less than 14% of all lymphocytes. There may or may not be an AIDS-related clinical condition present (27).

The natural history of HIV infection is outlined in Figure 1.3.

Figure 1.3: Natural history of HIV infection.



HIV indicates Human Immunodeficiency Virus; **RNA**: ribonucleic acid.

Source: Adapted from HIV PHC Manual 2019, Shah *et al* (29).

Viral transmission can occur predominantly via sexual intercourse or contaminated blood. Risk factors for acquisition are many, and can include a high HIV viral load, high risk sexual practices, presence of concurrent sexual transmitted infections, lack of circumcision, and more specific host and genetic risk factors (30-32). In the absence of ART, patients can transmit HIV to an uninfected person during any phase of infection (32).

1.2.4 Disease States and Treatment

Zidovudine was the first ART to be licenced to treat PLHIV in 1987. It initially demonstrated benefit in patients with AIDS. It subsequently demonstrated efficacy amongst patients with chronic HIV without AIDS (33-35).

Another major development occurred in 1996 when the first unequivocal evidence of the superiority of combination ART over monotherapy was published (36, 37). Following 1996, a progressive and rapid number of highly active antiretroviral therapies (HAART) became available.

Two studies that had major implications globally for the treatment of HIV were the SMART trial (2006) and the START trial (2015) (38, 39). In 2006, the SMART trial concluded that staying on ART was better than interrupting it (38). In 2015, the START trial concluded that all PLHIV should commence ART regardless of their $CD4^+$ counts (39). Prior to that, commencement of ART was dictated by a patient's $CD4^+$ count.

Currently, there are seven major classes of ART: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, post-attachment inhibitors, and integrase strand transfer inhibitors (INSTIs). In the most up-to-date guidelines from the European AIDS Clinical Society (EACS) entitled *EACS Guidelines 2021*, amongst treatment naïve PLHIV, the first line treatment recommendations include either two NRTI and one INSTI, one NRTI and one INSTI, or two NRTIs and one NNRTI. There are caveats to these recommendations however (40).

The benefits of ART are well recognised. In Ireland, according to a national treatment audit in 2017 that analysed 5,277 PLHIV on ART, 95% of PLHIV achieved viral suppression. Commencement of ART immediately after diagnosis is now seen as a key preventative measure as over 50% of HIV transmissions are from people who are undiagnosed (41). The HIV Prevention Trials Network (HPTN) 052 Study has shown that ART for HIV positive individuals in a serodiscordant relationship resulted in a 96% reduction in HIV transmission to a seronegative heterosexual partner (42). Since then, the Partner Study has shown that no phylogenetically-linked HIV transmission occurred amongst 1,114 MSM and heterosexual serodiscordant couples enrolled during median follow up of 1.3 years per couple (43).

ART can be used as a preventive measure against HIV acquisition. Post exposure prophylaxis (PEP) is the use of short-term ART to reduce the risk of acquisition of HIV infection following a potential exposure (44). While it has not been possible to demonstrate the benefits of PEP in

large prospective randomised control trials (RCTs) due to ethical reasons, initiation of ART has been shown to reduce dissemination and replication of virus in tissues if initiated early in macaque animal models (45). Observational data exists on the effectiveness of PEP in the setting of PEP following sexual exposure (PEPSE) and occupational exposure to HIV (46, 47).

Pre-Exposure Prophylaxis (PrEP) is ART offered to HIV-uninfected individuals to prevent acquisition of HIV infection (48). In 2012, the WHO recommended PrEP for serodiscordant HIV couples and MSM. This recommendation came with the condition that observational registry data was needed to ascertain optimal delivery approaches and optimal target groups (49). In 2014, these WHO recommendations were integrated into consolidated HIV guidelines for key target groups, entitled *Guidelines on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV*. These guidelines include a strong recommendation for offering PrEP as a HIV prevention option for MSM (50). PrEP became available in Ireland in 2017. It is now offered to patients as standard of care for preventing acquisition of HIV (51).

Effective ART has transformed HIV into a chronic and manageable condition. Normal life-expectancy has been reported amongst PLHIV who are virally suppressed on ART (52). Beyond viral suppression, PLHIV have reported improved quality of life outcomes (53). However, access to a timely diagnosis and engagement in care are key to maximising outcomes amongst PLHIV. Late presentation to care has been associated with increased rates of AIDS and increased rates of death, particularly within the first year of diagnosis (54).

1.3 Hepatitis B Virus

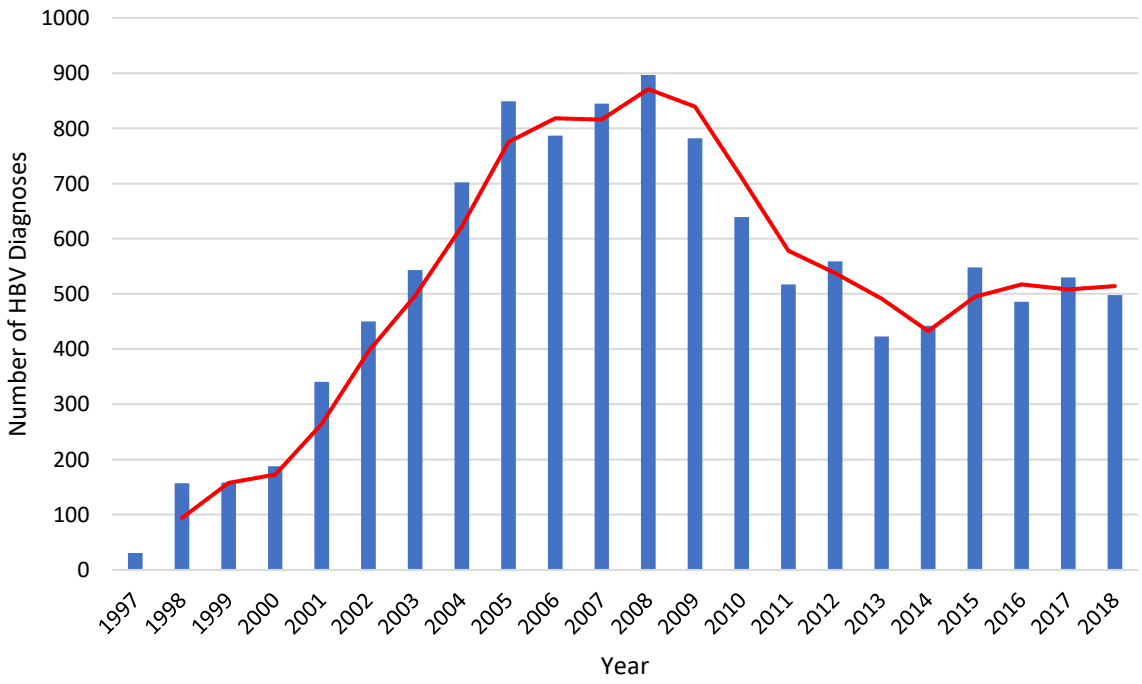
1.3.1 Epidemiology

HBV was first discovered in 1965. A significant breakthrough was made in 1982, when the first HBV commercial vaccine became available (55). In 2020, the majority of people living with HBV were born before HBV vaccination became widely available and administered in infancy. In 2019, a WHO global report estimates there are 296 million people living with chronic HBV (defined as HBV surface antigen (HBsAg) positivity), with 1.5 million new infections diagnosed annually (56).

In 2019, the WHO estimated that HBV caused 820,000 deaths globally, primarily due to liver cirrhosis and hepatocellular carcinoma (HCC). In 2019, the WHO estimated that globally 30.4 million people (10.5% of all people estimated to be living with HBV) were aware of their diagnosis, while 6.6 million (22%) of the people diagnosed were on appropriate treatment (56).

In Ireland, according to the most up-to-date available data from the HPSC, in 2018, there were 496 new notifications of HBV, with a crude rate of 10.4 per 100,000 population (Figure 1.4) (57).

Figure 1.4: Trend in new HBV notifications in Ireland, 1997 - 2018.



HBV indicates Hepatitis B Virus.

Red line represents trendline of notifications year-on-year.

Source: Adapted from *Annual Epidemiological Report for Hepatitis B 2018, HPSC* (57).

In Ireland in 2018, 95% of the HBV cases notified were chronically infected. Most chronically infected cases were amongst people who had migrated to Ireland from countries of high prevalence (COHP). A large proportion of these people were likely to have been infected at birth or in early childhood (57).

HBV is a BBV. The most common mode of transmission worldwide is mother to child transmission at birth. Other modes of transmission include injection drug use (IDU) or unsafe

injection practices, sexual practices that lead to exposure of blood, and unsafe healthcare or cosmetic practices (56). Amongst the identified risk factors in Ireland in 2018, the majority of acute HBV diagnoses were sexually acquired (48%). In that same year, the most common mode of acquisition amongst those identified to be chronically infected was mother to child transmission (57).

HBV is more prevalent in patients with HIV or HCV than in patients without HIV or HCV (23, 24). In 2018, 3% of HBV notifications were co-infected with HIV and 1% of HBV notifications were co-infected with HCV (57).

1.3.2 Virology

HBV is a double-stranded DNA virus and a member of the *Hepadnaviridae* family (58). The life cycle of HBV is dependent upon reverse transcription of a longer than full length RNA copy (59). Thus, HBV is a *Orthohepadnavirus* with a DNA genome. HBV is also the major aetiological agent of HCC, despite containing no known oncogenes. There have been ten types of HBV genotypes identified (A to J inclusive) and these genotypes vary geographically (60).

The HBV life cycle is a complex one. Initially, HBV viral envelope proteins interact with specific sodium taurocholate co-transporting polypeptide (NTCP) receptors on the plasma membrane of hepatocytes. This interaction triggers entry, uncoating, and endocytosis into the hepatocyte (61). The virion DNA undergoes translocation to the nucleus in the form of relaxed circular DNA (rcDNA). This viral DNA is converted to covalently closed circular DNA (cccDNA). CccDNA is the stable form of HBV DNA that is responsible for its persistence in infected hepatocytes and transmission to progeny cells. Transcription of the cccDNA into the viral RNA gene products then occurs. Following transcription, encapsidation into the cytoplasm, virion morphogenesis and secretion occur. Auto amplification can also occur when replicated progeny HBV DNA return to the nucleus by way of an intracellular pathway. HBV DNA sequences can integrate and can contribute to viral persistence (61, 62). The life cycle of HBV is summarised in Appendix 2.

1.3.3 Natural History

The clinical presentation of HBV infection can vary in both the acute and chronic phases. Acute HBV can present subacutely (63). Some patients however can present with symptoms and signs of hepatitis and rarely can present with fulminant hepatitis (64). Because chronic HBV infection is a dynamic process, there are different phases of infection. Patients may not experience all four phases, and the phases may not necessarily be sequential (63). The four phases defined by European Association for the Study of the Liver (EASL) are:

1) Phase 1: Hepatitis B e antigen (HBeAg) positive chronic HBV, previously termed ‘‘immune tolerant’’ phase, is an illness with flu-like symptoms, like infectious mononucleosis. This phase is characterised by the presence of serum HBeAg, very high levels of HBV DNA, and alanine transaminase (ALT) levels persistently within normal ranges. While necroinflammation and fibrosis may not be occurring in the liver, hepatocarcinogenesis may already be underway.

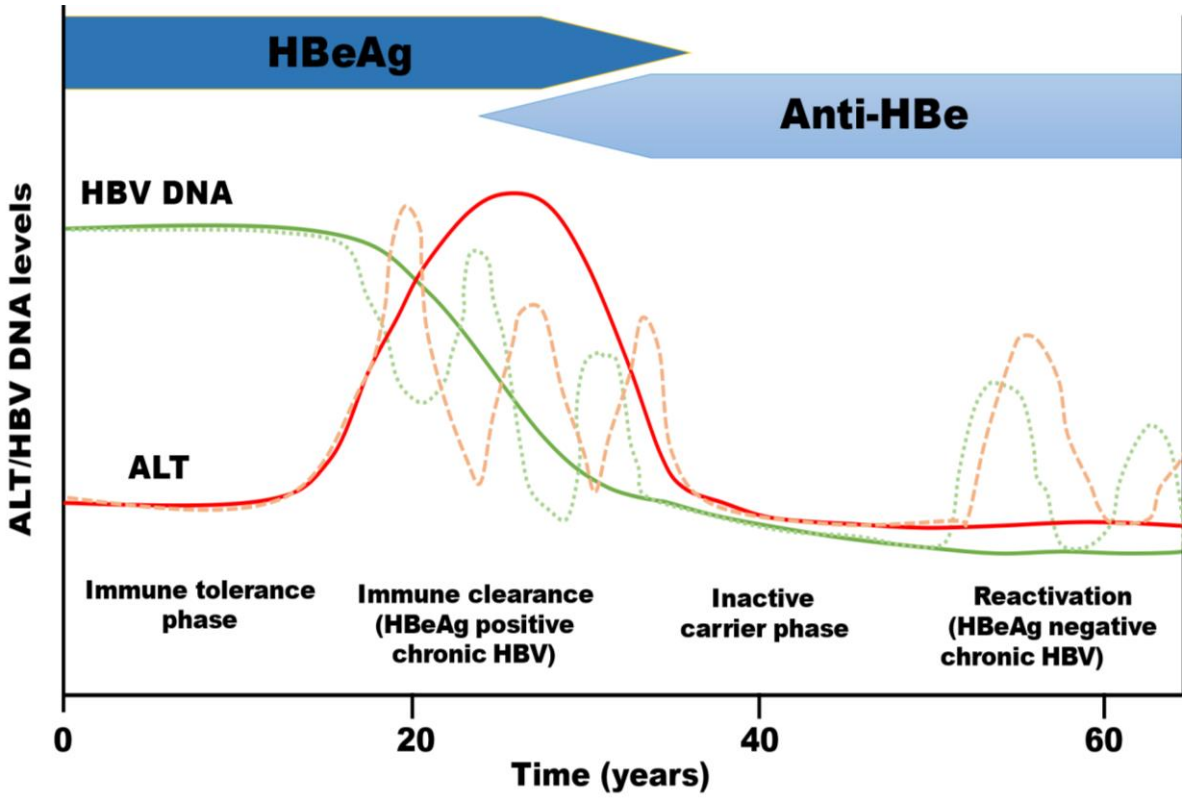
2) Phase 2: HBeAg positive chronic HBV is characterised by the presence of serum HBeAg, high levels of HBV DNA, and elevated ALT. Necroinflammation and fibrosis are occurring in the liver at moderate to severe rates.

3) Phase 3: HBeAg negative chronic HBV, previously termed “inactive carrier” phase, is characterised by the presence of serum antibodies to HBeAg (anti-HBe), undetectable or low HBV DNA levels and normal ALT. This may be accompanied by no or minimal necroinflammation and fibrosis.

4) Phase 4: HBeAg negative chronic HBV is characterised by the lack of serum HBeAg usually with detectable anti-HBe, and persistent or fluctuating moderate to high levels of serum HBV DNA as well as fluctuating or persistently elevated ALT. Liver histology during this phase shows necroinflammation and fibrosis (65).

The natural history of HBV infection is outlined in Figure 1.5.

Figure 1.5: Natural history of HBV infection.



HBV indicates Hepatitis B Virus; **HBeAg**: HBV e antigen; **Anti-HBe**: Aspartate transaminase; **ALT**: alanine transaminase; **DNA**: deoxyribonucleic acid.

Source: Adapted from Management of Hepatitis B, Yapali *et al* (63).

Both virologic and non-virologic factors affect disease progression in patients with chronic HBV (66). Non-virologic factors include sex, alcohol consumption, obesity, and concomitant infection with other hepatic viruses including HCV (66, 67). Virologic factors include HBeAg status, the HBV DNA and HBsAg levels, and the HBV genotype (66). The outcome of chronic HBV infection depends upon the severity of liver disease at the time the HBV replication is arrested. HBV can cause necroinflammation of the liver, fibrosis, cirrhotic liver disease and HCC (66).

1.3.4 Disease States and Treatments

Amongst patients with chronic HBV, without treatment and engagement in care, liver disease progresses at much higher rates, resulting in higher rates of cirrhotic liver disease and HCC. Several studies from the pre-nucleos(t)ide analogue era estimate that compensated cirrhosis (CC) occurs between 12% to 20 % of people with HBV at five years. Progression rates at five

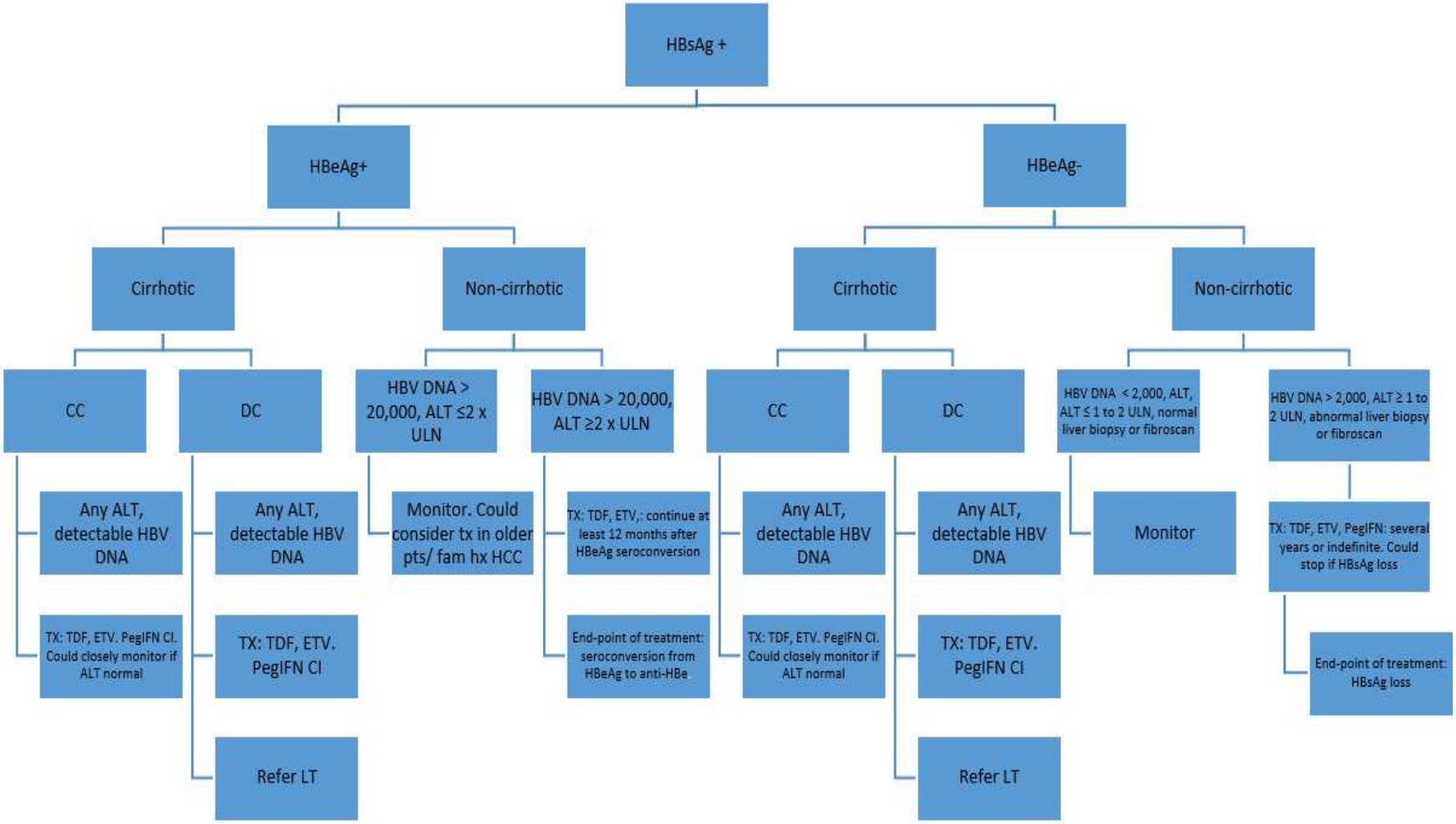
years from CC to decompensated cirrhosis (DC) are between 20% to 23% and to HCC are between 6% to 15% at five years amongst patients with DC (66). The lifetime risk of a liver-related death in untreated patients has been estimated to be between 40% to 50% for men and 15% for women (66).

The main goal of treatment for patients with chronic HBV is to improve survival and quality of life by preventing disease progression and complications (65). HCC and DC may result in the need for liver transplantation (LT). The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, the ALT level, and the HBV DNA level. Exceptions include treatment in pregnancy and patients who are immunosuppressed (65).

Pharmacological and non-pharmacological treatment responses can be divided into virological, serological, biochemical, and histological responses. If pharmacological treatment is indicated, it involves either forty-eight weeks of pegylated-interferon (PegIFN, not recommended in DC) or nucleos(t)ide analogues (NA). NAs with high barriers to viral resistance are preferred. These include tenofovir disoproxil fumarate (TDF) and entecavir (ETV). Patients who do not meet the threshold to commence treatment should be monitored for disease progression and/or complications (65).

Endpoints of pharmacological treatment include the induction of long-term suppression of HBV DNA. In patients who are HBeAg positive, the loss of HBeAg with or without anti-HBe seroconversion represents partial immune control and is a valuable endpoint. In addition to HBV markers, the normalisation of ALT is an important biomarker in patients who achieve HBV DNA suppression. HBsAg loss with or without Hepatitis B surface antibody (HBsAb) seroconversion is an optimal endpoint. This indicates profound suppression of HBV replication and viral protein expression (65). Figure 1.6 depicts the HBV treatment algorithm for chronic HBV.

Figure 1.6: Treatment algorithm for chronic HBV (65).



HBV indicates Hepatitis B Virus; **HBsAg**; Hepatitis B surface antigen; **HBeAg**: Hepatitis B e antigen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **ALT**: alanine transaminase; **DNA**: deoxyribonucleic acid; **TDF**: tenofovir disoproxil fumarate; **ETV**: entecavir; **PegIFN**: pegylated interferon; **CI**: contraindicated; **LT**: liver transplantation; **ULN**: upper limit of normal; **HCC:** hepatocellular carcinoma; **Anti-HBe**: anti-Hepatitis B e antibody; **pts**: patients; **fam hx**: family history.

Local practice in Ireland, informed by the EASL *Guidelines on the Management of HBV infection* (2017), recommends using TDF as first line pharmacological treatment for chronic HBV (65). Marcellin *et al* report that amongst a cohort of patients on TDF who were HBeAg positive or HBeAg negative, 99.3% maintained virological suppression and 80% achieved normal ALT at seven years follow up. Regression of fibrosis and cirrhosis in this treated cohort was seen in 51% and 28% of patients respectively (68). Marcellin *et al* report that the annual HCC incidence for patients on TDF is estimated to be 0.37% per year in patients without cirrhosis and 0.65% per year amongst patients with cirrhosis (69).

Patients with chronic HBV who develop HCC or DC may require LT. In Europe over the last 50 years, the most frequent indication for LT was due to DC (50%) (70). Of the patients with DC who received LT, 5% had chronic HBV resulting in DC. Of the patients with HCC who received LT, chronic HBV was the aetiology of HCC in 16% of patients. The one year all cause survival rate post LT is 86% in Europe (70). In Ireland, the one year all cause survival rate post LT is 93% and the five year survival is 79% (71).

1.4 Hepatitis C Virus

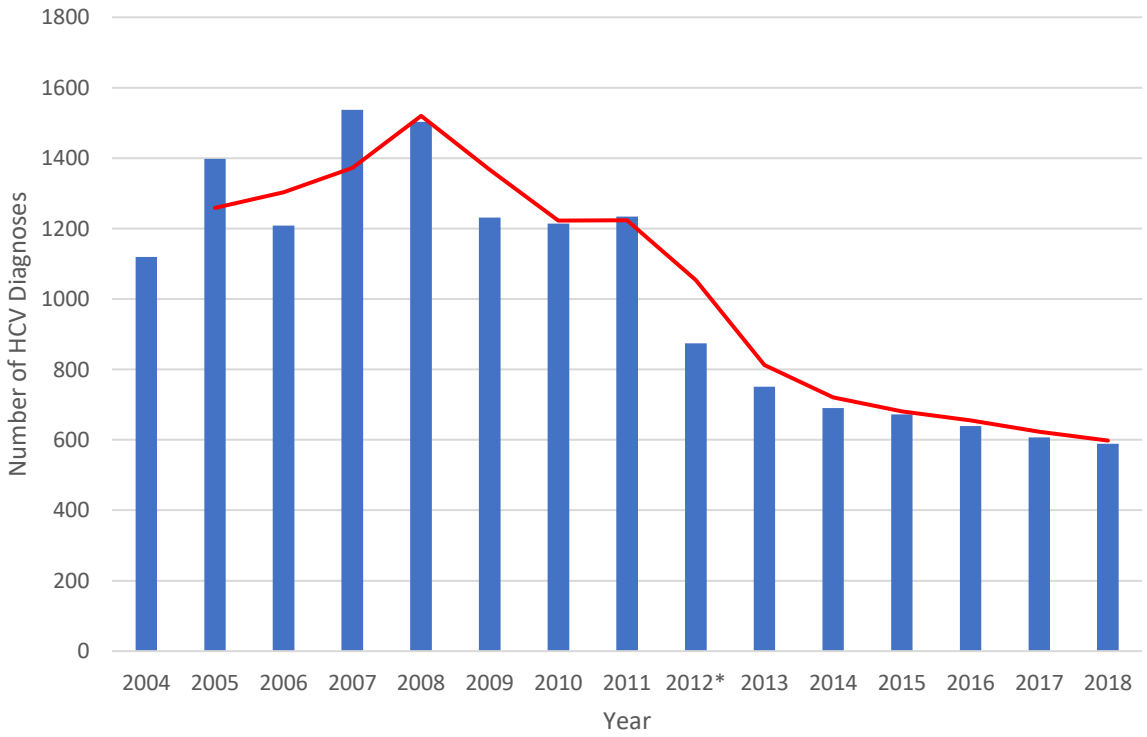
1.4.1 Epidemiology

HCV was first identified in 1989. Prior to that HCV was known as non-A non-B Hepatitis. Globally, 58 million people worldwide are living with chronic HCV with approximately 1.5 million new infections occurring each year (72).

In 2019, the WHO estimated that HCV caused 290,000 deaths globally, primarily due to DC and HCC. While approximately 30% of people clear the virus within the first six months of acquisition, the remainder will go on to develop chronicity. With the advent of direct-acting antiviral (DAA) medications, cure rates can be over 95%. However, access to diagnosis and treatment worldwide is low (72). The WHO estimates that of the 58 million people living with HCV infection globally in 2019, 15.2 million (21%) knew their diagnosis, and approximately 9.4 million (16%) of people have been treated with DAAs (72).

In Ireland, according to the most up-to-date available data, in 2019, there were 474 new notifications of HCV, with a crude rate of 10 per 100,000 population (73). Rates of infection are declining since 2012. However, rates of decline are slowing (Figure 1.7).

Figure 1.7: Trend in new HCV notifications in Ireland, 2007 - 2019.



HCV indicates Hepatitis C Virus.

*Case definition changed in 2012 – cases known to be resolved excluded from notification.
Red line represents trendline of notifications year-on-year.

Source: Adapted from *Annual Epidemiological Report for Hepatitis C 2019,* HPSC (73).

HCV has multiple modes of transmission. The most common mode of transmission is through exposure to blood. This is commonly as a result of IDU or unsafe injection practices, non-injection drug use that leads to exposure to blood, sexual practices that lead to exposure to blood, unsafe healthcare or cosmetic practices or vertical transmission (73). In Ireland amongst those who reported risk factors for acquisition of HCV in 2019, 67% of new notifications were amongst people who inject drugs (PWID) (73).

HCV infection is prevalent in patients with HIV or HBV (23, 24). In 2019, 4% of HCV notifications were co-infected with HIV and 1% of HCV notifications were co-infected with HBV. Of these new HCV notifications, 0.35% were tri-infected with HIV, HBV, and HCV.

1.4.2 Virology

HCV is a single-stranded RNA virus and belongs to the *Flavivirus* family. The life cycle of the virus is only partly understood, mainly due to difficulties in establishing an in-vitro model of replication because of a complex network of cell surface molecules (74).

The first process of the HCV life cycle is called the attachment phase. During the attachment phase, the HCV virion, bound by lipoproteins, interacts with several receptors on the target cell membrane of the hepatocyte. Entry into the cell occurs via clathrin-mediated endocytosis. This is the next process. Fusion and uncoating then occur when the viral and cellular membranes fuse. After uncoating, the positive-strand RNA genome is released into the cytoplasm and translation occurs using host and viral enzymes. The next process is membrane associated RNA replication. Replication results in multiple copies of the HCV viral RNA. The process of virion morphogenesis occurs next. Assembly and maturation of the virions take place in the endoplasmic reticulum. The virions are released from the cells most likely by exocytosis or transmitted to other cells via a cell-free mechanism (Appendix 3) (75).

HCV shows enormous genomic sequence variability (74). There are six major HCV genotypes, (one to six inclusive), each comprising multiple subtypes. Substantial regional differences exist in the distribution of HCV genotypes (76). While genotype is not an indicator of clinical impact, it is taken-into-account with respect to treatment choice (77).

1.4.3 Natural History

The transition from the acute to the chronic phase of HCV is predominantly subclinical. While all patients with both acute and chronic HCV will develop HCV antibodies, this does not confer immunity, and the risk of re-infection after clearance of acute HCV remains a possibility (78).

Chronic HCV infection causes hepatic inflammation, fibrosis, and cirrhosis. These are dynamic processes and depend on the host, the virus, and the environment. Progression to fibrosis and cirrhosis may take decades (74). Individual outcomes can be highly variable; in particular, co-infection with HIV or HBV can accelerate complications (79).

1.4.4 Disease States and Treatment

The end-stage consequence of fibrosis progression is cirrhosis of the liver. Cirrhosis of the liver progresses to DC. Fibrosis, measured commonly using a METAVIR scoring system, ranges from no fibrosis (F0) to cirrhosis (F4). Another sequela of chronic HCV is HCC. These disease states can result in the requirement for LT, and more commonly, death (77).

Amongst patients who are not engaged in care, progression to DC and HCC can be rapid. Thein *et al* reported a large meta-analysis of patients with chronic HCV, analysing the risk of progression to complications of HCV infection (80). The authors concluded that the risk of progression from fibrosis to cirrhosis after 20 years of untreated HCV was between 7% to 18% inclusive. This number rose to 41% after 30 years of infection (80).

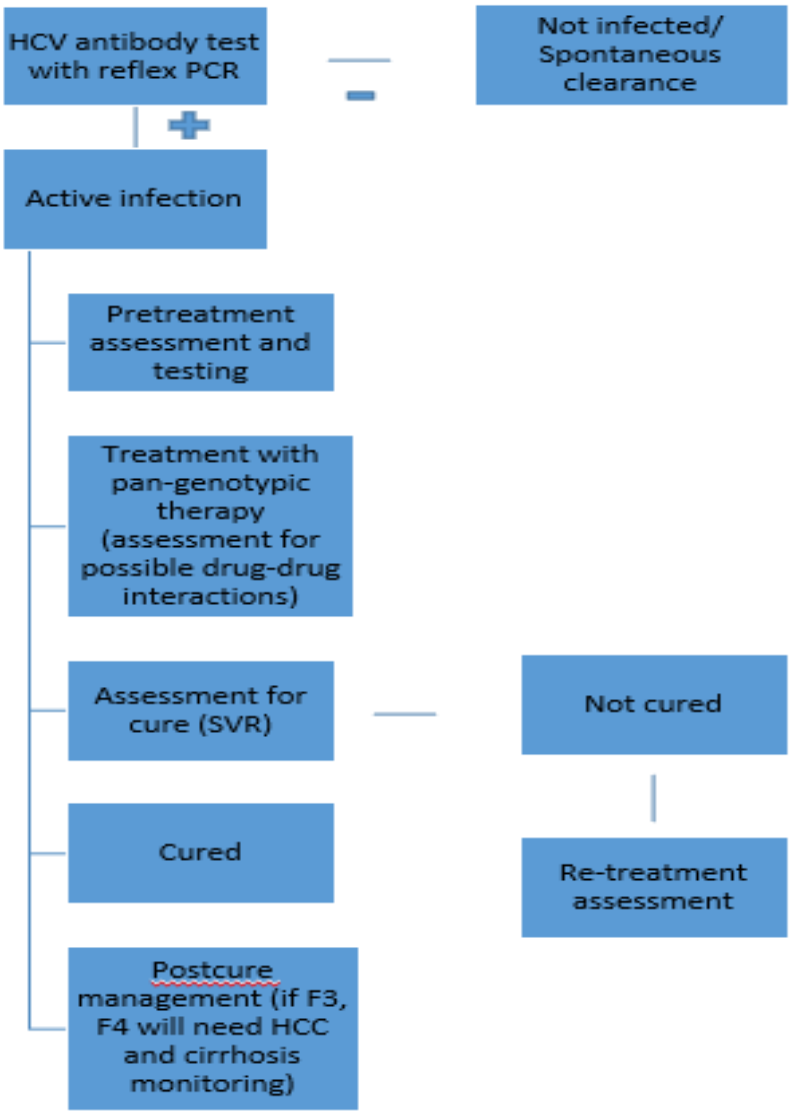
Patients who have cirrhosis are high risk for DC. Xu *et al* reported the five year risk of progressing from CC to DC to be between 27.7% to 39.5% inclusive (81). Amongst patients with cirrhosis, the one year risk of developing HCC was between 2.8% to 7.4% inclusive and the five year risk was between 8% to 16.1% inclusive. Amongst patients with DC, Thein *et al* reported the one year mortality to be between 15% to 20% (80). The one year survival for HCC all stages was reported by Greten *et al* to be 49% and reduced to 19% at three years (82).

Amongst patients with chronic HCV, DC and HCC may eventually result in the requirement for LT. Iqbal *et al* reported outcomes amongst 935 liver transplants in 806 patients who received LT in Ireland, from 1993 to 2015 inclusive (71). The survival rate post LT was 93% at one year, 79% at five years, and 68% at 10 years. The authors also reported the indications for LT during 2013 to 2014 inclusive. Of all patients who received LT, 21% and 27% of patients had required the transplant because of HCV and HCC respectively (71).

According to Irish data analysed by the National Centre for Pharmacoeconomics (NCPE) from the National Hepatitis C Treatment Registry (NHCTR), 6,358 patients were registered for treatment with DAA (January 2015 to February 2020 inclusive). Of all patients with available data who completed treatment during that timeframe, 96% of patients achieved a cure (i.e. sustained virologic response/SVR) (83). Overall SVR rates worldwide with DAAs are reported to be 95% and over (84-86).

Treatment of HCV has evolved significantly over the last decade. In 2016, the WHO set a goal to eliminate HCV by 2030 (3). In Ireland in 2014, DAA-containing regimens were approved for use. In 2015, the National Hepatitis C Treatment Programme (NHCTP) was established by the Health Service Executive (HSE) (87). Access to DAA treatment for patients with HCV was initially based on clinical prioritisation criteria. Subsequently, national and international guidelines (the WHO report, 2016, entitled *Combating Hepatitis B and C to Reach Elimination by 2030)* recommended that all people living with HCV should be assessed for treatment with DAAs, including PWID, and that access to treatment should no longer be based on clinical prioritisation criteria (3). Figure 1.8 shows a treatment algorithm for HCV.

Figure 1.11: Treatment algorithm for chronic HCV (77).



HCV indicates Hepatitis C Virus**; PCR**: polymerase chain reaction; **SVR**: sustained virologic response; **F3**: METAVIR fibrosis score 3; **F4**: METAVIR fibrosis score 4. **HCC**: hepatocellular carcinoma.

Following the introduction of DAAs to the treatment of HCV, Razavi *et al* reported that the total number of HCV infections was projected to decline in nearly every country studied. The authors concluded that this was likely due to a reduction in risk factors for new infections (e.g. screening of blood supply), ageing of the infected population (and the corresponding increase in mortality), and treatment of infected individuals (88). The authors also reported that, even though the total number of infected individuals was expected to decline, those who remained

infected were expected to progress to more advanced stages of liver disease. Thus, a sharp increase in cirrhosis, DC, HCC, and liver related deaths should be anticipated.

1.5 Emergency Department Viral Screen Programme

In 2014, a pilot viral screening programme was introduced in a busy inner-city ED of the largest tertiary referral, university-teaching hospital in Dublin, Ireland. This screening programme was called the EDVS Programme. The aim of this pilot programme was to assess the acceptability and feasibility of opt-out screening for HIV, HBV, and HCV in an ED setting (89).

This pilot EDVS Programme was introduced in response to numerous factors. These factors included new and increasing HIV, HBV, and HCV infection diagnoses in Ireland, the ongoing requirement to capture late infection diagnoses, the benefits of the early use of ART in PLHIV, HBV pharmacological treatments becoming off-patent, new access to potentially curative HCV therapies and changing migration patterns in Ireland affecting seroprevalence (90).

A key driver to the introduction of this pilot programme was a recommendation from a study by Tuite *et al* (2015). The aim of this study was to assess the epidemiology and seroprevalence of patients in Ireland accessing ambulatory care for HIV (91). Over the 12 month study period (July 2009 to June 2010 inclusive), 3,254 PLHIV attended one of six specialist HIV centres in Ireland. The authors reported that the HIV prevalence rate was estimated to be 1.09 per 1,000 population nationally, and 2.25 per 1,000 population in the Dublin area amongst 15 – 59 year olds. The authors concluded that Dublin was an area of high diagnosed HIV prevalence (defined internationally as 2 per 1,000 population or greater), and therefore likely to have a high undiagnosed population of PLHIV. The authors recommended routine opt-out screening for HIV in healthcare settings with the aim of improving timely diagnosis where a patient's HIV status was unknown. (91).

The EDVS was an opt-out screen for HIV, HBV, and HCV. This screen was offered to all patients who were able to give consent over the age of 18. Patients were offered an EDVS in the ED triage by a health care provider (ED triage nurse or doctor) if they were being phlebotomised for

other reasons. The EDVS screened for HIV (HIV Ag/Ab), HBV (HBsAg), and HCV (HCV Ab). The EDVS Programme also provided confirmatory testing and re-linkage to care for patients who had disengaged from care.

A EDVS registry database contained the EDVS Programme real-world individual patient-level data (PLD, herein referred to as EDVS real-world PLD registry database). Only patients with a positive EDVS were included in this database. Data was collected prospectively. Baseline demographic data on patients who tested positive for infection was collected: data included age, sex, and diagnosis. An EDVS Programme liaison nurse followed up on all the positive results and linked patients to care if required.

The results of the initial pilot EDVS Programme in 2014 were reported by O'Connell *et al* (2016) (89). The authors analysed data from the EDVS real-world PLD registry database. Of the 10,000 samples tested over the 10 month pilot project period (March 2014 to January 2015 inclusive), 7 new diagnoses of HIV, 20 new diagnoses of HBV, and 58 new diagnoses of HCV were made. In addition to these new diagnoses, many more patients who tested positive for infection and who were lost to follow up were re-linked to care.

O'Connell *et al* concluded that the pilot EDVS Programme demonstrated the ability to diagnosis new HIV, HBV, and HCV diagnoses in patients attending the ED and facilitated re-linkage to care for other patients who had been lost to follow up. In addition, the authors concluded that feasibility and acceptability of screening for HIV, HBV, and HCV in the ED setting had been demonstrated during this pilot study period. Subsequently, the EDVS Programme secured recurring funding. The EDVS is now offered as an opt-out screen to all eligible patients attending the ED in that institution as part of routine practice since July 2015 (89).

In 2020, Grant *et al* reported a follow up study of the first 35 months (July 2015 to June 2018 inclusive) of the EDVS Programme (92). Of all patients who underwent phlebotomy in ED during that 35 month study period (n = 88,854), 41,535 patients were screened for HIV, HBV, and HCV. There was an opt-out rate of 53% amongst patients who were being phlebotomized for other

reasons. There was a total of 2,409 positive tests. Of these, 457 patients tested positive for HIV, 208 patients tested positive for HBV, and 1744 tested positive for HCV. Similar to the 2016 pilot EDVS Programme study reported on by O'Connell *et al* (89), Grant *et al* concluded that although a high proportion of patients tested had known infection, the EDVS Programme identified many new patients with infection, and this resulted in their LTC. The EDVS Programme also facilitated the re-linkage to care of patients with known infection who had previously disengaged (92).

In a more up-to-date unpublished analysis of the EDVS real-world PLD registry database, patient demographics from the first five years of the EDVS Programme (July 2015 to June 2020 inclusive) were analysed (93). Of the unduplicated EDVS during this time period[i] (n = 70,386), a total of n = 3,360 patients with infection were identified. Of all these patients (n = 3,360), 83% (n = 2,790) had known infection and were linked to care prior to screening. The remainder of these patients (n = 570) were defined as requiring linkage to care (termed Require LTC).

It is important to highlight the definition of patients who Require LTC used in this five year analysis[i]. This term Require LTC is also used throughout the research presented here. Patients who Require LTC included patients with a new diagnosis of infection following screening, patients with a known diagnosis of infection but were not linked to care at the time of screening and therefore require re-linkage to care, and patients who were uncontactable at the time of screening, therefore the history of their infection status was unknown. All these patients were assumed to Require LTC.

In this five year analysis of the EDVS real-world PLD registry database[i], analyses were performed using SPSS version 27. Nominal data was presented as frequencies and percentages. Normally distributed continuous and ordinal data were presented as the mean and standard deviation (SD). Non-normally distributed data was presented as the median (interquartile range /IQR). Between group differences were investigated using unpaired 2-tailed t test, Pearson's chi-squared test (Chi), Fischer's exact test (Fishcer), or Mann-Whitney U test (MWU) as appropriate. The groups compared were patients who screened positive for infection who did not Require LTC, and patients who screened positive for infection who Require LTC.

A univariate binary regression analysis was performed. The aim was to identify predictors of patients who Require LTC amongst all patients who screened positive for infection following an EDVS. All factors that demonstrated a statistically significant association within the univariate model ($p \leq 0.05$) were used to create a multivariate model and evaluated with logistic regression analysis.

Table 1.1 shows patient demographics of all patients who screened positive for infection[i] (n = 3,360. No statistically significant difference was found in the proportion of males who Require LTC compared to those who did not Require LTC (Chi; p: 0.151). Patients who Require LTC were younger compared to those who did not Require LTC (MWU p: 0.047), and more likely to be non-Irish, particularly non-Irish European (Chi; p < 0.001), Asian (Chi; p: 0.005) or North African (Chi; p: 0.001). Patients who Require LTC were also more likely to be diagnosed with HBV (Chi; p < 0.001).

Table 1.1: Patient demographics (n = 3,360) from the first five years of the EDVS Programme (July 2015 – June 2020 inclusive)/univariate analysis (93).

	All	Require LTC[a]	Not Require LTC	p value[b]	Statistical test
Male	2344 (70%)	412 (72%)	1932 (69%)	0.151	Chi
Age, median (IQR)	45 (14)	43 (19)	45 (13)	**0.047**	MWU
Ethnicity					
Irish	2552 (76%)	351 (62%)	2201 (79%)	**<0.001**	Chi
Non-Irish European	335 (10%)	112 (20%)	223 (8%)	**<0.001**	Chi
Asian	94 (3%)	26 (5%)	68 (2%)	**0.005**	Chi
Sub-Saharan Africa	150 (4%)	34 (6%)	116 (4%)	0.057	Chi
North Africa	24 (1%)	10 (2%)	14 (1%)	**0.001**	Chi
South America	89 (3%)	13 (2%)	76 (3%)	0.548	Chi
North America	10 (0%)	3 (1%)	7 (0%)	0.388	Fischer
Unknown	105 (3%)	21 (4%)	84 (3%)		
Australia	1 (0%)	0	1 (0%)		
HIV Positive	744 (22%)	74 (13%)	670 (24%)	**<0.001**	Chi
HBV Positive[c]	337 (10%)	121 (21%)	216 (8%)	**<0.001**	Chi
HCV Positive	2297 (68%)	393 (69%)	1904 (68%)	0.742	Chi

LTC indicates linkage to care; **IQR**: interquartile range; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus; **Chi:** Pearson's chi-squared test; **MWU**: Mann-Whitney U test; **Fischer**: Fischer's exact test.

[a] Require LTC defined as patients with new infection, patients who require re-linkage to care, and patients who were uncontactable.
[b] This table reports if there is a statistically significant difference between patients who screened positive for infection and did not require LTC versus patients who screened positive for infection and did require LTC.
[c] For example, 10% of patients who screened positive for infection had HBV. There was a statistically significant difference found in the % of patients with HBV who Require LTC (21%) versus patients with HBV who did not Require LTC (8%).

In multivariate analysis (Table 1.2), being non-Irish European (OR: 1.59, 95% CI: 1.10 to 2.28) or HBV positive (OR: 1.83, 95% CI: 1.36 to 2.47) was associated with a statistically significant increased likelihood of Requiring LTC compared to patients who tested positive for infection who did not Require LTC. In contrast, being Irish (OR:0.62, 95% CI: 0.45 to 0.85) or HIV positive (OR: 0.49, 95% CI: 0.37 to 0.65) was associated with a statistically significant increased likelihood of not Requiring LTC compared to patients who tested positive for infection and who Require LTC.

Table 1.2: Multivariate regression analysis of predictors for patients who Require LTC[a] (93).

	N (%)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Male	2344 (70%)	1.16 (0.95 -1.42)	1.14 (0.93 -1.40)
Age <45 years at diagnosis	1593 (47%)	1.15 (0.96 -1.38)	1.09 (0.90 -1.31)
Irish	2552 (76%)	0.43 (0.35 -0.52)	**0.62 (0.45 -0.85)**
Non-Irish European	335 (10%)	2.82 (2.20 -3.61)	**1.59 (1.10 -2.28)**
Asian	94 (3%)	1.91 (1.21 -3.03)	1.00 (0.58 -1.71)
SubSaharan Africa	150 (4%)	1.47 (0.99 -2.17)	
North Africa	24 (1%)	3.54 (1.57 -8.01)	2.16 (0.90 -5.18)
South America	89 (3%)	0.83 (0.46 -1.51)	
North America	10 (0%)	2.10 (0.54 -8.16)	
HIV Positive	744 (22%)	0.47 (0.36 -0.61)	**0.49 (0.37 -0.65)**
HBV Positive[b]	337 (10%)	3.21 (2.52 -4.10)	**1.83 (1.36 -2.47)**
HCV Positive	2297 (68%)	1.03 (0.85 -1.26)	

LTC indicates linkage to care; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus; **CI**: confidence interval.

[a] Require LTC defined as patients with new infection, patients who require re-linkage to care, and patients who were uncontactable.
[b] For example, the OR of being HBV positive and Requiring LTC is 1.83.

1.6 Discussion

HIV, HBV, and HCV are three BBVs that have common modes of transmission. There tends to be significant overlaps in affected population groups and high levels of co-infection. Integrated screening also reflects existing patterns of service delivery (1). Progress of viral disease management, the availablity of new and tolerable effective pharmacological treatments, changing migration patterns, the increased seroprevalence of these three infections, and the

requirement to diagnose new infections promptly were drivers for the establishment of the EDVS Programme (90).

Studies of the EDVS Programme have highlighted points of discussion, to include screening opt-out rates of 53%, duplicate screening, and high risk patient characteristics amongst patients who Require LTC (90, 92, 93).

The most recent analysis of the EDVS Programme highlighted those patients who screened positive for infection and who Require LTC are more likely to be non-Irish European and HBV positive. As previously discussed, this cohort of patients who Require LTC also includes patients with known infection who are lost to follow up and require re-linkage to care. A patient who is lost to follow up may be as the result of either/and the healthcare system or patient-level factors influencing retention in care (94).

Patients who disengage from care or are lost to follow up are at risk of complications. Retention-in-care rates for chronic HBV can vary. In a Irish tertiary teaching hospital, 37% of patients with chronic HBV had disengaged from care after one year (90).

Lieveld *et al* (2017) state that lost to follow up is a barrier to efficiently instituting HBV liver-related care amongst patients with HBV (95). The authors analysed 343 patients with chronic HBV and found that 161 (47%) of patients had ever been lost to follow up. Lieveld *et al* concluded that properly educating patients with respect to HBV's natural history on the liver, and its favourable treatment options may increase understanding of the disease, help increase retention in care and compliance, and improve treatment outcomes (95).

In this recent analysis, being non-Irish European (and therefore likely non-English speaking) was associated with Requiring LTC. Language barriers resulting in ineffective communication has been reported as an obstacle to engaging patients in care. Language barriers pose challenges in terms of effective communication between a patient and a health care provider. Patients who do not speak the local language have reported barriers to accessing healthcare and decreased satisfaction with that healthcare system, decreased understanding of their diagnosis, and lower

rates of medication compliance (96). Al Shamsi *et al* (2020) reported on a systematic review of the implications of language barriers for healthcare systems. The authors concluded that online translation tools such as Google Translate and MediBabble can play an important role in overcoming language barriers in a healthcare setting (96).

It is important to highlight that the EDVS Programme is a screening programme. The principles of the programme are based on a seminal work by Wilson and Junger (1968) entitled *Principles and Practice of Screening for Disease* (9). These 10 principles should be applied when screening for a disease, and include:

- The condition sought should be an important health problem.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- There should be an agreed policy on whom to treat as patients.
- There should be an accepted treatment for patients with recognised diseases.
- Facilities for diagnosis and treatment should be available.
- Case-finding should be a continuous process.
- The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole (9).

These studies of the EDVS Programme have highlighted many of the principles and practice of screening for disease as outlined by Wilson and Junger (9, 89, 92, 93). Feasibility and acceptability of screening for HIV, HBV, and HCV in the ED has been shown. The studies have also demonstrated utility in identifying patients with a new infection, linking them to care, and re-linking patients with a previously known diagnosis to care (89, 92, 93). Wilson and Junger also state that the cost of case-finding should be economically balanced (9). The research question of this theses developed as a result – is screening for these three infections in the ED setting cost-effective? The aim of this research was to perform a cost-effectiveness analysis (CEA) of screening for HIV, HBV, and HCV in the ED setting.

1.7 Conclusion

Presented in this introduction chapter is the epidemiology, virology, natural history, disease states, treatments, and treatment outcomes for HIV, HBV, and HCV. The EDVS Programme is discussed, including several studies demonstrating the feasibility and acceptability of the screening programme. The EDVS Programme demonstrates the core principles of any screening programme. The research question was derived from these core principles. The research question of interest is introduced: is screening for HIV, HBV, and HCV in the ED in an Irish healthcare setting cost-effective?

The following chapters will address this research question, and include:

- Chapter 2: describes current international and national screening practices for HIV, HBV, and HCV. This chapter also introduces economic analyses, including cost-effectiveness analyses and cost utility analyses.

- Chapter 3: describes the model structure of this cost-effectiveness model.

- Chapter 4: describes the input parameters used in this cost-effectiveness model.

- Chapter 5: describes the results of this CEA.

CHAPTER 2 BLOODBORNE VIRAL SCREENING, ECONOMIC ANALYSES, BACKGROUND KNOWLEDGE

2.1 Bloodborne Viral Screening

Chapter 1 has introduced the reader to the important concept of screening for BBV. It has also provided an introduction to HIV, HBV, and HCV. While some screening programmes screen individuals for HIV, HBV, or HCV, screening for all three infections together is less common and less well studied. To our knowledge, there are no guidelines on general population screening for all three infections in the ED setting nationally or internationally. Chapter 2 introduces the reader to current international, European, and (where available) national guidelines on screening for these BBVs.

2.1.1 Current Screening Practices

2.1.1.1 Human Immunodeficiency Virus

In the US, the CDC's guidelines entitled *Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations* (2014) recommend general population screening for HIV for all people between the ages of 13 to 65 years at least once in their lifetime. For those people in high risk categories (as described in guidelines from the British HIV Association/BHIVA and European Centre for Disease Prevention and Control/ECDC, discussed below), annual screening at a minimum is recommended (97-99).

The ECDC's *HIV Combination Prevention Report* (2020) recommends screening for HIV in high risk settings (99). The ECDC report recommends that HIV screening should diversify, and that HIV screening should be made available through multiple entry points. This would ensure prompt infection diagnosis and prevent late presentation of patients with infection to care. The ECDC suggests mechanisms to diversify HIV screening, to include HIV self-screening, HIV screening provided by lay-people and civil society, home sampling, routine indicator condition-guided HIV screening offered in healthcare systems, and partner notifications (99).

In BHIVA's most up-to-date guidelines entitled *Adult HIV Testing Guidelines* (2020), BHIVA recommends screening for HIV in high risk populations as opposed to general population screening. The BHIVA guidelines highlight four main categories of people to screen for HIV. The

first category includes people in high risk groups. High risk groups include PWID, MSM, female sexual contacts of MSM, black Africans, people who are commercial sex workers, prisoners, trans women, people who come from a country of high prevalence (COHP, with a HIV seroprevalence of 1% or higher), people who have sex with people from a COHP, and people born to a mother with HIV. These guidelines also state that trans men in certain circumstances should be considered a high risk group (98).

In BHIVA's guidelines, people in the second category include people attending certain healthcare services. These healthcare services are antenatal services, sexual health services, addiction and substance misuse services, termination of pregnancy services, and healthcare services for HBV, HCV, tuberculosis, and lymphoma. The third category includes people presenting with symptoms or signs of HIV indicator conditions. The fourth category includes all people accessing primary or secondary healthcare, including EDs, in areas of high or extremely high HIV seroprevalence (2 to 5 per 1,000 population and accessing phlebotomy, or higher than 5 per 1,000 population with or without accessing phlebotomy) (98).

There are no national guidelines on HIV screening in Ireland. While the HPSC in Ireland references the ECDC's guidance (2011) entitled *HIV Testing: Increasing uptake and Effectiveness in the European Union*, national strategies for HIV screening in Ireland are informed by multiple international guidelines, including those discussed above (100).

2.1.1.2 Hepatitis B Virus

In the US, the American Association for the Study of Liver Diseases' (AASLD) guidelines entitled *Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B Guidance (*2018) recommend screening for HBV for those living in high seroprevalence settings of 2% or higher, US-born people not vaccinated as infants whose parents were born in regions with high HBV endemicity (i.e. with a seroprevalence of 8% or higher), women who are pregnant, patients needing immunosuppressive therapy and those in high risk categories similar to the high risk categories defined in ECDC's guidelines below (101, 102).

In the US, the CDC's *Recommendations for Routine Testing and Follow up for Chronic Hepatitis B Virus Infection* (2019) recommend the same screening practices as AASLD for HBV screening. The guidelines include a recommendation to routinely screen patients in high risk categories. The guidelines also include a recommendation to screen people with ALT or aspartate transaminase (AST) elevation of unknown aetiology, donors of blood, plasma, organs, tissues, or semen, patients requiring haemodialysis, children born to HBsAg positive women, household contacts, people who share needles, sexual contacts of people who are HBsAg positive, and PLHIV (103). These guidelines recommend screening settings to include homeless shelters, jails, sexual health and genitourinary medicine clinics, and refugee clinics (103). The CDC also comments that because the demand for care will increase as screening increases, often the lack of sufficient resources for management of people with infection can be a barrier to implementation of screening programmes (7).

In guidelines from the WHO entitled *Guidelines on Hepatitis B and C Testing* (2017) and the ECDC entitled *Public Health Guidance on HIV, Hepatitis B and C Testing in the EU/EEA (*European Union/ European Economic Area)*: An Integrated Approach* (2020), targeting high risk populations for screening for HBV is recommended (1, 104). The ECDC defines high risk patients as PWID, MSM, trans people, people who are commercial sex workers, people who migrate from COHP, people who are homeless, women who are pregnant, patients requiring haemodialysis, patients who receive blood products, organs or surgical interventions before adequate safety and quality regulations have been enforced, sexual or drug injection partners, and household contacts of people with HBV (1).

In 2018, the ECDC performed a systematic review entitled *Hepatitis B and C Testing Strategies in Healthcare and Community Settings in the EU/EEA*. The aim was to examine the evidence base for interventions to improve HBV and HCV screening in different screening settings in the EU and EEA countries. The review found that while screening settings were important, the most successful screening programmes were aimed at key high risk populations, as opposed to targeting screening settings (102).

The EASL's guideline entitled *Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection* (2017) recommends high risk based screening for HBV, including the screening

of women who are pregnant in the first trimester (65). The National Institute for Health and Care Excellence (NICE, United Kingdom/UK) in a surveillance report entitled *Hepatitis B and C Testing: People at Risk of Infection* (2017) recommends targeting high risk populations and women who are pregnant in certain settings to include primary care, prisons and immigration removal centres, drug services, and sexual health and genitourinary medicine clinics (105). NICE does not recommend either general population or high risk screening in the ED setting but it does highlight that the ED is a setting of interest for BBV screening (105).

Similar to HIV, there are no national guidelines on HBV screening in Ireland. Screening practices are informed by multiple international guidelines including those discussed above.

2.1.1.3 Hepatitis C Virus

In the US, the CDC's guidelines entitled *Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-related Chronic Disease* (1998) recommend the screening of high risk populations for HCV (106). These guidelines were updated in 2012 with a recommendation to offer birth cohort screening for HCV to all persons born from 1945 through 1965 without prior identification of HCV risk factors (8). This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of patients with HCV infections, due in part to patient underreporting of their risk and provider limitations in ascertaining risk factor information (107).

Since the birth cohort screening was adopted in 2012, there has been an increase in younger people diagnosed with acute and chronic HCV in the US. This is understood to be because of the opioid epidemic and increasing rates of IDU in this cohort (108). These issues highlight concerns associated with risk-based screening programmes. Also highlighted is the need to further expand screening for both risk-based screening and general population screening.

The WHO (2017) and some European bodies including Public Health England (PHE, 2016), EASL (2020), BHIVA (2013) and British Association of Sexual Health and HIV (BASHH, 2016) strongly support the screening of high risk groups for HCV (77, 104, 109-111). Guidelines entitled *United Kingdom National Guideline on the Management of the Viral Hepatitides A, B and C*

(2015) include a recommendation to screen PLHIV at diagnosis for both HBV and HCV. In addition, these guidelines recommend screening people who achieved HCV SVR following treatment and people who have spontaneously cleared HCV infection, offering them annual HCV RNA screening and more frequent screening should they have an unexplained rise in ALT or AST levels (111).

In 2017, Ireland developed *National Clinical Guidelines for Hepatitis C Screening* (112). These guidelines state that HCV screening should be offered to high risk individuals, to include PWID, people who are non-injection drug-users, prisoners or former prisoners, people who are homeless with high risk behaviour, people who are migrants from a COHP, infants of HCV RNA positive mothers, MSM, patients requiring haemodialysis, and patients who are the recipients of human products. These guidelines state that screening should be considered in those with tattoos, people who are household contacts, patients who are recipients of solid organ transplants, patients who have received medical or dental treatment in a COHP, sexual partners, and people who are commercial sex workers.

The *National Clinical Guidelines for Hepatitis C Screening* (2017) also recommend birth cohort screening for HCV (112). These guidelines recommend offering HCV screening to patients born from 1965 through 1985 (that is, birth cohort screening) on a once-off basis. Birth cohort screening is recommended to people born during a particular period of time because there is evidence (such as epidemiological trends) of an elevated risk of exposure relative to the overall general population (113). However, the initial conditionality of these guidelines was that this was dependant on a health technology assessment (HTA).

In 2021, a HTA was performed and published by the Health Information and Quality Authority (HIQA) in Ireland entitled *Health Technology Assessment of Birth Cohort Testing for Hepatitis C* (113). The aim of this HTA was to establish the clinical benefit, cost-effectiveness, and budget impact associated with introducing birth cohort screening in Ireland. Three alternative programmes were evaluated. These were: no birth cohort screening, systematic birth cohort screening, and opportunistic birth cohort screening.

As part of this HTA, the cost utility analysis (CUA) reported that both systematic and opportunistic birth cohort screening programmes were estimated to be more costly and more effective than a no birth cohort screening programme (113). Compared with a no birth cohort screening programme, an ICER of €8,357/QALY (95% CI: €843 to €19,699) was estimated for opportunistic birth cohort screening. Compared with opportunistic birth cohort screening, an ICER of €9,237/QALY (95% CI: €1,384 to €21,632) was estimated for systematic birth cohort screening. In a fully incremental analysis, systematic birth cohort screening was considered the most cost-effective strategy of the three alternative strategies.

The summary recommendation from this HTA was that birth cohort screening to diagnose HCV would be cost-effective. Over a five year period, it was estimated that the budget impact of introducing this screening programme would be between €44 million and €65 million, depending upon the strategy chosen. The HTA also recommended that a pilot study be undertaken to introduce birth cohort screening and recommended further research in the area to be considered to include surveying members of the public in order to reduce potential uncertainty around the screen uptake rates. These recommendations were made to the Minister of Health in Ireland (113).

2.1.1.4 Tri-infection (HIV, HBV, HCV)

Many guidelines recommend screening for co-infection or tri-infection amongst patients with mono-infection (65, 98). While there are no guidelines for screening for all three infections together, the ECDC's *Public Health Guidance on HIV, Hepatitis B and C Testing in the EU/EEA: An Integrated Approach* (2018) does advocate for an integrated approach (1). The ECDC comments that the three viruses have common modes of transmission. There are appreciable overlaps in affected population groups and high levels of co-infection and tri-infection. Integrated screening also reflects existing patterns of service delivery (1).

2.1.2 Cost-effectiveness of Screening

Cost-effectiveness of screening for HIV, HBV, and HCV is dependent on many factors, including the population under consideration (e.g. general population versus high risk population

screening), how frequently screening takes place, and in what setting screening occurs (114-116).

In the US, the CDC (2013) reported that routine HIV screening was cost-effective if one undiagnosed person was diagnosed per 1,000 screens (117). In the UK, NICE (2016) reported that screening for HIV in a setting with a seroprevalence of 0.2% or higher was cost-effective (115).

A further CEA in France by Yazdanpanah *et al* (2010) showed that one-time general population screening for HIV was cost-effective, with an ICER of €57,400/QALY (118). The same authors performed a CEA of HIV screening in Portugal (2013), where a ICER of €29,000/QALY was reported with one-time general population screening for HIV (119). This study also reported that more frequent screening of high risk people was cost-effective; this included annual screening of MSM and screening every three years in settings with high seroprevalence, producing ICERs of €21,000/QALY and €34,000/QALY respectively.

Within the ED setting, in the US, HIV screening has been shown to be cost-effective with an ICER of €31,214/QALY (2011) (120). NICE, in the UK, reviewed cost-effectiveness data on HIV screening in the ED setting and concluded that while HIV screening for everyone attending the ED would incur an additional cost, this would be cost-effective in areas of HIV seroprevalence (8% or higher) (115).

While the ECDC's guidelines entitled *Hepatitis B and C Testing Strategies in Healthcare and Community Settings in the EU/EEA* (2018) recommend HCV and HBV screening in EDs in areas of intermediate or high seroprevalence (2% or higher), they do not cite any cost-effectiveness evidence (102). In the UK, there is no current NICE recommendation for ED screening for HCV and HBV, citing the absence of cost-effectiveness evidence for hepatitis screening in this setting (2017) (105). Williams *et al*, in the UK, reported a CEA of ED screening for HBV and HCV (2020). The authors concluded that screening in the ED for HBV and HCV was cost-effective, with HBV and HCV costing €11,663/QALY and €9,487/QALY respectively. They also reported that ED

screening remained cost-effective at a HBV or HCV (RNA) seroprevalence of 0.25% or higher (114).

While these guidelines and studies reported cost-effectiveness results for mono-infection and co-infection, to our knowledge, there has been no CEA of ED screening for HIV, HBV, and HCV internationally.

2.2 Cost-effectiveness Analysis

A CEA is a form of economic evaluation (EE). Drummond *et al* define an EE in healthcare as the comparison of alternative strategies in terms of their costs and consequences (121). EEs are increasingly used to inform health care decision makers about which healthcare interventions to fund from available resources (10).

CEAs are used to apply principles of resource allocation within healthcare systems (122). Given the need for most healthcare systems to make resource allocation decisions across a whole range of disease areas, CEAs are increasingly being used. A CEA is based on a single or generic measure of health (e.g. percentage reduction in blood cholesterol in patients with coronary artery disease (123), or true positive cases of breast cancer in breast cancer screening (124)).

2.2.1 Cost Utility Analysis

A CUA is a form of CEA in which the incremental cost/QALY is estimated (125). Although other measures of effect (health outcome) have been suggested, the use of QALY is the most frequently used measure in a CUA (10). In line with *Guidelines for the Economic Evaluations of Health Technologies in Ireland* (2020), the EE, undertaken as part of the research presented here, was a CUA (12).

The QALY seeks to reflect the fact that healthcare interventions and programmes aim to impact an individuals' length of life and health-related quality of life (HRQOL). QALYs are calculated by assigning a value or weight (utility) to each possible health state experienced by the patient.

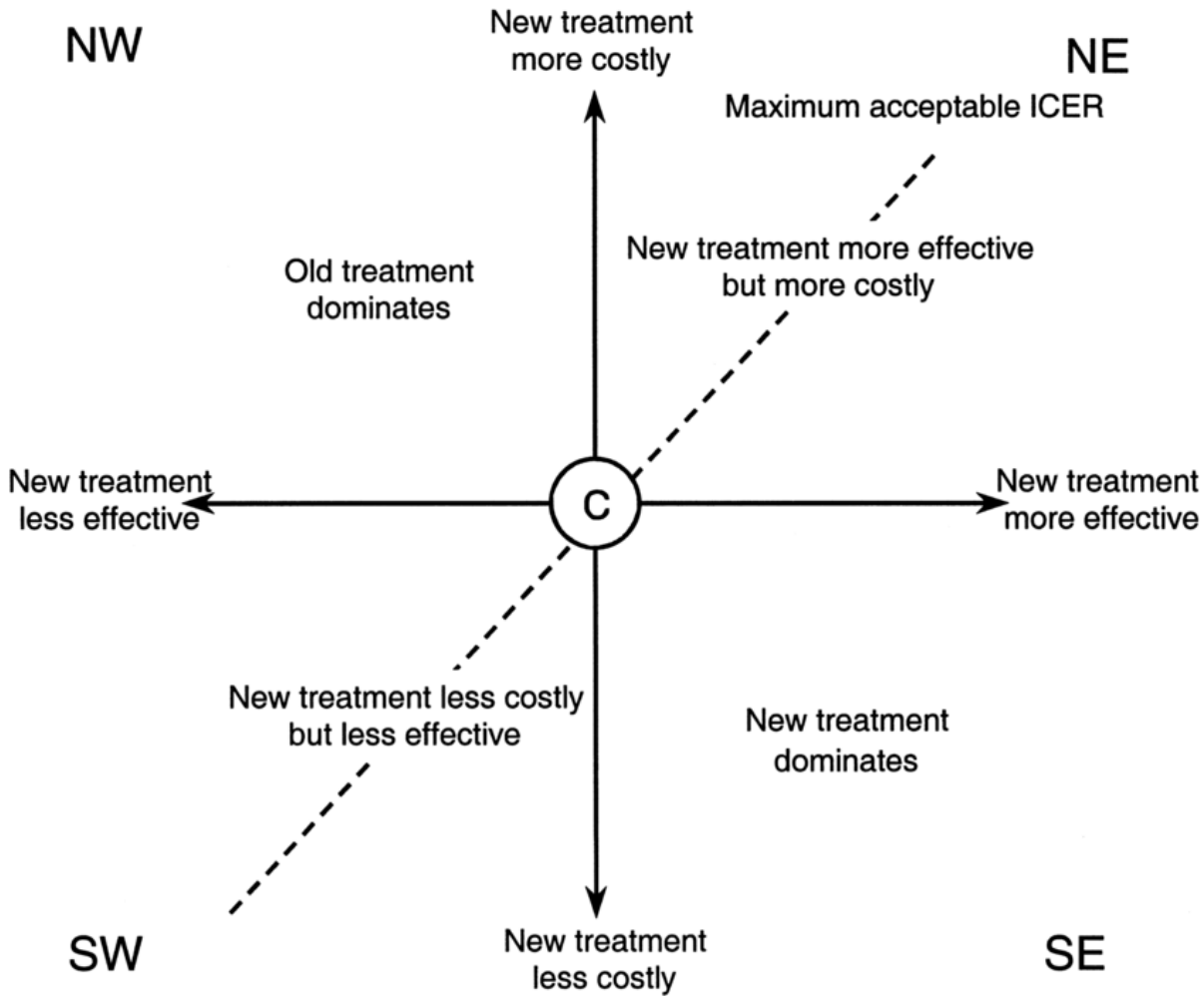
Utilities are measured on an interval scale and range in value from zero (death) to one (perfect health). Health states considered worse than death are permitted (score of less than zero) (12).

There are limitations to the use of QALYs in a CEA. The valuations of QALYs may be inconsistent because utility weights used in the calculation are instrument dependent. The benefits to the use of QALYS are that CEA outputs can be compared across all disease states. QALYs remains the only generic measure of health that have been used in a large range of clinical areas (10). *National guidelines* state that the preferred evaluation type in an EE is a CUA, with the outcomes expressed in terms of QALYs (12). These guidelines also state that the QALY can simultaneously incorporate changes in the quantity of life and changes in the quality of life as a result of the technology being assessed, and measured in terms of QALYs gained.

2.2.2 Cost-effectiveness Plane

In a CEA, standard cost-effectiveness decision rules involve relating differences in costs between strategies under comparison to differences in effects (10). If an intervention under consideration costs less than the comparator and generates a greater effect, this is referred to as the dominant strategy. Clearly this is the more cost-effective strategy. However, an intervention may still be cost-effective if it costs more but generates a greater effect than the comparator. The cost-effectiveness plane visually represents this concept, plotting the health effects on the x axis, and costs on the y axis (126). The comparator (i.e. standard of care or current practice) is plotted at the origin. The x and y values represent incremental health outcomes and incremental costs of the intervention under consideration versus current practice. Figure 2.1 shows the cost-effectiveness plane. In this illustrated plane the comparator (current practice) is described as the 'old treatment' and the intervention under investigation is referred to as the 'new treatment'.

Figure 2.1: Cost-effectiveness plane[a].



NW indicates north-west; **SW**: south-west; **NE**: north-east; **SE**: south-east; **ICER**: incremental-cost-effectiveness ratio.

[a] The cost-effectiveness plane is divided into four quadrants. If a CEA delivers results (in the form of ICER) in the NE quadrant, this new intervention is more expensive but generates more health gain. Other quadrants are relevant if a new intervention generates poorer health outcomes (NW or SW) or lower costs (SW or SE) (126).

Source: Adapted from The Design and Analysis of Stochastic Cost-Effectiveness Studies for the Evaluation of Health Care Interventions, Briggs *et al* (127).

2.2.3 Incremental Cost-effectiveness Ratio

Standard decision rules in a CEA have centred on the calculation of the ICER (10). The ICER is usually the main output of a CEA (128). The ICER is a measurement of the additional cost per extra unit of effect (e.g. QALY) for the intervention under consideration compared to the comparator. In order for health care decision makers to decide if whether choosing a new intervention is an efficient use of resources, ICERs reported from CEAs are compared with a pre-

determined threshold. This threshold is referred to as a cost-effectiveness threshold (or willingness-to-pay/WTP threshold). In the field of health, a cost-effectiveness threshold is the maximum amount a health care decision maker is willing to pay in order to gain a unit of outcome (e.g. QALY), given other competing demands on the decision makers resources (129).

2.2.4 Willingness-to-pay Threshold

If the ICER of a CEA is below the WTP threshold, the intervention under consideration is deemed to be cost-effective under standard decision rules (130). At the time of performing this CEA, the HSE, which is the publicly funded healthcare system in Ireland and is responsible for the provision of health and personal social services, considered two WTP thresholds. These were €20,000/QALY and €45,000/QALY (12). These thresholds were reported in *national guidelines* (12). However, the Irish Pharmaceutical Healthcare Association (IPHA) has published an updated *Framework Agreement on the Supply and Pricing of Medicines in Ireland* (Dec 2021), and no WTP thresholds have been made explicit (131).

2.2.5 Perspective

Before a CEA commences, the study perspective should be determined in order to establish which costs and consequences are to be considered. While the health payer perspective is taken by the research presented here and by many jurisdictions, the societal perspective is advocated for frequently (132). The health payer perspective aims to inform the decision maker about the optimal allocation of their budget (121). National guidelines state that the publicly-funded health and social care system in Ireland should be adopted when assessing costs and that all health effects accruing to individuals should be included in the assessment of outcomes (12).

The health payer perspective takes into account the perspective of the health system. Costs are direct costs; included are treatment costs, administration and monitoring costs, and other health service resource costs associated with managing the disease under evaluation. The societal perspective includes a broader analysis of costs associated with the disease under evaluation. Both direct and indirect costs are included when the societal perspective is taken. Indirect costs include productivity losses arising from a patient's inability to work, transportation costs, over-

the-counter treatment purchases, and even health costs associated with, for example, educational attainment as a consequence of a new technology (12, 133).

2.2.6 Time Horizon

It is important to choose an appropriate time horizon for a CEA. A time horizon should be sufficiently long to reflect all the major differences in the interventions being studied in terms of cost and effect (10). In line with this, this CEA uses a lifetime time horizon.

2.2.7 Uncertainty

All CEAs will contain some degree of uncertainty. A key requirement for health care decision makers following a CEA is the ability to translate this uncertainty into assessing the probability that the decision made is the correct decision (10). There are a number of techniques used to handle uncertainty. This includes deterministic SA in the form of a one way SA (OWSA) or a multivariate SA, and probabilistic SA (PSA) (132). *National guidelines* recommend performing both deterministic SA and PSA (12).

A OWSA investigates the impact on the ICER of extreme variations in key, uncertain parameters (134). PSA values are randomly sampled from parameter distributions (135). One advantage of PSA over a OWSA is that all uncertain parameters can be simultaneously incorporated into an analysis. PSA results provide an estimation of the total impact of uncertainty in the model, or the confidence that can be placed in the analysis results (136).

2.2.8 Decision Modelling

Decision analysis is a systematic approach used in healthcare (and in other fields including law, business or engineering) to inform decision makers under conditions of uncertainty (10). The process is designed to help health care decision makers think clearly about the main elements of complex decisions. A decision analytic model uses mathematical relationships to define a series of possible consequences. Based on the inputs of the model, the likelihood of each consequence is expressed in terms or probabilities. Each consequence has a cost and an outcome (or effect) (10). Inputs for the model are obtained from available data. Data can be synthesised from

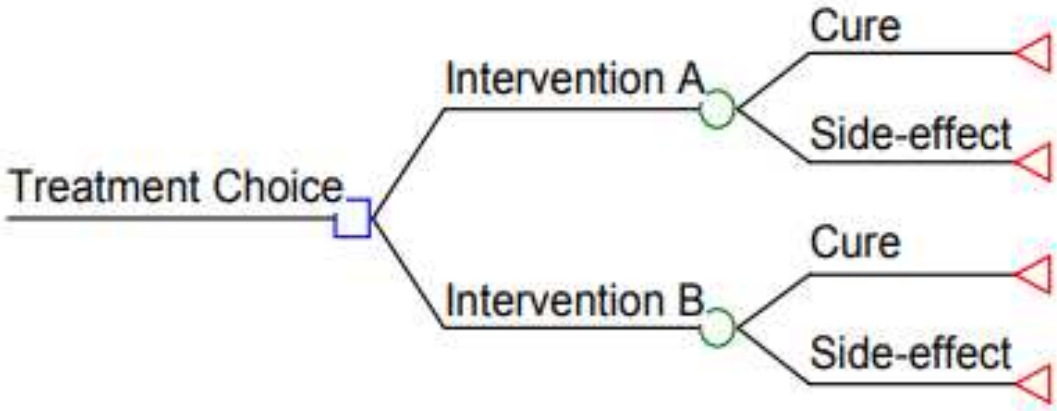
different sources, including epidemiological sources, clinical sources, and economic sources (137).

By using decision analysis, a complex problem can be disaggregated into smaller problems and elements, which can be easier to understand. These components are then employed in building a model of the problem's essential elements (10). The main modelling approaches used in CEAs are decision tree modelling, Markov modelling, and individual sample modelling (137). These types of modelling approaches assume independence of individuals within the model. Where interaction between the individuals is important, other methods such as discrete-event simulation or system dynamics are preferable (137).

2.2.8.1 Decision Tree Modelling

Decision tree modelling involves the use of a decision tree. A decision tree is a branching structure in which various node symbols are used to represent different kinds of events, including decisions and uncertainties (138). A node's branches represent the outcomes or alternatives associated with that event. Every series of actions and outcomes are clearly represented with a distinct path. Decision trees are an appropriate choice in evaluations pertaining to diseases with distinct events that occur with a given probability, within a relatively limited time frame (137). Figure 2.2 shows a simple decision tree model that compares two theoretical interventions A and B, both of which are associated with a cure effect and side effects.

Figure 2.2: A simple decision tree model[a].



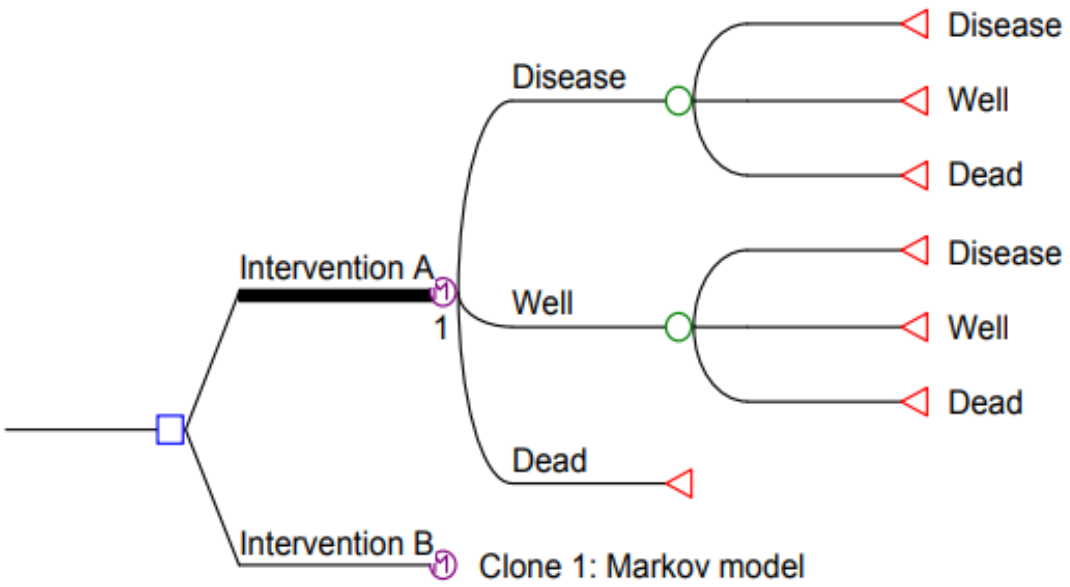
[a] The expected cost for each intervention is calculated by multiplying the cost for each branch by the overall probability of that branch occurring (137).

2.2.8.2 Markov Modelling

Markov modelling is a commonly used approach. Markov modelling is used to simulate both short-term processes (e.g. development of a tumour) and long-term processes (e.g. an individual's lifespan). Markov modelling is particularly suited to modelling chronic diseases (139). This type of modelling can handle the added complexity of simulating processes with multiple possible consequences (10).

In a Markov model, all patients are categorised into a disease state, and the prognosis of these patients is reflected as a set of possible transitions between disease states over a series of discrete time periods, also called cycles (138). In order for a Markov process to terminate, it must have an absorbing state (i.e. a state which a patient cannot transition out of), the most common of which is death (139). Costs and effects are usually incorporated into these Markov models. As a rule, these inputs are calculated as a mean value per state per cycle. Expected output values are calculated by adding the costs and effects across the states and weighting these according to the time the patient is expected to be in each state (138). Figure 2.3 shows a simple Markov model that compares two interventions A and B.

Figure 2.3: A simple Markov model[a].



[a] Patients who are in the Disease state may remain in this state or progress to the Well or Dead states. Patients in the Well state may remain here or progress to Disease or Dead. Patients who are in the absorbing Dead state cannot transition out of this state.

2.2.8.3 Individual Sample Modelling

Individual sample modelling, also referred to as individual patient-level simulation, allows individual patients to be run through a model via microsimulation. Microsimulation allows individual patient elements, such as patient characteristics and prior events, to be incorporated into the model. These individual PLD elements can be characterised by specific probabilities, costs, and utility values (137).

In a CEA, national guidelines state that the choice of modelling used should depend on the research question, and that there is no one favoured modelling technique (12). For this research, a bespoke CUA model (herein referred to as a CEA model) was developed. It comprises a decision tree model that feeds into a Markov model.

2.3 Background Knowledge

Knowledge on this research was informed by my role as an Infectious Diseases and General Internal Medicine doctor. In addition, I am currently completing a Master of Science (MSc) Degree in Applied Health Economics with the University of South Wales (due date of completion August 2022). I completed a diploma in Applied Health Economics in 2020 with the University of South Wales. This diploma and MSc allow me to independently access information and use this information to critically assess, evaluate, and disseminate the evidence base related to health economics medicine. My experience as a physician with knowledge in health economics has provided me with the necessary skills to study the research question of this thesis.

2.4 Conclusion

Presented in this chapter is information pertaining to current international and national screening practices and guidelines for HIV, HBV, and HCV screening. The role of EEs including CEAs and CUAs are discussed. In addition, several CEAs analysing BBV screening practices are reported.

Guidelines for the Economic Evaluations of Health Technologies in Ireland (2020), an important guideline frequently referenced in this thesis, is introduced (12). My background knowledge in this area of health economics has been informed by my role as a doctor, but also as a MSc student in Applied Health Economics.

This chapter provides background information to support the research question of this thesis that was introduced in Chapter 1: is screening for HIV, HBV, and HCV in the ED in an Irish healthcare setting cost-effective?

CHAPTER 3 MODEL STRUCTURE OF THE COST-EFFECTIVENESS ANALYSIS

3.1 Introduction

Screening for HIV, HBV, or HCV, especially in the long term, represents a cost-effective strategy for the management of BBV infections (140). Screening for BBV infections potentially presents a dual health and economic benefit. The first benefit is that of diagnosing a treatable infection and preventing complications. The second is the benefit of preventing onward transmission, including the associated costs and effects averted as a result of screening. Consequently, there is considerable scope for case-finding activities to be cost-effective (51, 141, 142). An important case-finding activity is screening for infection. Screening programmes for BBVs can be considered a health technology (12).

Panel screening for all three infections represents an important opportunity to diagnose mono-infection, co-infection, and tri-infection. Feasibility and acceptance of panel screening in the ED setting for HIV, HBV and HCV in Ireland and the UK has been demonstrated (92, 143). To our knowledge the cost-effectiveness of screening in the ED internationally for all three infections has not been evaluated.

3.2 The Emergency Department Viral Screen Programme

3.2.1 Current study[i]

The establishment of the EDVS Programme in our institution has been discussed in Chapter 2. To date, there has been no CEA of this EDVS Programme. Further to our knowledge, no CEA of panel screening for HIV, HBV, and HCV in the ED has been published internationally.

The primary objective of this thesis was to perform a CEA of opt-out ED-based panel screening for HIV, HBV and HCV for all phlebotomised patients aged 18 years or over in an Irish healthcare setting.

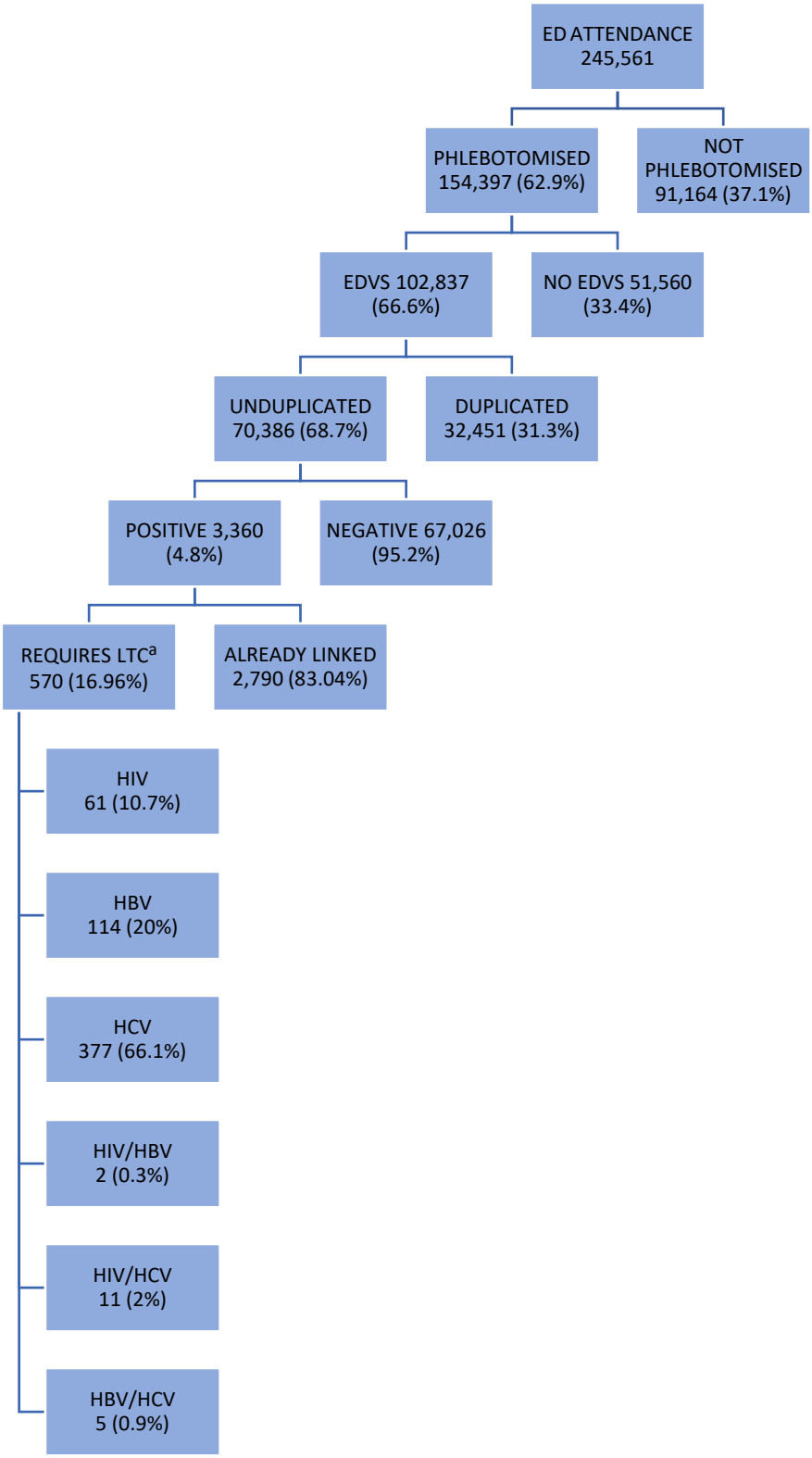
This current study period included data from the EDVS real-world PLD registry database from the first five years of the EDVS Programme (July 2015 to June 2020 inclusive). During the current study period[i], there were 245,561 patient attendances to the ED. Of all the patient attendances,

62.9% were phlebotomised. Of all the phlebotomised patients, 66.6% underwent an EDVS. There was an opt-out rate of 33.4%. This was lower than the opt-out rate of 53% reported by Grant *et al* when the authors analysed the first 35 months of the EDVS Programme (92).

It is important to highlight that recurrent patient attendances to the ED resulted in patients having multiple screens. Duplicate screens were excluded from the analysis (costs of duplicate screens were included however). Of all the unduplicated EDVS, 4.8% of patients who underwent an EDVS screened positive for infection, including mono-infection, co-infection, or tri-infection (HIV, HBsAg, HCV Ab±RNA).

Patients who Require LTC[i] (section 3.3.3.2) accounted for 16.96 of all patients who had a positive EDVS. Thus, 83.04% of patients screened were already linked to care. Some patients with co-infection were identified as Requiring LTC. While patients with tri-infections had a positive EDVS, this diagnosis was known, and they were linked to care prior to the EDVS. Therefore, no patients with tri-infection were identified as Requiring LTC. Figure 3.1 shows screening uptake, prevalence and patients who Require LTC from the EDVS Programme[i].

Figure 3.1: The EDVS Programme[i]: a flowchart of screening uptake, proportion of patients with a positive EDVS, and patients who Require LTC.



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] Require LTC defined as patients with new infection, patients who require re-linkage to care, and patients who were uncontactable. For further breakdown, see Table 3.1.

Table 3.1 provides a further breakdown of patients who Require LTC[i]. These patients who Require LTC (section 3.3.3.2) refers to patients with newly diagnosed infection, patients with known infection who disengaged from care and patients who tested positive who were uncontactable and therefore the history of their infection status was unknown.

Table 3.1: EDVS Programme: breakdown of results from patients who Require LTC, including diagnosis status history, patients who Linked to Care and patients who DNA.

Diagnosis status history (n = 570)	**HIV**	**HBV**	**HCV[a]**	**HIV/HBV**	**HBV/HCV[a]**	**HCV[a]/HIV**
New (n)	46	67	148	2	5	11
Known disengaged/LTFU (n)	11	34	200	0	0	0
Unknown (n)	4	13	29	0	0	0
Total (n)	61	114	377	2	5	11
Linked[b] vs DNA[c]						
Linked (n(%))	51 (83.6%)	69 (60.5%)	183 (48.5%)	2 (100%)	3 (60%)	11 (100%)
DNA (n(%))	10 (16.4%)	45 (39.5%)	194 (51.5%)	0	2 (40%)	0

EDVS indicates Emergency Department Viral Screen; **LTC:** linkage to care; **LTFU**: lost to follow up; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

[a] HCV RNA +.
[b] Linked to Care defined as patients contacted, informed, and attended for one or more consultant-led hospital outpatient reviews (section 3.3.3.2).
[c] DNA defined as patients who were offered LTC but did-not-attend for same in a one year follow up (section 3.3.3.4).

3.3 Methods

3.3.1 Decision Problem

The decision problem was defined as whether screening for HIV, HBV, and HCV in an inner-city ED was cost-effective. Two strategies were being compared. The ED screening intervention strategy was referred to as the EDVS Screen strategy. The comparator strategy was referred to as the No EDVS Screen strategy. A No EDVS Strategy is standard of care in ED settings.

3.3.2 Model Analysis

A bespoke cost-effectiveness decision model was developed to simulate expected lifetime costs and effects associated with the EDVS Screen strategy versus those associated with the No EDVS Screen strategy in the ED setting. The design of this model was informed by *national guidelines* (12). In addition, a targeted literature review of national and international data, using PubMed, Google Scholar, and OVID-Medline databases, from January 2001 to December 2021 inclusive, informed the choice of sub-health states in our model. The model was programmed in TreeAge Pro 2020® (TreeAge Software Inc, Williamstown, MA, USA).

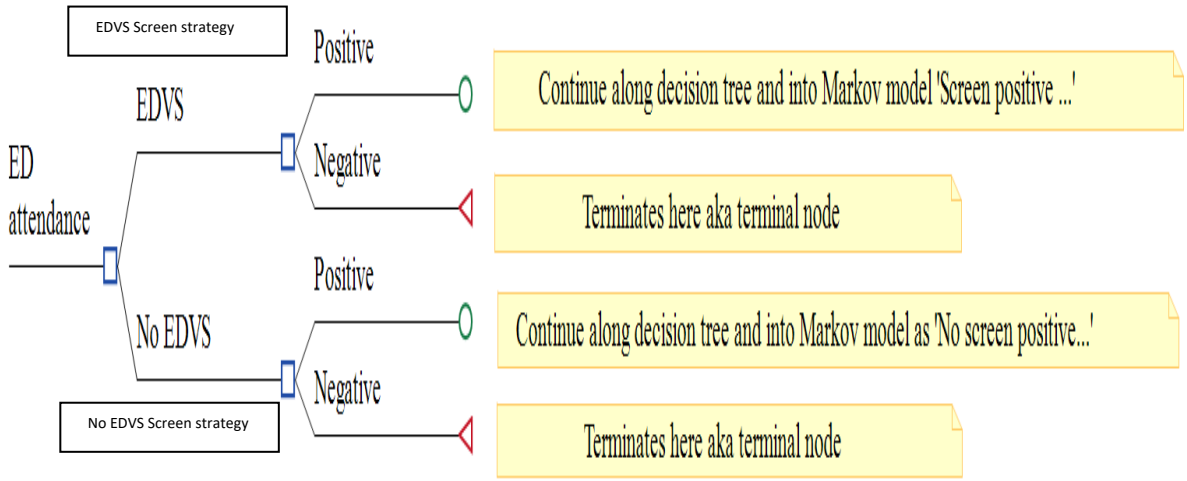
This model compared the EDVS Screen strategy to the No EDVS Screen strategy. Results were reported as an ICER. The EDVS Programme in our institution informed the cost-effectiveness model. The EDVS real-world PLD registry database[i] was analysed, and results informed how patients flow through the decision tree and many of the input parameters of the cost-effectiveness model (input parameters discussed in Chapter 4).

The cost-effectiveness model comprised a decision tree that fed into a Markov model. At the start of the decision tree, all patients attended the ED. As per the decision problem, the EDVS Screen strategy was then compared to the No EDVS Screen strategy. This represented the decision branch, or the first branch, of the decision tree.

The second branch of the decision tree categorised patients into those who tested positive for infection and those who tested negative for infection following an EDVS. The probabilities of screening positive or negative for infection were based on data from the EDVS real-world PLD registry database[i]. These probabilities are described along with the other input parameters of this model in Chapter 4.

If patients screened positive for infection, they continued along the decision tree as described below. If patients screened negative for infection, their journey through the decision tree terminated following this negative diagnosis, as represented by a terminal node in the decision tree. Figure 3.2 shows a simplified version of the first and second branches of the cost-effectiveness model's decision tree.

Figure 3.2: A simplified version of the cost-effectiveness model's decision tree: the first and second branches of the decision tree (EDVS Screen strategy versus No EDVS Screen strategy).



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen.

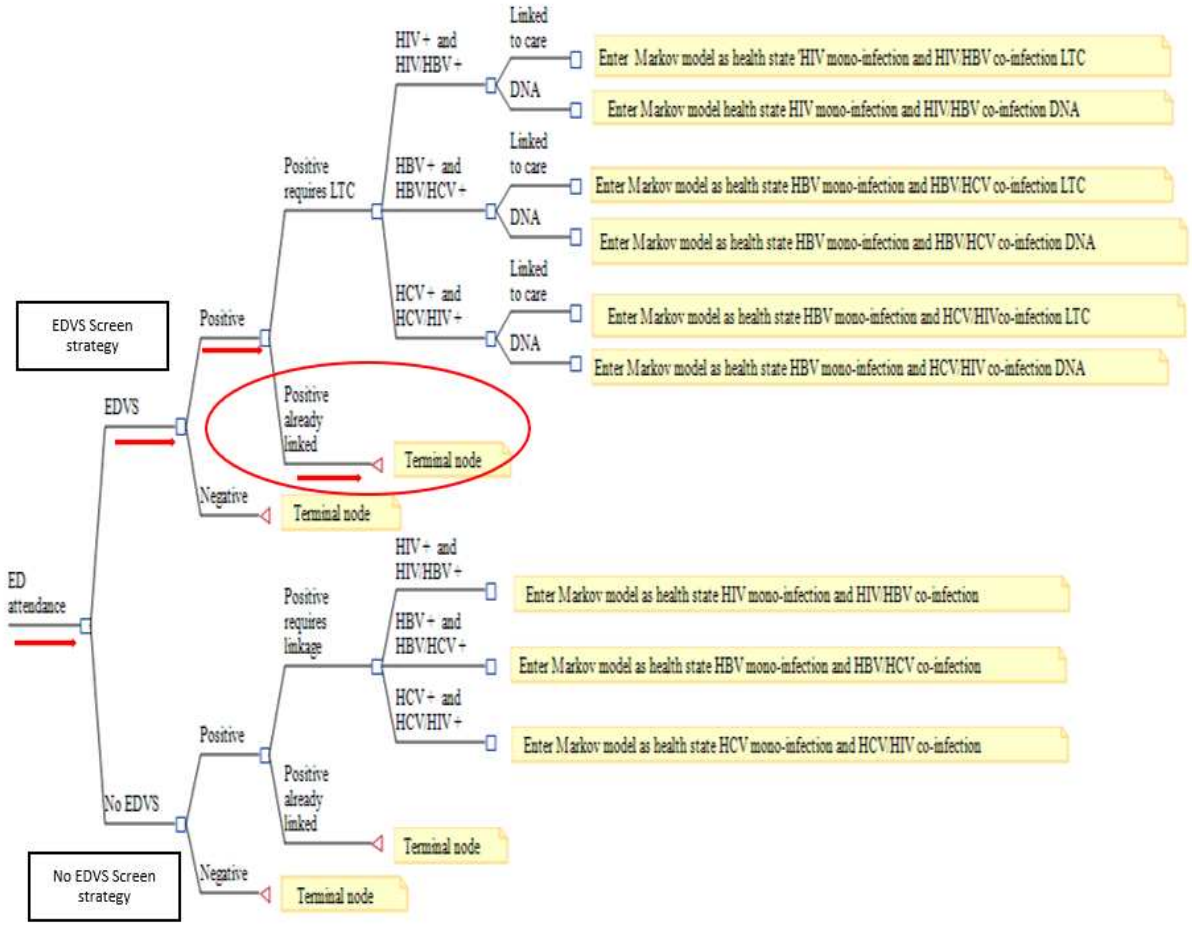
3.3.3 Terminology

Prior to further describing the cost-effectiveness model structure, it is important to highlight definitions used in the cost-effectiveness model. These definitions were used to specify how patients flowed through the decision tree and entered the Markov model.

3.3.3.1 Already Linked

The term Already Linked referred to patients who underwent an EDVS. Patients who were Already Linked screened positive for infection, and they were Already Linked to care for a known diagnosis of this infection prior to the EDVS. Figure 3.3 shows how these patients flowed through the decision tree component of the model. These patients who were Already Linked terminated at a decision tree terminal node and did not enter the Markov model.

Figure 3.3: The cost-effectiveness model's decision tree: patients who screened positive and were Already Linked (EDVS Screen strategy versus No EDVS Screen strategy)[a].



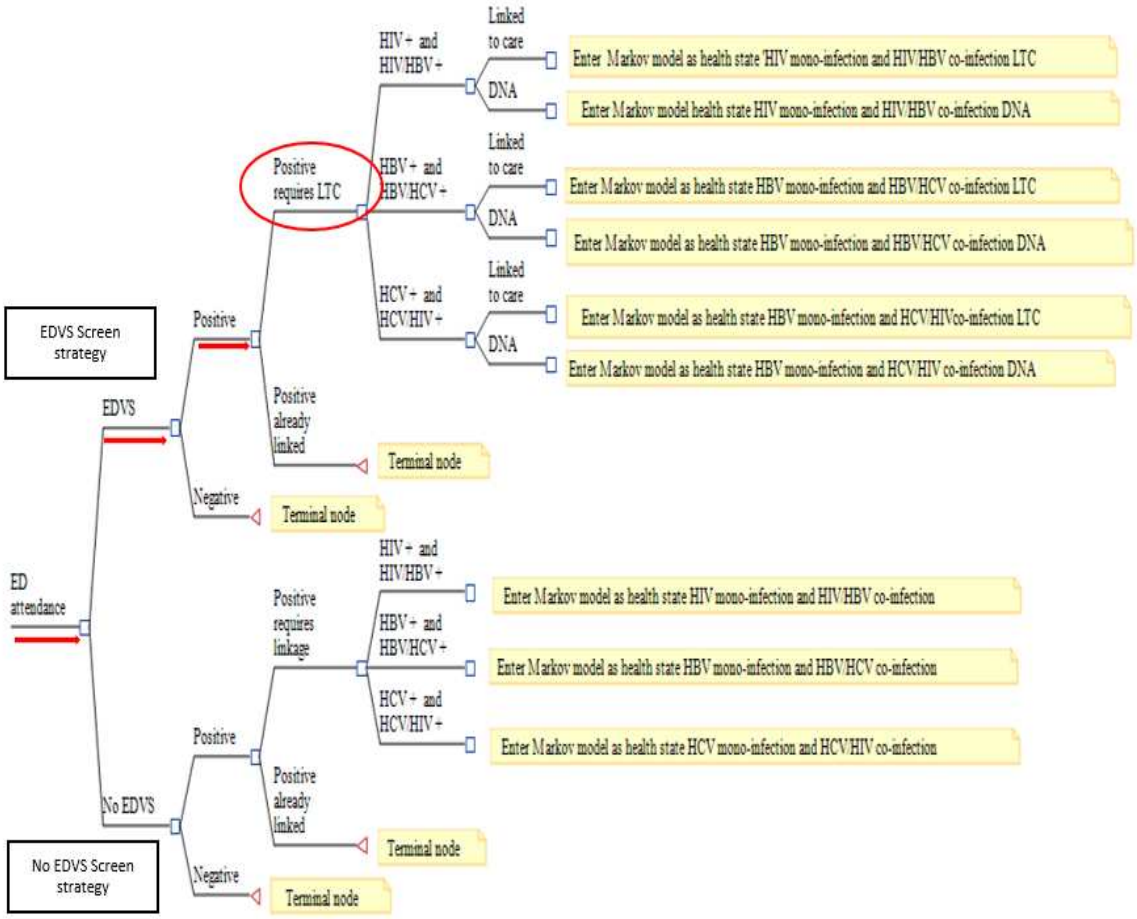
ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

[a] Red arrows indicate how these patients flowed through the decision tree and entered the Markov model.

3.3.3.2 Require(s/ing) Linkage to care

The term Require(s/ing) LTC referred to patients with newly diagnosed infection following screening, patients with known infection who disengaged from care and required re-linkage to care following screening, and patients who tested positive who were uncontactable following screening and therefore the history of their infection status was unknown. Patients were followed for one year post diagnosis and categorised as Requiring LTC if they had not linked to care during that time. These patients then entered into one of the three decision tree health states (according to infection) prior to entering the Markov model. Figure 3.4 shows how patients who Require LTC flowed through the EDVS Programme decision tree.

Figure 3.4: The cost-effectiveness model's decision tree: patients who screened positive and Require LTC (EDVS Screen strategy versus No EDVS Screen strategy)[a].



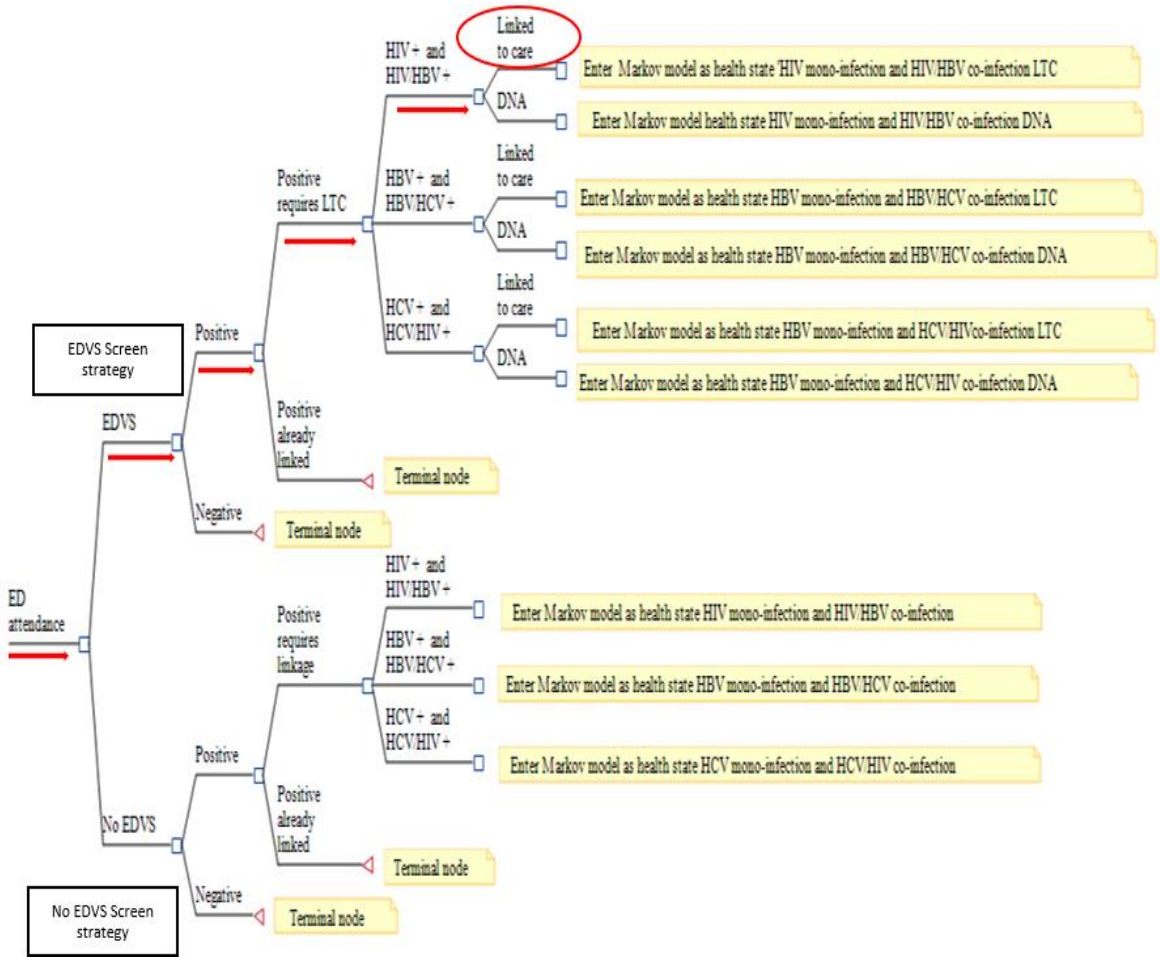
ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

[a] Red arrows indicate how these patients flowed through the decision tree and entered the Markov model.

3.3.3.3 Linked to Care

The term Linked to Care referred to patients who Require LTC and subsequently Linked to Care. These patients who Linked to Care were defined as patients contacted, informed, and attended for one or more consultant-led hospital outpatient reviews. Figure 3.5 shows how these patients who Linked to Care flowed through the decision tree component of the model using one of the three health states (i.e. HIV mono-infection or HIV/HBV co-infection) as an example.

Figure 3.5: The cost-effectiveness model's decision tree: patients who screened positive and Linked to Care (EDVS Screen strategy versus No EDVS Screen strategy)[a].



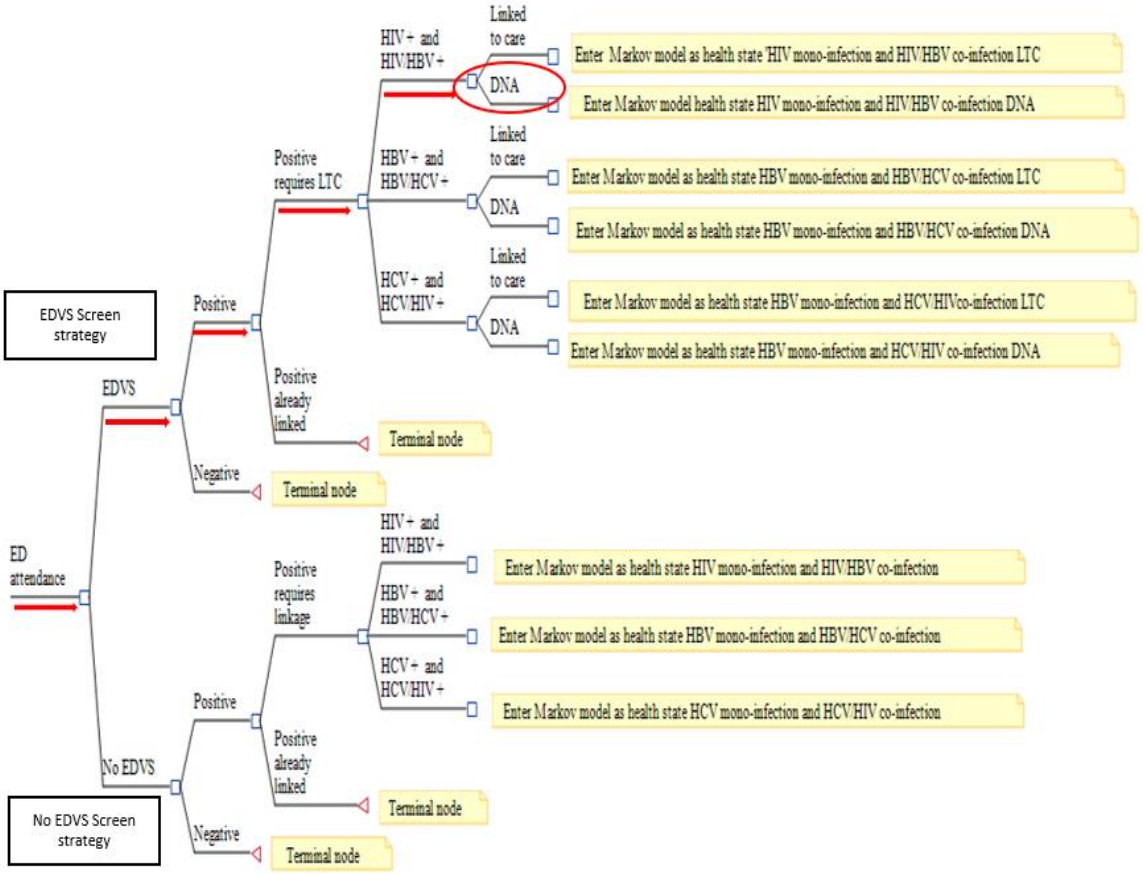
ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

[a] Red arrows indicate how these patients flowed through the decision tree and entered the Markov model.

3.3.3.4 Did-not-attend (DNA)

Once it was established that patients Require LTC, all patients who were contactable were offered LTC. While a proportion of patients Linked to Care, a proportion did-not-attend (DNA). These patients who DNA were defined as patients who were offered LTC but DNA for same in a one year follow up. Figure 3.6 shows how these patients who DNA flowed through the decision tree component of the model using one of the three health states (i.e. HIV mono-infection or HIV/HBV co-infection) as an example.

Figure 3.6: The cost-effectiveness model's decision tree: patients who screened positive and DNA (EDVS Screen strategy versus No EDVS Screen strategy)[a].



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

[a] Red arrows indicate how these patients flowed through the decision tree and entered the Markov model.

3.3.4 Model Structure Overview

The bespoke cost-effectiveness model comprised a decision tree that fed into a Markov model. The decision tree ended with the patients who screened positive for infection and who Require LTC entering the Markov model in one of three health states. However, for the patients who Already Linked and patients who screened negative, their journey through the cost-effectiveness model terminated at a decision tree terminal node and they did not enter the Markov model. When patients entered the Markov model, they transitioned through sub-health states for the remainder of the model's lifetime time horizon.

The EDVS Screen Strategy arm and the No EDVS Screen strategy arm were structured the same way, with the same probabilities of flowing through each branch.

Patients who Require LTC divided into three health states prior to entering the Markov model. These three health states were:

- HIV mono-infection or HIV/HBV co-infection

- HBV mono-infection or HBV/HCV co-infection

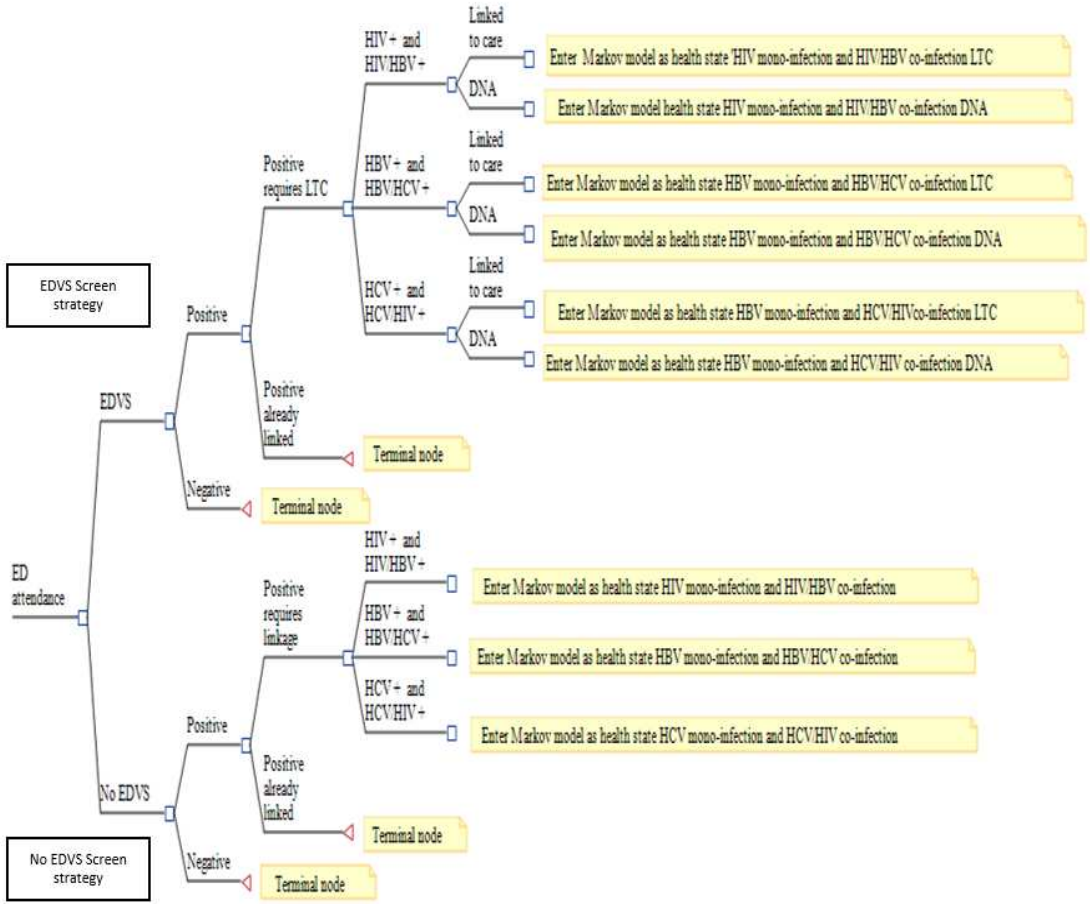
- HCV mono-infection or HCV/HIV co-infection.

A pragmatic approach was taken in the model, whereby, for each virus, patients with mono-infection and co-infection were categorised together. This approach was considered reasonable given the small numbers of patients in the EDVS real-world PLD registry database[i] who were co-infected (Chapter 4, section 4.2.2).

3.3.5 Decision Tree

The flow of patients through the EDVS Screen strategy arm and the NO EDVS Screen strategy arm of the decision tree was informed by data from the EDVS real-world PLD registry database[i]. Thus, the probabilities of flowing through the decision tree was based on data from the EDVS real-world PLD registry database[i]. Figure 3.7 shows the overall cost-effectiveness model's decision tree, comparing the EDVS Screen strategy to the No EDVS Screen strategy.

Figure 3.7: The cost-effectiveness model's decision tree: EDVS Screen strategy versus No EDVS Screen strategy.



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus.

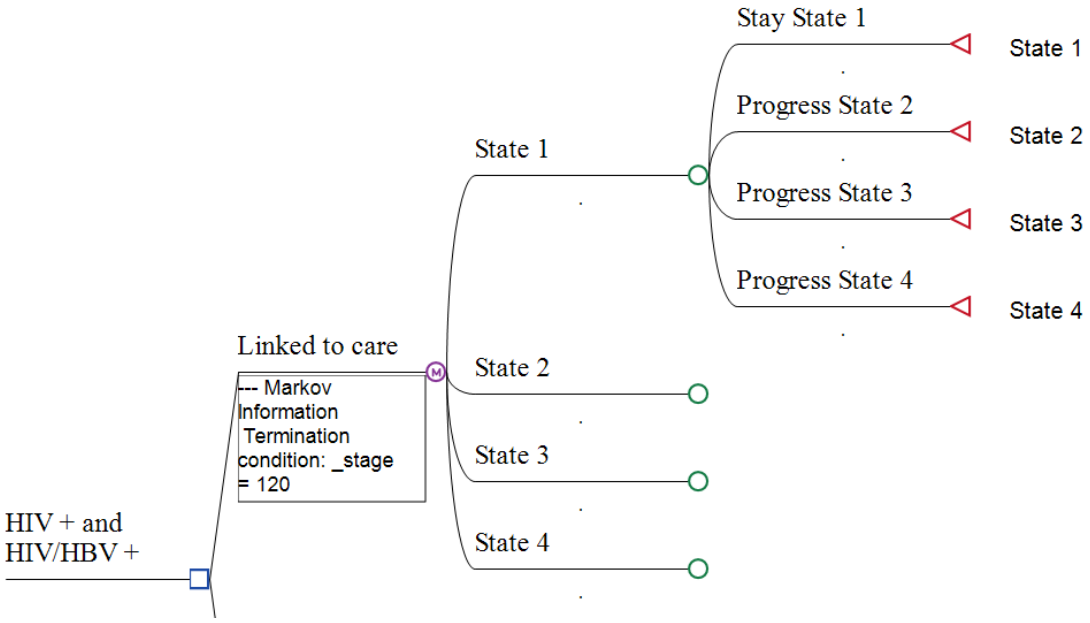
In the EDVS Screen strategy, a proportion of patients who Require LTC subsequently Linked to Care, and a proportion of patients DNA.

In the model, it was assumed that the same cohort of patients who had flowed through the EDVS Screen strategy arm would also simultaneously flow through the No EDVS Screen strategy arm. This was to simulate the movement of all patients under the hypothetical situation where they had not been able to avail of the EDVS Programme. Thus, the proportions of patients assumed to be positive for HIV, HBV, HCV (mono-infection and co-infection) were the same in both arms of the model. However, to reflect reality, it was assumed that patients would be diagnosed at a later time point in No EDVS Screen strategy arm (as described in Chapter 4).

3.3.6 Markov Model

For patients who Require LTC, they entered the Markov model in one of three health states. These health states immediately divided into sub-health states. Sub-health states are described in sections 3.3.7 and 3.3.8. These sub-health states were the same for the EDVS Screen strategy and the No EDVS Screen strategy arms of the model. Figure 3.8 shows the HIV mono-infection or HIV/HBV co-infection sub-health states in the Markov model.

Figure 3.8: The cost-effectiveness model's Markov model: sub-health state 1 of HIV mono-infection or HIV/HBV co-infection health state, including the absorbing states[a].



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **DNA**: did-not-attend; **HIV**: Human Immunodeficiency Virus; **HBV:** Hepatitis B Virus.

[a] Absorbing states of each Markov cycle refers to the sub-health state that patients are in at the end of that cycle, based on transition probabilities.

In a Markov model, each cycle represents one year in a patient's lifetime (139). Our cost-effectiveness model adopted a lifetime time horizon. Patients in the EDVS Screen strategy arm entered the Markov model at the age of 43 years. This was based on the mean age of patients in the EDVS Programme[i].

In the No EDVS Screen strategy arm, patients entered the Markov model at the age of 53 years. This was an assumption and based on available studies that analysed patient characteristics of those who presented late for care (28, 144). In our model, QALYs accrued over this 10 year time

frame were included in the model inputs. It was assumed that patients in both arms of the model would continue to visit their General Practitioners at the same rate over this time period; therefore, costs across both strategy arms cancel out. This assumption is further described in Chapter 4.

3.3.7 Health States Definition

For patients who Require LTC, they were in one of three health states prior to entering the Markov model as previously described (see Table 3.1).

3.3.7.1 HIV Mono-infection or HIV/HBV Co-infection

In the HIV mono-infection health state, there were 61 patients with HIV mono-infection who Require LTC. There were 46 patients with a new HIV diagnosis, 11 patients with known HIV infection who had disengaged from care, and four patients for whom infection status history was not known. Of the 61 patients who Require LTC, 83.6 % of patients Linked to Care and 16.4% DNA.

There were two patients with HIV/HBV co-infection who Require LTC. There were two patients with a new HIV/HBV diagnosis, no patients with known HIV/HBV infection who had disengaged from care and no patients for whom infection status history was not known. Of the two patients who Require LTC, both patients Linked to Care.

3.3.7.2 HBV Mono-infection or HBV/HCV Co-infection

In the HBV mono-infection or HBV/HCV co-infection health state, there were 114 patients with HBV mono-infection who Require LTC. There were 67 patients with a new HBV diagnosis, 34 patients with known HBV infection who had disengaged from care, and 13 patients for whom infection status history was not known. Of the 114 patients who Require LTC, 60.5% of patients Linked to Care and 39.5% patients DNA.

There were five patients with HBV/HCV co-infection who Require LTC. There were five patients with a new HBV/HCV diagnosis, no patients with known HBV/HCV infection who had disengaged

from care and no patients for whom infection status history was not known. Of the five patients who Require LTC, 60% of patients Linked to Care and 40% of patients DNA.

3.3.7.3 HCV Mono-infection or HCV/HIV Co-infection

In the HCV mono-infection or HCV/HIV co-infection health state, there were 377 patients with HCV (RNA +) mono-infection who Require LTC. There were 148 patients with a new HCV diagnosis, 200 patients with known HCV infection who had disengaged from care and 29 patients for whom infection status history was not known. Of the 377 patients who Require LTC, 48.5% of patients Linked to Care and 51.5% of patients DNA.

There were 11 patients with HCV/HIV (RNA +) co-infection who Require LTC. There were 11 patients with a new HCV/HIV diagnosis, no patients with known HCV/HIV infection who had disengaged from care and no patients for whom infection status history was not known. Of the 11 patients who Require LTC, all patients Linked to Care.

The above describes the EDVS Screen strategy arm of the model. All patients who Require LTC in the No EDVS Screen strategy arm enter the Markov model as Linked to Care.

3.3.8 Health States and Sub-health States Markov Model

Each of the three health states divided into a varying number of sub-health states. Patients could remain in their entry sub-health state, or transition between sub-health states. The transition between these sub-health states can be illustrated using transition state diagrams. The transition state diagrams that describe the potential transitions for patients who are HIV positive, HBV positive or HCV positive are provided in Figure 3.9, Figure 3.10, and Figure 3.11 respectively.

3.3.8.1 HIV Mono-infection or HIV/HBV Co-infection Sub-health States

In the HIV mono-infection or HIV/HBV co-infection health state, patients entered the Markov model in one of four sub-health states. These sub-health states were based on $CD4^+$ count at

time of diagnosis[i]. Table 3.2 includes a breakdown of patients in each sub-health state and the sub-health state definition.

Table 3.2: HIV mono-infection or HIV/HBV co-infection sub-health states at diagnosis and patient no. based on data from the EDVS real-world PLD registry database[ia].

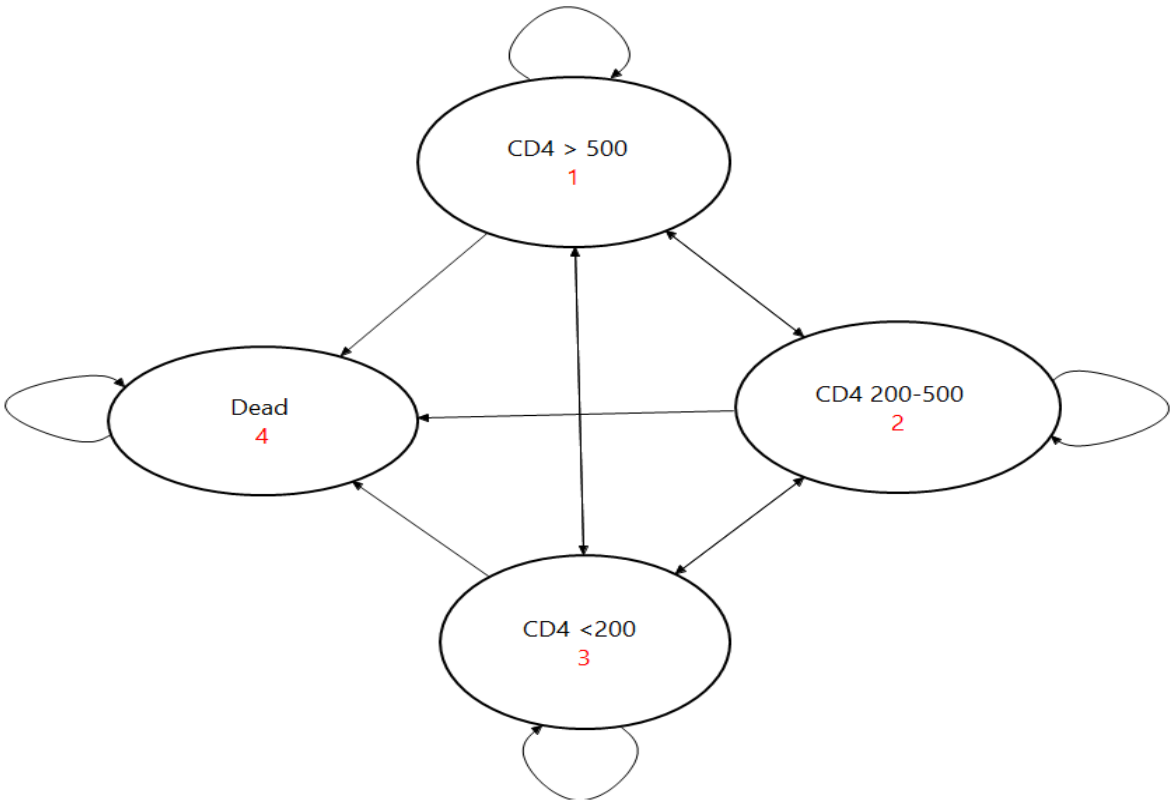
HIV mono-infection (n = 51)	**State 1**	**State 2**	**State 3**	**State 4**
Definition	$CD4^+$ >500	$CD4^+$ 200 - 500	$CD4^+$<200	Dead
Patients (n(%))	34 (67%)	6(11%)	10 (20%)	1 (2%)
HIV/HBV co-infection (n = 2)				
Patients (n(%))	1 (50%)	0	1 (50%)	0

EDVS indicates Emergency Department Viral Screen; **HIV**: Human Immunodeficiency Virus; **PLD**: patient-level data.

[a] There were a total of n = 53 patients in this HIV mono-infection or HIV/HBV co-infection health state.

Figure 3.9 shows a transition state diagram for the HIV mono-infection or HIV/HBV co-infection health state. This transition state diagram was derived from the CDC's (US) *Medical Monitoring Project* (MMP) (145). MMP is a commonly referenced multisite surveillance system of PLHIV who receive medical care in the US.

Figure 3.9: A transition state diagram of the four HIV mono-infection or HIV/HBV co-infection sub-health states[a].



HIV indicates Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a] Transition to Dead (State 4) possible from all sub-health states because background rates of mortality are included in the cost-effectiveness model.

3.3.8.2 HBV Mono-infection or HBV/HCV Co-infection Sub-health states

In the HBV mono-infection or HBV/HCV co-infection health state, patients entered the Markov model in one of ten sub-health states. Table 3.3 includes a breakdown of patients in each sub-health state and the sub-health state definition.

Table 3.3: HBV mono-infection or HBV/HCV co-infection sub-health states at diagnosis and patient no. based on data from the EDVS real-world PLD registry database[a].

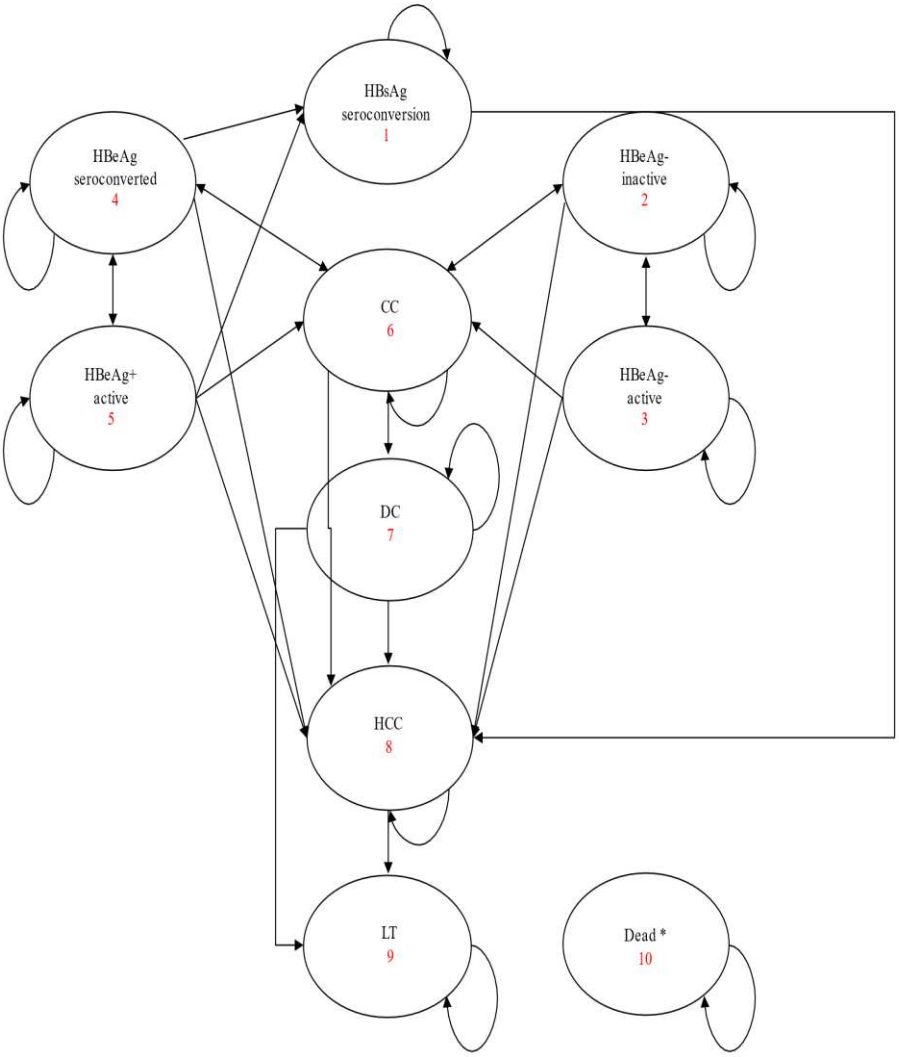
HBV mono-infection (n = 69)	**State 1**	**State 2**	**State 3**	**State 4**	**State 5**	**State 6**	**State 7**	**State 8**	**State 9**	**State 10**
Definition	HBsAg seroconverted	HBeAg– inactive	HBeAg– active	HBeAg seroconverted	HBeAg+ active	CC	DC	HCC	LT	Dead
Patients (n (%))	10 (14.5%)	36 (52.2%)	8 (11.6%)	1 (1.4%)	5 (7.2%)	7 (10.2%)	2 (2.9%)	0	0	0
HBV/HCV co-infection (n = 5)										
Patients (n (%))	0	5 (100%)	0	0	0	0	0	0	0	0

HBV indicates Hepatitis B Virus; **HCV:** Hepatitis C Virus; **EDVS:** Emergency Department Viral Screen; **PLD:** patient-level data**; HBsAg** indicates Hepatitis B surface antigen; **HBeAg**, Hepatitis B e antigen; **CC**, compensated cirrhosis; **HCC**, hepatocellular carcinoma; **LT**, liver transplantation.

[a] There were a total of n = 74 patients in this HBV mono-infection of HBV/HCV co-infection health state.

Figure 3.10 shows a transition state diagram for HBV mono-infection or HBV/HCV co-infection health state. This transition state diagram was based on a 2006 systematic review by Shepherd *et al* and a 2007 systematic review by Takeda *et al* of EEs of treatment of chronic HBV (146, 147).

Figure 3.10: A transition state diagram of the HBV mono-infection or HBV/HCV co-infection sub-health states [a].



HBV indicates Hepatitis B Virus; **HCV:** Hepatitis C Virus; **HBsAg** indicates Hepatitis B surface antigen; **HBeAg**, Hepatitis B e antigen; **CC**, compensated cirrhosis; **HCC**, hepatocellular carcinoma; **LT**, liver transplantation.

[a] Transition to Dead (State 10) possible from all sub-health states because background rates of mortality are included in the cost-effectiveness model.

3.3.8.3 HCV Mono-infection or HCV/HIV Co-infection Sub-health States

In the HCV mono-infection or HCV/HIV co-infection health state, patients entered the Markov model in one of seven sub-health states. Table 3.4 includes a breakdown of patients in each sub-health state and the sub-health state definition.

Table 3.4: HCV mono-infection or HCV/HIV co-infection sub-health states at diagnosis and patient no. based on data from the EDVS real-world PLD registry database[ia].

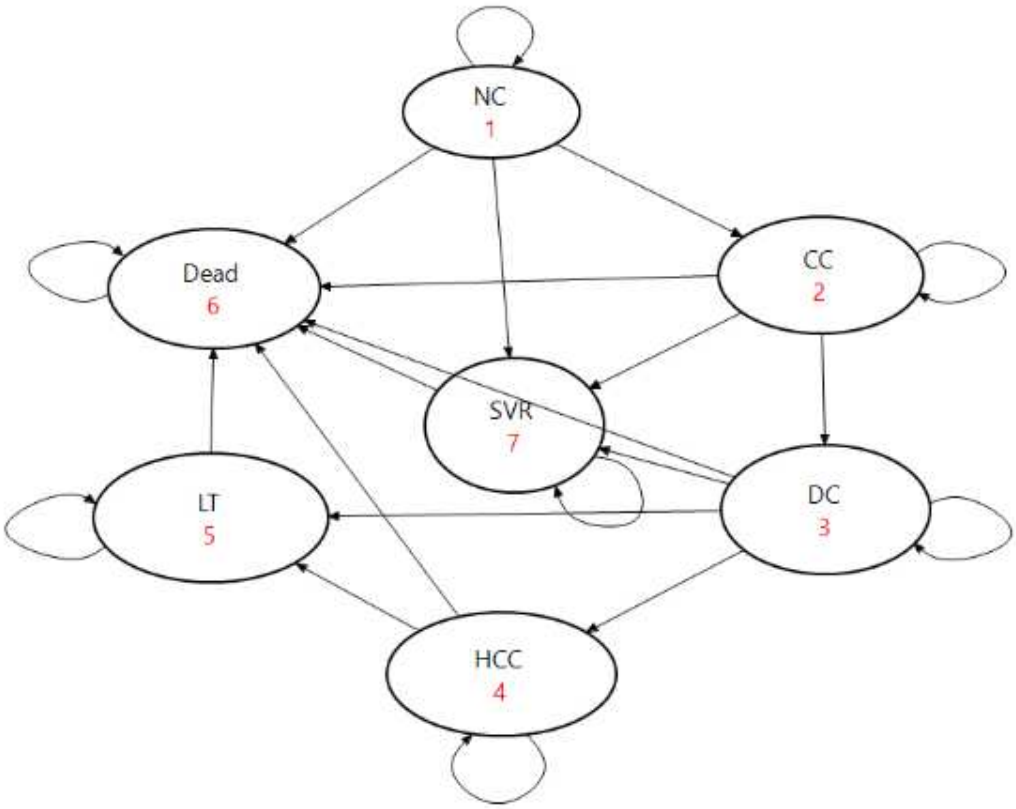
HCV mono-infection (n = 132)	**State 1**	**State 2**	**State 3**	**State 4**	**State 5**	**State 6**	**State 7**
Definition	Non-cirrhotic	Compensated cirrhosis	Decompensated cirrhosis	HCC	LT	Dead	HCV SVR
Patients (n(%))	111 (84%)	9 (7%)	12 (9%)	0	0	0	0
HCV/HIV co-infection (n = 11)							
Patients (n(%))	10 (90.9%)	1 (9.1%)	0	0	0	0	0

HIV indicates Human Immunodeficiency Virus; **HCV:** Hepatitis C Virus; **EDVS:** Emergency Department Viral Screen; **PLD:** patient-level data; **HCC** indicates hepatocellular carcinoma; **LT**, liver transplantation; **SVR**, sustained virologic response.

[a] There were a total of n = 143 patients in this HCV mono-infection or HCV/HIV co-infection health state.

Figure 3.11 shows a transition state diagram for HCV mono-infection or HCV/HIV co-infection health state. This transition state diagram was based on a UK 2020 evaluation of the cost-effectiveness of opt-out HBV and HCV screening in the ED by Williams *et al* (114).

Figure 3.11: A transition state diagram of the seven HCV RNA positive mono-infection or HCV/HIV co-infection sub-health states [a].



HCV indicates Hepatitis C Virus; **HIV:** Human Immunodeficiency Virus; **RNA:** ribonucleic acid; **NC** indicates non-cirrhotic; **CC**, compensated cirrhosis; **HCC**, hepatocellular carcinoma; **LT**, liver transplantation; **SVR**, sustained virologic response.

[a] Transition to Dead (State 6) possible from all sub-health states because background rates of mortality are included in the cost-effectiveness model.

3.4 Validation

A health economist reviewed the model in TreeAge Pro 2020® (TreeAge Software Inc, Williamstown, MA, USA). Expert opinion was elicited from an Infectious Diseases Medical Consultant in Ireland who is the lead clinician over the EDVS Programme, and who diagnoses and treats patients with HIV, HBV, and HCV. The expert validated the structure of the model and the care pathways and confirmed that the parameter values were reasonable. Care pathways and treatments were based on international guidelines.

3.5 Discussion

This bespoke cost-effectiveness model was developed to simulate expected lifetime costs and outcomes associated with the introduction of an EDVS Programme in an Irish healthcare setting.

The development of this cost-effectiveness model was required to allow us to estimate costs and effects beyond the available real-world data time horizon. As such, differences in lifetime costs and effects, accumulated in the EDVS Screen strategy and the No EDVS Screen strategy, will be determined and reported. This chapter has reported on the steps taken to structure this cost-effectiveness model. The expected flow of patients through health states and sub-health states (where appropriate) over a lifetime horizon has been described.

The proposed model was informed by a two-step approach. Firstly, it used prospective data from the EDVS real-world PLD registry database[i] to demonstrate how patients flowed through the decision tree. Secondly, a targeted literature review of national and international data, using PubMed, Google Scholar, and OVID-Medline databases, from January 2001 to December 2021 inclusive, informed the choice of sub-health states in our model.

National guidelines informed this cost-effectiveness model; these guidelines state that any cost-effectiveness decision model should be clearly described, and the assumptions made should be made evident (12). These guidelines also state that the comparator should be standard of care; a No EDVS Screen strategy is the current standard of care in Ireland.

A 2003 report by the ISPOR task force entitled *The Principles of Good Practice for Decision Analytic Modelling in Healthcare Evaluation*, highlighted the value of a well-designed cost-effectiveness model in healthcare evaluation (132). The report highlighted three criteria for assessing the quality of cost-effectiveness models: model structure, input data, and model validation. In this chapter, our model structure is clearly described, and the decision tree is based on applicable and validated real-world practice in the form of the EDVS Programme. The authors also concluded that while assumptions are made with model structures, these assumptions should be disclosed and analysed in a SA. The authors also stated that any results are conditional based on these assumptions.

This cost-effectiveness model analysed the EDVS Programme in our institution; it evaluates cost-effectiveness in an Irish healthcare setting. The review of the EDVS real-world PLD registry database has highlighted some valuable real-world inefficiencies that should be addressed. One such inefficiency is duplicate EDVS. Of all the EDVS during this study period[i] (n = 102,837), 31.3% (n = 32,451) of these screens were duplicates. A possible method to reduce these inefficiencies could be to highlight in the patient's electronic health record that if a patient has had an EDVS in the preceding three months, they shouldn't have another within that time frame (unless they had a specific indication/new acquisition risk). However, the bigger issue that duplication of EDVS highlights is the disproportionate and frequent use of the ED by certain (and likely vulnerable high risk) patient groups. Further study of the EDVS Programme is needed in this area.

The analysis[i] also highlights a 33.4% (n = 51,560) opt-out rate of screening amongst phlebotomised patients in the ED. This opt-out rate has improved compared to an opt-out rate of 53% (n = 47,319) reported by Grant *et al* when the authors analysed the first 35 months of the EDVS Programme (92). An initiative to increase uptake of screening could be to provide further education for patients and healthcare providers on the benefits of the programme. While there is no data available on the patient characteristics of those that opted-out of an EDVS, it could be useful to analyse this group of patients. Additionally, there could be scope to analyse patients who were not phlebotomised in the ED. Exclusion of these groups in our cost-effectiveness model could have potentially led to biases. More study is needed in this area however and is planned for late 2022/2023.

3.6 Limitations

A limitation of the model structure included some of the model's assumptions. The main assumptions to highlight include:

- The EDVS Screen strategy was compared to a No EDVS Screen strategy. An assumption was made that patients in the hypothetical No EDVS Screen strategy follow the same pathway through the decision tree and into the Markov model as the EDVS Screen strategy. This assumption was felt to be justified because these patients would have been attending the ED irrespective of undergoing an EDVS.

- The model assumed that there was no background rate of screening for patients in the No EDVS Screen strategy. The functionality of the model would not allow for the inclusion of background rates of testing. Consequently, while these patients may have still been diagnosed with infection following an EDVS, they may not Require LTC. While we don't think this would impact overall cost-effectiveness results, we postulate that the ICER may be underestimated. However, overall impact on the ICER of background rates of testing in this analysis is unknown.

- In the EDVS Programme[i], there were low numbers of patients with co-infection. In a pragmatic approach to modelling, it was assumed that mono-infection and co-infection health states were similar and as such, they were categorised together into one of three health states.

- Tri-infections were diagnosed but none Require LTC. While tri-infections were represented in the decision tree (in the form of a positive EDVS), no patients with tri-infection were analysed in the Markov model. While this model structure was appropriate for our patient cohort, this point may need to be reviewed should this analysis be used for other patient cohorts where patients with tri-infection Require LTC.

- For patients who Require LTC, it was assumed that patients with infection who were uncontactable required LTC. This may not, however, be the case, as some of these uncontactable patients may be Linked to Care in another healthcare institution. Therefore, this may have falsely elevated the number of patients who Require LTC in our model. Because both strategies included this assumption however, this was felt to unlikely impact the cost-effectiveness results.

- When analysing patients who DNA, they were only followed for one year post EDVS. Thus, it was assumed that they Required LTC if they hadn't engaged in care within a year of the EDVS. Some patients may have Linked to Care in repeat EDVS, thereby falsely elevating the number of patients who Require LTC in our model. Because both strategies included this assumption however, this was felt to unlikely impact the cost-effectiveness results.

3.7 Conclusion

Although there were assumptions made regarding this model structure, much of the model was based on applicable and validated real-world practice in the form of the EDVS Programme. We have developed a cost-effectiveness model that reflects the lifetime pathways of patients attending an Irish healthcare setting who were both screened and not screened for HIV, HBV, and HCV. The structure was clearly described, and assumptions highlighted.

CHAPTER 4 INPUT PARAMETERS OF THE COST-EFFECTIVENESS MODEL

4.1 Introduction

A bespoke cost-effectiveness model consisting of a decision tree that flows into a Markov model was developed and discussed in Chapter 3. The aim of this model was to simulate expected prevalence, lifetime costs, and effects associated with the EDVS Programme in our institution (and thus ED screening for HIV, HBV, and HCV in an Irish healthcare setting).

Input parameters required for this model are discussed in Chapter 4. These parameters include probability (converted from prevalence), time dependant variables, and fixed variables. Probabilities were derived from the EDVS real-world PLD registry database[i]. Time dependent and fixed variables were obtained from a targeted literature review of national and international data. Databases searched were PubMed, Google Scholar, and OVID-Medline databases, from January 1990 to December 2021 inclusive.

4.2 Prevalence and Probability

4.2.1 Overview of the Emergency Department Viral Screen Programme

The EDVS is an opt-out screen for HIV, HBV, and HCV. It is offered to all patients who are being phlebotomised for other reasons in the ED setting in our institution. Data was analysed from the first five years of the Programme (July 2015 to June 2020 inclusive).

Data dictated how patients flowed through the model's decision tree. During this study period[i], there was 245,561 patient attendances to the ED. 62.9% of all ED attendees were phlebotomised. Of all patients phlebotomised, 66.6 % of patients underwent an EDVS.

It is important to highlight that some patients had recurrent ED attendances during this time frame[i]. Consequently, some patients were phlebotomised multiple times and they had multiple EDVS. While EDVS per-patient per-screen costs were included in the model, duplicate screen results were excluded from the analysis.

During this study period[i], of all unduplicated EDVS analysed, 4.8 % (n = 3,360) of patients tested positive for infection (mono-infection, co-infection, or tri-infection). A subsequent 16.96% (n = 570) of all positive patients (n = 3,360) Require LTC. Overall, of all the unduplicated patients with a positive or negative EDVS (n = 70,386), 0.81% of patients Require LTC (n = 570) (Chapter 3, Figure 3.1).

As discussed in Chapter 3, patients who Require LTC (n = 570) were defined as patients with newly diagnosed infection, patients with known infection who disengaged from care, and patients who tested positive who were uncontactable and therefore their infection status history was unknown. These patients who were uncontactable were assumed to Require LTC. Patients were followed for one year post diagnosis and categorised as patients who Require LTC if they had not engaged in care during that time.

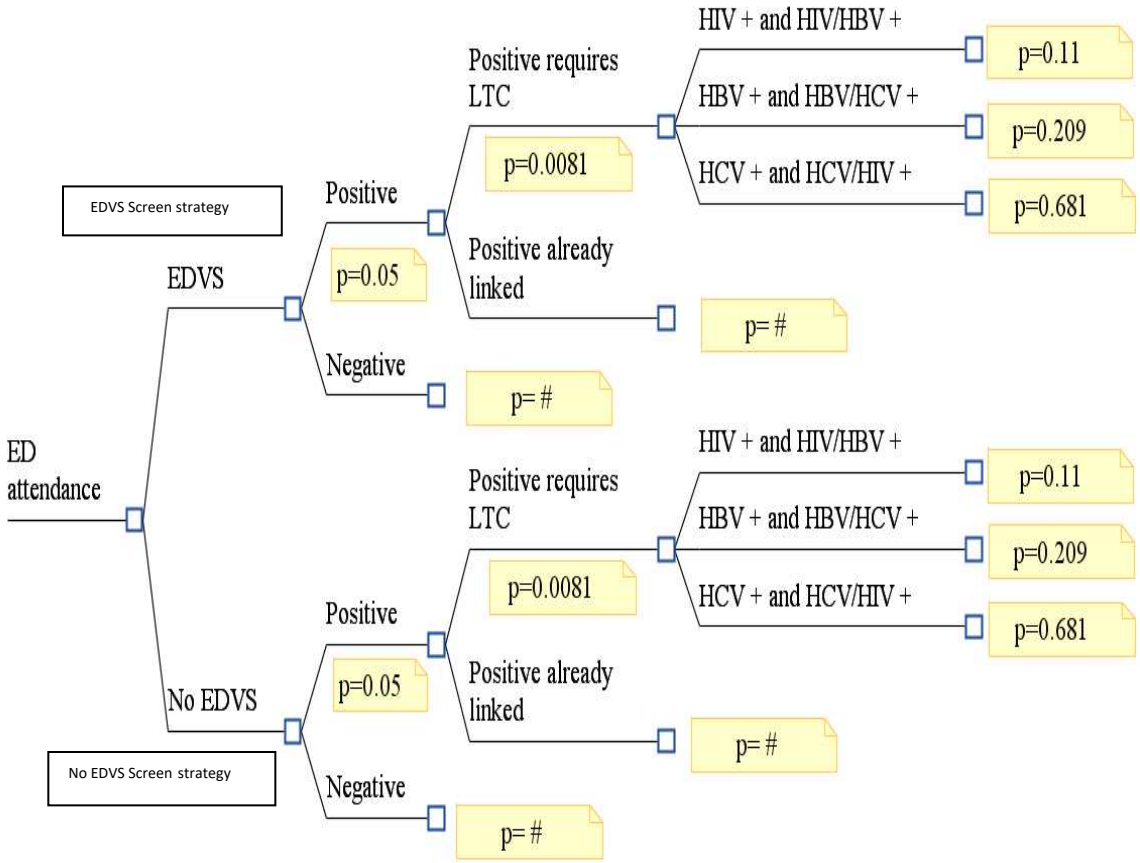
The decision tree of the cost-effectiveness model parameterised seroprevalence from the EDVS Programme[i]. This seroprevalence was converted to probability using the following equation (148):

- $P = a/b$

Where: *p = probability; a = the number of "events" (% infections); b = the total number at risk (100%).*

The probabilities used in the decision tree component of the cost-effectiveness model are shown in Figure 4.1. The EDVS Screen strategy represented the intervention arm of the decision tree. The comparator arm was the No EDVS Screen strategy. Patients in the No EDVS Screen strategy arm were assumed to be subject to the same probabilities of screening positive and requiring LTC as the EDVS Screen strategy.

Figure 4.1: The cost-effectiveness model's decision tree: probabilities of flowing through the decision tree (EDVS Screen strategy versus No EDVS Screen strategy)[ab].



ED indicates Emergency Department; **EDVS**: Emergency Department Viral Screen; **LTC**: linkage to care; **p**: probability, converted from prevalence; **#:** probability: (1 – ∑other probabilities that stem from the same node); **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] Based on data from the EDVS Programme 1/7/2016 to 30/6/2020 inclusive.
[b] As an example, in both the EDVS Screen strategy and No EDVS screen strategy, the probability of screening positive for an infection was 0.05. The probability of positive patients Requiring LTC was 0.0081.

4.2.2 Health States and Sub-health States

There were three health states in the model (Figure 4.2). In a pragmatic approach, given the low number of patients with co-infection in the EDVS Programme[i] who Require LTC, patients with mono-infection and co-infection were categorised together. The three health states were:

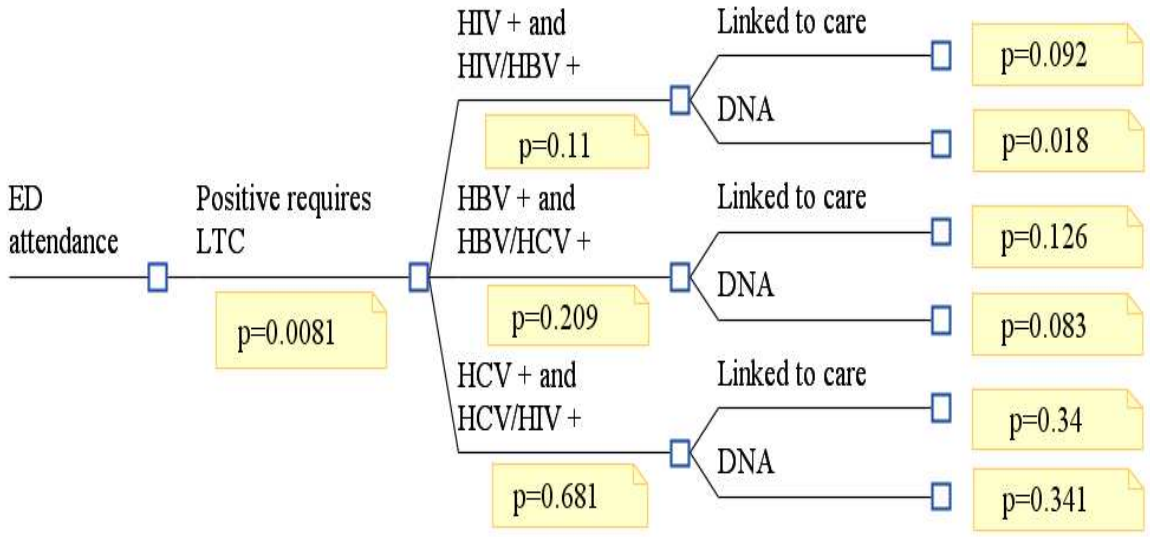
- HIV mono-infection or HIV/HBV co-infection

- HBV mono-infection or HBV/HCV co-infection

- HCV mono-infection or HCV/HIV co-infection.

Within each of these three health states, there were patients who Linked to Care and patients who DNA. These health states were divided into a varying number of sub-health states (Chapter 3). The probability of patients being in one of the three health states and whether they Linked to Care or DNA is shown in Figure 4.2.

Figure 4.2: The cost-effectiveness model's decision tree: probabilities of being in one of the three health states, including patients who Linked to Care and patients who DNA[a].



ED indicates Emergency Department; **LTC**: linkage to care; **DNA**: did-not-attend; **p**: probability, converted from prevalence; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] As an example, the probability of patients with HIV mono-infection or HIV/HBV co-infection who Linked to Care was 0.092.

4.2.2.1 HIV Mono-infection or HIV/HBV Co-infection

According to the EDVS real-world PLD registry database[i], of all the patients who underwent an EDVS, the seroprevalence of new and known HIV was 1.07% (n = 751). This included patients who tested positive for mono-infection, co-infection, or tri-infection.

Amongst patients who tested positive for infection and Require LTC (n = 570), patients with HIV mono-infection accounted for 10.7% (n = 61). A subsequent 83.6% (n = 51) of these patients Linked to Care and 16.4% (n = 10) DNA in a one year follow up. HIV/HBV co-infection accounted for 0.3% (n = 2) of all patients in the EDVS Programme who tested positive for infection and

Require LTC (n = 570). A subsequent 100% (n = 2) of these patients Linked to Care in a one year follow up.

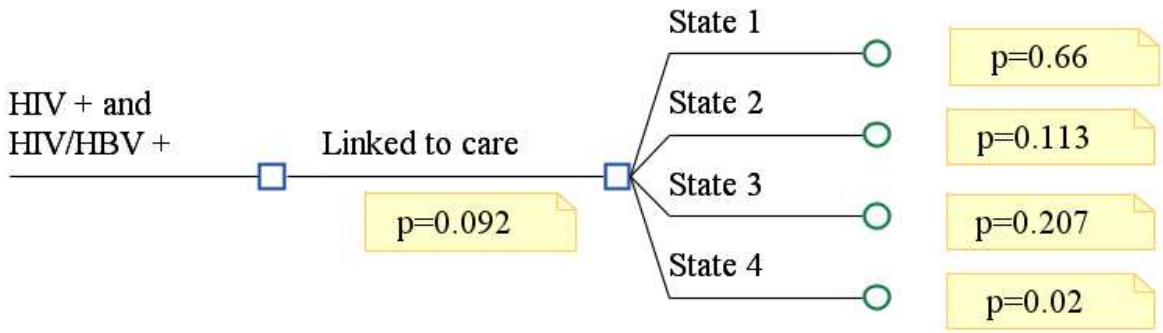
For the HIV mono-infection or HIV/HBV co-infection health state, as sourced from the EDVS real-world PLD registry database[i], the prevalence of HIV mono-infection and HIV/HBV co-infection were combined, converted to probability, and input into the decision tree using the following equation:

- *P = a/b*
- *P = (10.7% + 0.3%) / 100%*
- *P = 0.11*

Where: *P = probability; a = the number of "events" (% infections); b = the total number at risk (100%).*

In the HIV mono-infection or HIV/HBV co-infection health state, patients entered the Markov model in one of four sub-health states (Chapter 3, Table 3.2). Figure 4.3 shows the cost-effectiveness model's sub-health state probabilities for patients in the HIV mono-infection or HIV/HBV co-infection health state for patients who Linked to Care.

Figure 4.3: The cost-effectiveness model: probabilities of the HIV mono-infection or HIV/HBV co-infection health state and sub-health states for patients who Linked to Care.



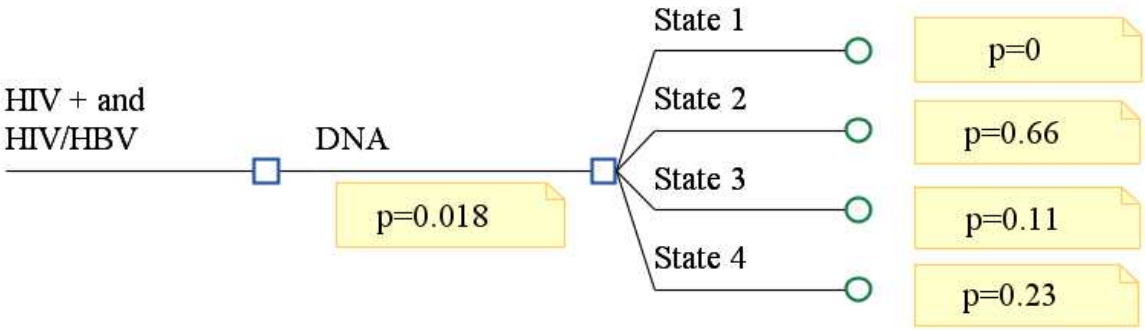
p indicates probability, converted from prevalence; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a] State 1: $CD4^+ > 500$; State 2: $CD4^+$ 200-500; State 3: $CD4^+ < 200$; State 4: dead.
[b] As an example, the probability of all patients with HIV or HIV/HBV who LTC and had a $CD4^+ > 500$ prior to entering the Markov model was 0.66.

In this health state, patients who DNA entered the Markov model according to the probabilities shown in Figure 4.4. These probabilities were informed by definitions of late presentation amongst PLHIV by Rava *et al*. Rava *et al* estimated the prevalence and risk factors of late presentation in a cohort of PLHIV in Spain (from 2004 to 2018 inclusive; n = 14,876). They defined late presentation as PLHIV with a $CD4^+$ less than 350 (Rava *et al*, 2021) (144). In addition, rates of $CD4^+$ decline were derived from a collaboration of 23 cohort studies by Wolbers *et al*. Wolbers *et al* analysed $CD4^+$ cell slopes and progression to AIDS or death amongst PLHIV before they started ART. Wolbers *et al* found that amongst 2,820 PLHIV pre commencing ART, the median $CD4^+$ cell count decline was 61 cells/µl per year (Wolbers *et al*) (149). Median $CD4^+$ count of patients with HIV in stage 1 in the EDVS Programme was 730 cells/µl. Rates of $CD4^+$ decline over a 10 year period was then calculated for these patients.

The No Screen strategy also assumed the same probabilities as patients who DNA, presenting in more advanced sub-health states and at older ages (144).

Figure 4.4: The cost-effectiveness model: probabilities of the HIV mono-infection or HIV/HBV co-infection health state and sub-health states for patients who DNA[abcd].



DNA indicates did-not-attend; **p**: probability, converted from prevalence; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a] Same probabilities for the No EDVS Screen strategy.
[b] State 1: $CD4^+$ > 500; State 2: $CD4^+$ 200-500; State 3: $CD4^+$ < 200; State 4: dead.
[C] As an example, the probability of all patients with HIV or HIV/HBV who DNA and had a $CD4^+$ 200-500 (state 2) prior to entering the Markov model was 0.66.
[d] Probabilities derived from a definition of pate presentation by Rava *et al* (144) and an analysis of $CD4^+$ cell slope decline from Wolbers *et al* (149).

4.2.2.2 HBV Mono-infection or HBV/HCV Co-infection

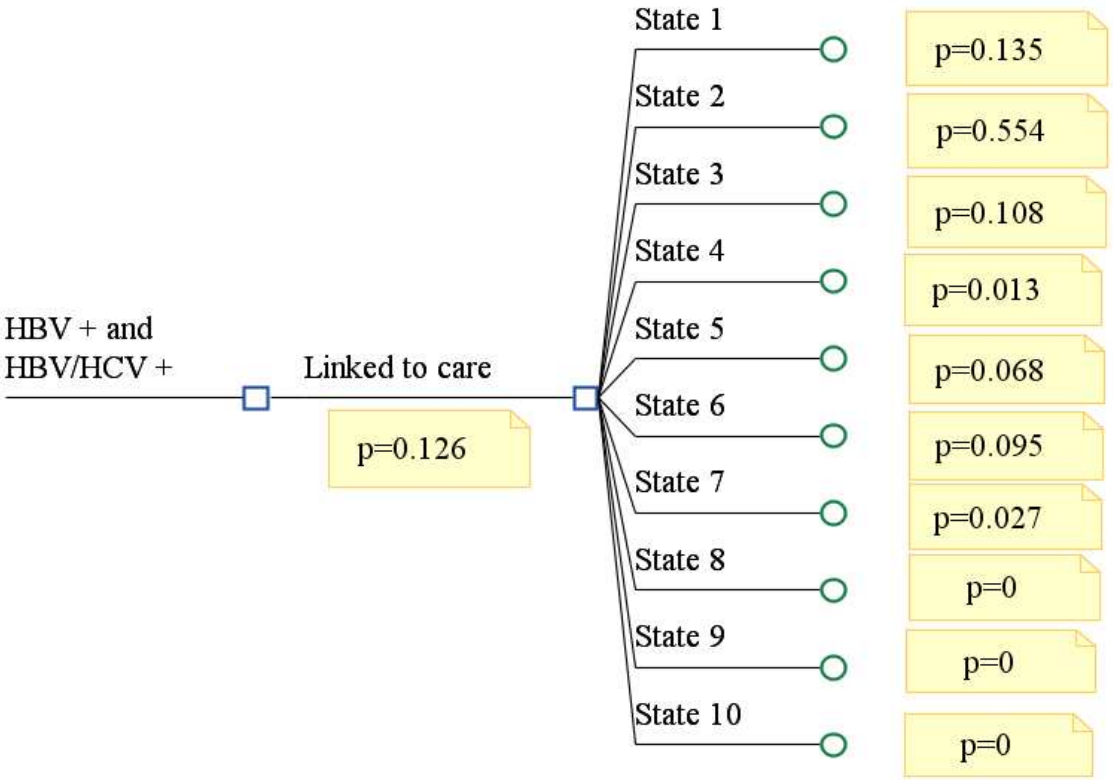
According to the EDVS real-world PLD registry database[i], the seroprevalence of newly diagnosed and previously known HBV was 0.5% (n = 346). This included patients who tested positive for mono-infection, co-infection, and tri-infection.

Amongst patients who tested positive for infection and Required LTC (n = 570), HBV mono-infection accounted for 20% (n = 114). A subsequent 60.5% (n = 69) of these patients Linked to Care and 39.5% (n = 45) DNA. HBV/HCV co-infection accounted for 0.9% (n = 5) of all patients in the EDVS Programme who tested positive for infection and Require LTC (n = 570). A subsequent 60% (n = 3) of these patients Linked to Care and 40% (n = 2) patients DNA in a one year follow up.

For the HBV mono-infection or HBV/HCV co-infection health state, the prevalence of HBV mono-infection and HBV/HCV co-infection, were combined and converted to probability. Figure 4.2 shows the EDVS Programme probabilities for patients in all three health states including patients who Linked to Care and patients who DNA.

In the HBV mono-infection or HBV/HCV co-infection health state, patients entered the Markov model in one of ten sub-health states (Chapter 3, Table 3.3). Prevalence was converted to probabilities. Figure 4.5 shows the EDVS Programme sub-health state probabilities for patients in the HBV mono-infection or HBV/HCV co-infection health state for patients who Linked to Care.

Figure 4.5: The cost-effectiveness model: probabilities of the HBV mono-infection or HBV/HCV co-infection health state sub-health states for patients who Linked to Care[ab].



p indicates probability; **HBsAg**: HBV surface antigen; **HBeAg**: HBV e antigen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **LT**: liver transplantation; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] State 1: HBsAg seroconversion; State 2: HBeAg- inactive; State 3: HBeAg- active; State 4: HBeAg seroconverted; State 5: HBeAg+ active; State 6: CC; State 7: DC; State 8: HCC; State 9: LT; State 10: dead.
[b] As an example, the probability of all patients with HBV or HBV/HCV who Linked to Care and had HBsAg seroconversion (state 1) prior to entering the Markov model was 0.135.

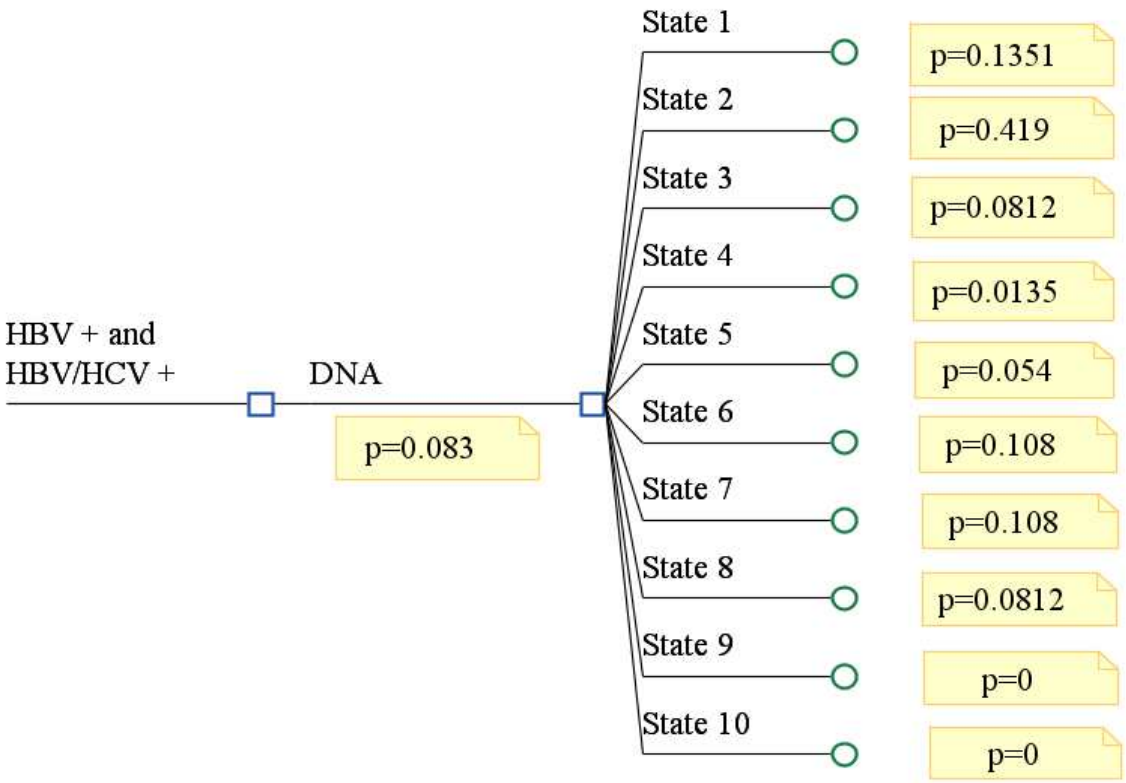
In this health state, patients in the DNA Cohort entered with the probabilities shown in Figure 4.6. Given that the EDVS real-world PLD registry database[i] does not contain data on patients who DNA, these probabilities were informed from an external source. While the rates of progression of fibrosis in both HCV and HBV infection can vary and are not linear, a consensus definition agreed upon by relevant stakeholders including experts in viral hepatitis from EASL and experts from HIV in Europe Initiative defined late presentation as either the presence of significant fibrosis (equal to or greater than F3) without prior antiviral treatment, or the

establishment of DC and/or HCC without prior antiviral treatment (Mauss *et al*, 2014) (28). Therefore, patients who DNA care present at later ages and in more advanced health states.

Probabilities of entering in certain sub-health states were guided by this late presentation definition. Probabilities were further guided by Poh *et al* (2015). Poh *et al* conducted a 10 year surveillance study of 673 patients in Singapore with chronic HBV. The authors analysed the rates of cirrhosis and HCC amongst these patients (2003 and 2004 inclusive and followed for 10 years). Amongst patients without cirrhosis, Poh *et al* calculated the 10 year incidence of developing cirrhosis to be 16.2% (1.6% per year) and HCC to be 7.8% (0.8% per year). The overall incidence of HCC amongst patients with cirrhosis was 29.7% (3% per year) (150).

Patients in the No EDVS Screen strategy had the same probabilities as the patients who DNA in this health state (28).

Figure 4.6: The cost-effectiveness model: probabilities of the HBV mono-infection or HBV/HCV co-infection health state and sub-health states for patients who DNA[abcd].



DNA indicates did-not-attend; **p**: probability, converted from prevalence; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] Same probabilities for the No EDVS Screen strategy.
[b] State 1: HBsAg seroconversion; State 2: HBeAg- inactive; State 3: HBeAg- active; State 4: HBeAg seroconverted; State 5: HBeAg+ active; State 6: CC; State 7: DC; State 8: HCC; State 9: LT; State 10: dead.
[c] As an example, the probability of all patients with HBV or HBV/HCV who DNA and had HBsAg seroconverted (state 1) prior to entering the Markov model was 0.1351.
[d] Probabilities derived from late presentation definition by Mauss *et al* (28) and rates of cirrhosis and HCC development study by Poh *et al* (150).

4.2.2.3 HCV Mono-infection or HCV/HIV Co-infection

According to the EDVS real-world PLD registry database[i], the seroprevalence of HCV RNA mono-infection, co-infection or tri-infection was 1.56% (n = 1,103). Overall HCV antibody seroprevalence was 3.63% (n = 2,558).

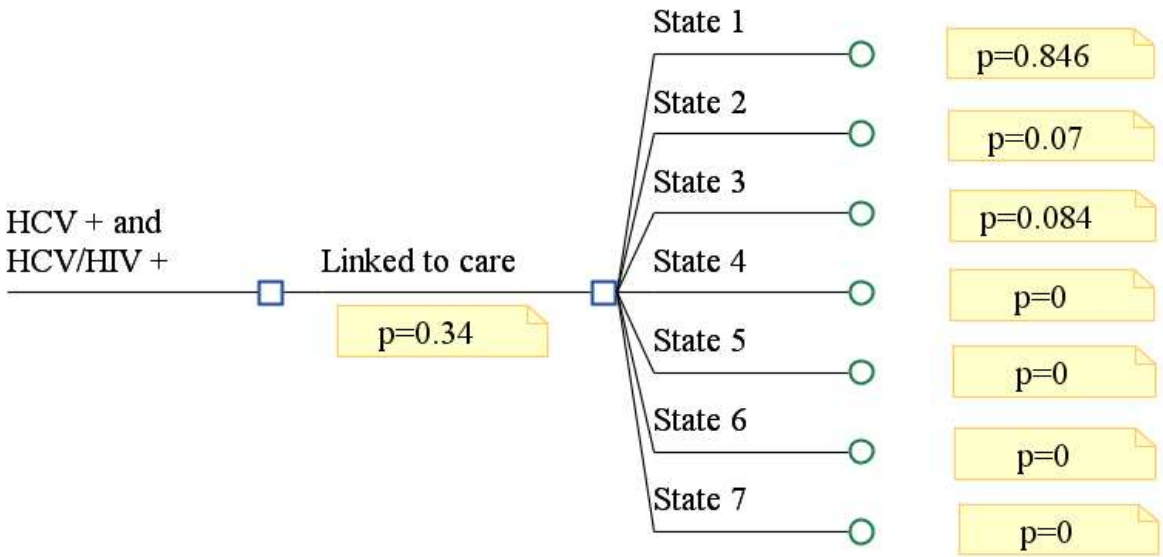
Amongst patients who tested positive for infection and Require LTC (n = 570), HCV mono-infection accounted for 66% (n = 377). A subsequent 48.5% (n = 183) of these patients Linked to Care and 51.5% (n = 194) of patients DNA. HIV/HCV co-infection accounted for 1.9% (n = 11) of

all patients in the EDVS Programme who tested positive for infection and Require LTC (n = 570). A subsequent 100% (n = 11) of these patients Linked to Care and no patients DNA in a one year follow up.

The prevalence of HCV mono-infection and HCV/HIV co-infection were combined and converted to probability. Figure 4.3 shows the EDVS Programme probabilities for patients in all three health states including patients who Linked to Care and patients who DNA.

In the HCV mono-infection or HCV/HIV co-infection health state, patients entered the Markov model in one of seven sub-health states (Chapter 3, Table 3.4). Prevalence was converted to probabilities. Figure 4.7 shows the EDVS Programme sub-health state probabilities for patients in the HCV mono-infection or HCV/HIV co-infection health state for patients who Linked to Care.

Figure 4.7: The cost-effectiveness model: probabilities of the HCV mono-infection or HCV/HIV co-infection health state sub-health states for patients who Linked to Care [ab].



p Indicates probability, converted from prevalence; **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

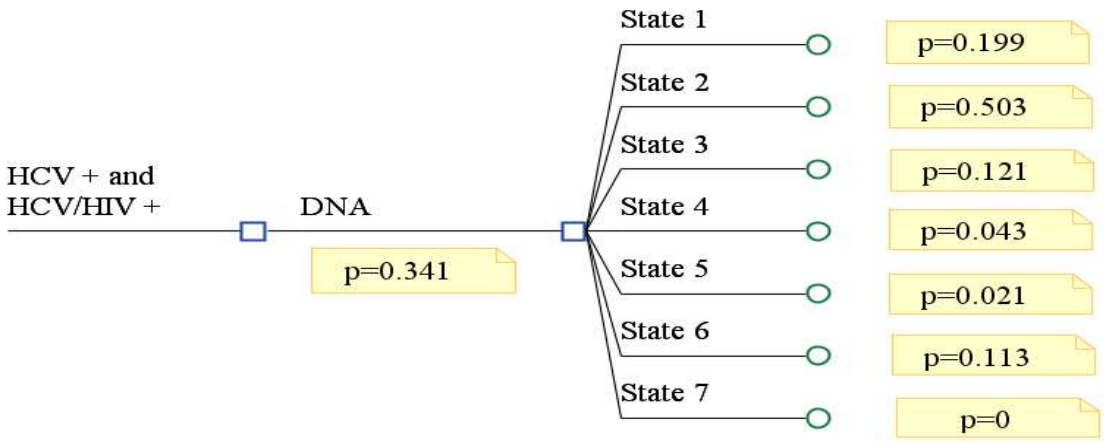
[a] State 1: non-cirrhotic; State 2: cirrhotic; State 3: decompensated cirrhosis; State 4: HCC; State 5: LT; State 6: dead; State 7: HCV SVR.
[b] As an example, the probability of all patients with HCV or HCV/HIV who LTC and are non-cirrhotic (state1) prior to entering the Markov model was 0.846.

In this health state, patients who DNA entered with the probabilities shown in Figure 4.8. Given that the EDVS real-world PLD registry database[i] does not contain data on patients who DNA, these probabilities were informed from an external source.

As previously mentioned, rates of progression of fibrosis in both HCV and HBV infection can vary and are not linear (28). Late presentation for patients with HBV or HCV, highlighted by Mauss *et al* (2017) (28), is discussed above. Probabilities are informed by studies by Hoshida *et al* who reported rates of development of HCC to be between 1% to 7% per year amongst patients with HCV (2014) (151). Probabilities are also derived from Xu *et al* who reported rates of decompensated liver disease of 13.4% per year in patients with cirrhosis as a result of HCV (2016) (152). Xu *et al* analysed the liver biopsy results of 2,799 patients in the US with HCV from 2001 to 2012 inclusive. They analysed patients risks of developing DC, HCC, and progressing to require LT.

Patients in the No EDVS Screen strategy had the same probabilities as the patients who DNA in this health state (28).

Figure 4.8: The cost-effectiveness model: probabilities of the HCV mono-infection or HCV/HIV co-infection health state and sub-health states for patients who DNA[abcd].



DNA indicates did-not-attend; **p**: probability, converted from prevalence; **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] Same probabilities for the No EDVS Screen strategy.
[b] State 1: non-cirrhotic; State 2: cirrhotic; State 3: decompensated cirrhosis; State 4: HCC; State 5: LT; State 6: dead; State 7: HCV SVR.
[c] As an example, the probability of all patients with HCV or HCV/HIV who DNA and are non-cirrhotic (state 1) prior to entering the Markov model was 0.199.
[d] Probabilities derived from a definition of late presentation by Mauss *et al* (28) and rates of progression from studies by Hoshida *et al* and Xu *et al* (151, 152).

4.3 Transition Probabilities

4.3.1 Introduction

The probabilities of patients moving between health states or sub-health states in the Markov model is termed transition probabilities (153). Transition probabilities depend on the health state or the sub-health state patients are in. Each sub-health state is assigned an outcome and a cost. In our analysis, outcomes were measured using QALYs; the QALY is a measure that combines length and quality of life. The quality of life is measured by utility values (patient preference values). Cumulative outcomes and costs for a given cohort are calculated at the end of the Markov process (154). In order for a Markov process to terminate, it must have at least one state that the patient cannot leave (absorbing state); the most common absorbing state is death (139).

In our model, the probabilities of transitioning from one sub-health state to another were based on a targeted national and international literature review. Because health outcomes and costs were calculated over a lifetime time horizon, cohort experience into the future was extrapolated from available international data. Transition probabilities were not based on data from the EDVS real-world PLD registry database[i] as this data was collected over a short time horizon.

Transition probabilities are time dependant variables. Patients in health states and their sub-health states have a background mortality. Background mortality is time dependent and increases with age (155). In our study, in addition to mortality associated with disease progression, background mortality was incorporated into transition probabilities using a multiplicative approach. The same background mortality rate was applied to all health states. Background mortality rates were derived from the most recent available Central Statistics Office (CSO) *National Life Tables, 2015 - 2017* (155).

Using a multiplicative approach, the following equation was used to incorporate background mortality rate and convert it to probability. The equation uses, as an example, the probability of transitioning from sub-health state 1 ($CD4^+ > 500$) to sub-health state 2 ($CD4^+$ 200 - 500) for patients in the HIV mono-infection or HIV/HBV co-infection health state.

- *p_trans_state1tostate2_HIV x ratetoprob(prob_background_mortality_rate)[start_age+_stage;1]*

Where: *p_trans_state1tostate2_HIV = probability of transitioning from sub-health state 1 to sub-health (p= 0.32); ratetoprob = 1 – $e^{-rate*time}$; prob_background_mortality_rate = rate to probability conversion of background age-related mortality (background mortality rate at age 43 = 0.00113808303128085); start_age = start age at EDVS Screen (43); _stage;1= the number of cycles in the Markov process that have passed (1 = first cycle).*

4.3.1.1 HIV Mono-infection or HIV/HBV Co-infection

Patients engaged in HIV care in Ireland were assumed to receive pharmacological treatment in the form of ART (22). Brennan *et al* (2015) reported an Irish resource utilisation and cost of HIV ambulatory care micro-costing study. Brennan *et al* undertook a micro-costing study in an HIV outpatient clinic in a single regional centre in Ireland. All patients who attended for HIV care in 2012 were included (n = 326 patients; 3,659 patient months). Costs considered included staff costs, hospital resource costs, diagnostic test costs, and drug acquisition costs. The mean cost of providing ambulatory HIV care was €973 (95% CI €938 - €1,008) per patient month. The majority of costs (88%) were due to the cost of ART. This study informed the cost inputs for our model (156). All costs were inflated to 2020 using the Consumer Price Inflation Index (157).

First line ART used in this study by Brennan *et al* was an NNRTI-based regimen (efavirenz/emtricitabine/tenofovir disoproxil fumarate) (156). In addition, according to a national treatment audit (2017) that analysed 5,277 PLHIV in Ireland on ART, 95% of PLHIV achieved viral suppression (158). This data informed transition probabilities between sub-health states for patients in this model with HIV.

The HIV mono-infection or HIV/HBV co-infection sub-health state transition probabilities were based on a study by Goshu *et al* (2015) (159). Goshu *et al* performed a targeted literature review (1990 to 2021 inclusive) of modelling progression of HIV health states using Markov modelling. This literature review examined the transition probabilities of over 700 PLHIV on ART. Goshu *et*

al used the same sub-health state definitions as our model, basing transition probabilities on patients' $CD4^+$ counts. Table 4.1 shows the HIV mono-infection or HIV/HBV co-infection sub-health state transition probabilities and distributions used in this model. Distributions are further discussed in Chapter 5.

Table 4.1: HIV mono-infection or HIV/HBV co-infection: sub-health state transition probabilities and distributions[ab].

Transition probabilities HIV mono-infection or HIV/HBV co-infection	**State 1**	**State 2**	**State 3**	**State 4**	**Distribution**	**Source**
State 1 ($CD4^+$ > 500)	#	0.32	0.06	0.02	Dirichlet	(159)
State 2 ($CD4^+$ 200-500)	0.05	#	0.24	0.04	Dirichlet	(159)
State 3 ($CD4^+$ < 200)	0.02	0.28	#	0.10	Dirichlet	(159)
State 4 (Dead)	-	-	-	#	N/A	(159)
Hospitalised State 3 ($CD4^+$ < 200)			0.82		N/A	EDVS real world PLD registry database[i]

# Indicates the complement probability: (1 – ∑other probs); **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a] The table depicts probabilities of movement from the state described in vertical title-column to the state described in horizontal title-column. As an example, the probability of patients moving from sub-health state 1 to health state 2 is 0.32.
[b] Distributions informed by standard deviation from source data.

A transient transition probability of hospitalisation was included for patients in sub-health state 3 who have higher rates of hospitalisation. This transition probability was derived from the EDVS real-world PLD registry database[i]. Of all the patients who Require LTC in the HIV mono-infection of HIV/HBV co-infection health state and presented with a $CD4^+$ < 200 (i.e. sub-health state 3, n = 11), 82% required a hospital admission following diagnosis.

4.3.1.2 HBV Mono-infection or HBV/HCV Co-infection

In the model, it was assumed that patients who engaged in HBV care in Ireland would receive pharmacological treatment in the form of NAs if required. It was assumed that the first-line NA received by all such patients in the model was TDF. The was informed by local practice and by EASL *Clinical Practice Guidelines on the Management of Chronic Hepatitis B Infection* (2017) (65).

The HBV mono-infection or HBV/HCV co-infection sub-health state transition probabilities were based on a 2020 UK CEA by Williams *et al* of the cost-effectiveness of opt-out HBV and HCV screening in the ED (114). Williams *et al* derived transition probabilities from a HTA by Shepherd *et al* (2006), an open-labelled trial by Marcellin *et al* (2013), and a previous EE by Martin *et al* (2019) that modelled transition probabilities using a Dirichlet distribution of patients on HBV treatment. Table 4.2 shows HBV mono-infection or HBV/HCV co-infection sub-health state transition probabilities used in this model.

Table 4.2: HBV mono-infection or HBV/HCV co-infection: sub-health state transition probabilities[ab].

Transition probabilities HBV mono-infection or HBV/HCV co-infection	State 1	State 2	State 3	State 4	State 5	State 6	State 7	State 8	State 9	State 10	Source
State 1 (sAg seroconverted)	#	-	-	-	-	-	-	0.0001	-	-	(114)
State 2 (eAg – inactive)	-	#	0.029	-	-	0.01	-	0.005	-	-	(114)
State 3 (eAg – active)	-	0.96	#	-	-	0.01	-	0.028	-	-	(114)
State 4 (eAg seroconverted)	0.02	-	-	#	0.03	0.01	-	0.001	-	-	(114)
State 5 (eAg + active)	0.018	-	-	0.0557	#	0.01	-	0.0028	-	-	(114)
State 6 (CC)	-	0.96	-	-	-	#	0.01	0.0065	-	-	(114)
State 7 (DC)	-	-	-	-	-	-	#	0.025	0.03	0.39	(114)
State 8 (HCC)	-	-	-	-	-	-	-	#	-	0.56	(114)
State 9 (LT)	-	-	-	-	-	-	-	-	#	0.21	(114)
State 10 (Dead)	-	-	-	-	-	-	-	-	-	#	(114)

TDF indicates tenofovir disoproxil fumarate; **sAg**: HBV surface antigen; **eAg**: HBV e antigen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **#**: the complement probability: (1 – ∑other probs); **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] The table depicts probabilities of movement from the state described in vertical title-column to the state described in horizontal title-column. As an example, the probability of patients moving from sub-health state 2 to sub-health state 3 is 0.029.

[b] Transition probabilities are derived from a previous CEA (114). Transition probabilities were modelled probabilistically using a Dirichlet distribution, assuming a sample of size of 200.

4.3.1.3 HCV Mono-infection or HCV/HIV Co-infection

In the model, patients engaged in HCV care in Ireland were assumed to receive pharmacological treatment in the form of DAAs as per the EASL's recommendations for the treatment of HCV (2020) (77). According to the Irish National Hepatitis C Database (a database of patients living with HCV in Ireland), 96% of patients in Ireland achieved SVR after treatment with DAA (2020) (160). This National Hepatitis C Database contains prospective PLD on over 6,000 patients who were treated for HCV from 27 treatment sites around Ireland. This data informed transition probabilities for patients in this model with HCV.

It was assumed for the purpose of this analysis that all patients were treated with Harvoni® (ledipasvir and sofosbuvir) for 12 weeks. This assumption was made because the majority (66%) of patients with HCV in the EDVS Programme[i] were infected with HCV genotype 1 (161). Harvoni® is used first line to treat genotype 1 (77). Similar to national disease epidemiology, the majority of the remaining patients in the EDVS Programme[i] with HCV had genotype 3. The treatment for genotype 3 was Daklinza® and Sovaldi® (daclatasvir and sofosbuvir) for 12 weeks (77). Over the life of this study, this treatment for genotype 3 has been replaced by newer DAAs. Differences in DAA treatment costs have been addressed in a OWSA (Chapter 5).

In addition to SVR rates, the National Hepatitis C Database demonstrated that patients with non-cirrhotic HCV mono-infection who achieved SVR post DAA treatment were discharged from care one year after treatment (160). Patients with cirrhosis who achieve SVR and other health states in the HCV cohort remained in the care cascade as per national and international practice (EASL, 2020) (77). It was assumed in our model that patients who did not achieve SVR remained in the care cascade. While in practice they may be offered further treatment for HCV if eligible, in our model they were only offered treatment once.

The HCV mono-infection or HCV/HIV co-infection sub-health state transition probabilities were informed by a targeted search of international studies. In the EDVS Programme[i], 81.9% of people who tested positive for new or known HCV infection were PWID, and 51% of new HCV diagnoses were amongst PWID. As a result of the high proportion of PWID in the EDVS Programme, pre-cirrhotic sub-health state (state 1) transition probabilities were derived from data pertaining to PWID. Erman *et al* (2019) reported on a systematic review and meta-analysis of estimation of

fibrosis progression rates for patients with chronic HCV (162). The majority (43%) of patients in this systematic review and meta-analysis were PWID. Erman *et al* reviewed Ovid-MEDLINE, Ovid-EMBASE and PubMed databases (January 1990 to January 2018 inclusive) to identify observational studies of hepatic fibrosis in patients with chronic HCV who are treatment-naïve. This study by Erman *et al* informed transition probabilities for the pre-cirrhotic sub health state (state 1) in this model.

In this model, for CC and the sub-health states pertaining to more advanced disease status including HCC, data derived from a published HTA by Shepherd *et al* (2007) was used to inform transition probabilities between health states (163). Shepherd *et al* reported transition probabilities supported by data from a variety of studies investigating the natural history of HCV infection, including studies by Wright *et al*, Grieve *et al*, Fattovich *et al*, and Siebert *et al* (164-167). These transition probabilities include the likelihood of developing HCC and the likelihood of progressing to LT amongst patients with HCV. Table 4.3 shows the HCV mono-infection and HCV/HIV co-infection sub-state transition probabilities used in this model.

Table 4.3: HCV mono-infection or HCV/HIV co-infection: sub-health state transition probabilities[a]

Transition probabilities HCV mono-infection or HCV/HIV co-infection post-DAA	State 1	State 2	State 3	State 4	State 5	State 6	State 7	Source
State 1 (NC)	#	0.00464	-	-	-	-	0.96	(160, 162, 168)
State 2 (CC)	-	#	0.00156	0.00056	-	-	0.96	(114, 160, 168)
State 3 (DC)	-	-	#	6.0E-4	0.0012	0.0052	0.96	(114, 160, 168)
State 4 (HCC)	-	-	-	#	0.03	0.43	-	(114, 160)
State 5 (LT)	-	-	-	-	#	0.057 [b]	-	(114, 160)
State 6 (Dead)	-	-	-	-	-	#	-	(114, 160)
State 7 (SVR)	#	-	-	-	-	-	0.96	(114, 160, 168)

DAA indicates direct-acting antivirals; **NC**: non-cirrhotic; **CC** compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **SVR**: sustained virologic response; **#**: the complement probability: (1 – ∑other probs); **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] The table depicts probabilities of movement from the state described in vertical title-column to the state described in horizontal title-column. As an example, the probability of patients moving from sub-health state 5 to sub-health state 6 is 0.057.
[b] Post LT > 6 months to death.

Table 4.4 shows the distributions used for the transition probabilities for HCV mono-infection or HCV/HIV co-infection sub health states.

Table 4.4: HCV mono-infection or HCV/HIV co-infection sub health state transition probabilities and distributions[ab].

Transition probabilities HCV mono-infection or HCV/HIV co-infection post-DAA	**Mean**	**Distribution**	**Source**
From State 1 to State 2 (NC-CC)	0.00464	Beta	(162)
From State 1 to State 7 (NC-SVR)	0.96	Gamma	(160, 168)
From State 2 to State 3 (CC-DC)	0.00156	Beta	(114)
From State 2 to State 4 (CC-HCC)	0.00056	Beta	(114)
From State 2 to State 7 (CC-SVR)	0.96	Gamma	(168)
From State 3 to State 4 (DC-HCC)	6.0E-4	Beta	(114)
From State 3 to State 5 (DC-LT)	0.0012	Beta	(114)
Form State 3 to State 6 (DC-Dead)	0.0052	Beta	(114)
From State 3 to State 7 (DC-SVR)	0.96	Gamma	(160, 168)
From State 4 to State 5 (HCC-LT)	0.03	Beta	(114)
From State 4 to State 6 (HCC-Dead)	0.43	Beta	(114)
From State 5 to State 6 (LT-Dead)	0.057[a]	Beta	(114)

DAA indicates direct-acting antivirals; **NC**: non-cirrhotic; **CC** compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **SVR**: sustained virologic response; **#**: the complement probability: (1 – ∑other probs); **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] Post LT > 6 months to death.
[b] Distributions informed by standard deviation from source data.

4.4 Costs

4.4.1 Introduction

Costs are fixed variables; they are not time dependent. Cost inputs were applied to the model to calculate outcomes in terms of cost/QALY. Costs were based on available local, national, and international data. All costs were in Euro. All costs were inflated to 2020 using the Consumer Price Inflation Index (157).

4.4.1.1 Emergency Department Viral Screen Programme

The funding for the EDVS Programme was established following the success of the EDVS pilot Programme in 2014. As a result, a tri-partite contribution of €140,000 per annum each (a total of €420,000 per annum) was agreed and provided by the Acute Hospitals Division of the HSE, the Social Inclusion Division of the HSE, and the hospital where the EDVS Programme was established.

In line with the model cycle length, the EDVS Programme[i] costs were calculated on a mean annual basis (169). The mean annual cost of the total EDVS Programme was €306,187 (169). This total annual cost includes costs of the EDVS, staff costs and VAT as described in Table 4.5.

Table 4.5: EDVS Programme annual costs 2017 - 2020[a]. Mean annual cost is €306,187.

Costs	2020	2019	2018	2017
Full EDVS care set	€123,920	€145,232	€171,552	€163,776
Positive results additional test[b]	€4,145	€5,091	€4,294	€7,900
VAT @ 23%	€29,455	€34,574	€40,445	€39,485
Staff pay costs[cd]	€125,287	€123,732	€119,175	€86,685
Total	€282,807	€308,629	€335,466	€297,846

EDVS indicates Emergency Department Viral Screen; **VAT**: value-added tax.

[a] 2016 costs not available.
[b] Testing only, not staff costs.
[C] Pay costs did not include VAT.
[d] Staff pay costs were derived from the *EDVS Programme finance report*; all staff pay costs were provided fully calculated as per table by the EDVS Programme finance department (169).

The cost of the EDVS was €8 per screen. This included HIV Ag/Ab, HBsAg and HCV Ab. The €8 cost included the EDVS care set and consumables. For pragmatic reasons, the 'other' costs (confirmatory tests, staff pay costs and VAT @ 23%) were averaged over the total number of patients screened during this study period[i] (n = 102,837). These 'other' costs were calculated as costing a mean of €6.89 per-patient. The EDVS cost (€8) and the 'other' cost (€6.89) resulted in a total EDVS Programme per-patient cost of €14.89 (Appendix 4 breaks down the calculation of per-patient cost EDVS).

Confirmatory test costs were included in the mean annual cost of the EDVS Programme. A per local practice, patients who tested positive for HIV Ag/Ab, a reflex VIDAS® HIV DUO test was performed (170). HIV DUO is a fourth generation HIV assay testing for HIV-1 p24 antigen and HIV-1 and HIV-2 antibodies (171). If the fourth generation testing was positive, the sample was referred to the National Virus Reference Laboratory for typing.

For patients who tested positive for HCV Ab, a reflex HCV antigen test was performed. Reflex HCV antigen testing was introduced to the EDVS Programme in 2019. Its introduction streamlined the day-to-day running of the EDVS Programme, including the results follow up for the EDVS liaison nurse. Overall costs to the EDVS Programme following its introduction did not change however (169). Reflex testing, i.e. testing for HCV antigen in the sample obtained for HCV Ab testing, has been shown to substantially increase the proportion of patients who screen positive for HCV Ab who are tested for viraemia (i.e. RNA) and receive subsequent LTC (172). Therefore, reflex testing should be applied whenever possible when HCV Abs are detected (77). If the reflex testing was positive, a confirmatory HCV RNA was performed. If HBsAg was positive, the sample was tested for a full panel of HBV markers.

Staff pay costs included an EDVS liaison nurse and laboratory staff. An EDVS liaison nurse was hired full-time to follow up results, link patients to care, and manage the day-to-day running of the EDVS Programme. Laboratory staff required a person at half-time.

4.4.1.2 HIV Mono-infection or HIV/HBV Co-infection

For the HIV mono-infection or HIV/HBV co-infection health state, mean per-patient annual outpatient non-pharmacological and pharmacological treatment costs were derived from a previously described Irish micro costing study by Brennan *et al* (2015) (156). Brennan *et al* reported on real-world micro-costing in an outpatient setting in an Irish tertiary referral university teaching hospital in the second largest city in Ireland. There were 326 patients included in the analysis of this study and results of bottom-up costing were reported as mean per-patient annual outpatient costs.

Brennan *et al* analysed outpatient costs (156). Like our study, the authors categorised patients based on their $CD4^+$ count. All patients who attended for outpatient ambulatory HIV care during 2012 were included in the analysis. Costs were calculated on a mean annual basis. The main per-patient cost was for ART, but other costs included in the analysis were additional pharmacological treatment costs supplied by the hospital pharmacy (i.e. prophylactic antibiotics), diagnostic tests (laboratory, radiology, cardiology), and staff costs. The study did not include a breakdown of total staff costs.

In our study, mean per-patient annual outpatient costs were included. However, a once-off cost for hospitalisation for patients in sub-health state 3 ($CD4^+ < 200$) was included. Admission diagnosis was based on data from the EDVS real-world PLD registry database[i]. The most common reason for hospitalisation amongst patients in the EDVS Programme in sub-health state 3 ($CD4^+ < 200$) was for management of *Pneumocystis Jirovecii* pneumonia (PJP). This was calculated as a once off cost of €8,240; this cost was derived from a 2013 study by Farnham *et al* (117). Farnham *et al* analysed lifetime costs of care and quality of life for PLHIV in the US. Costs were converted from US dollar to Euro and were inflated to 2020 using the Consumer Price Inflation Index (157).

As previously described, in a pragmatic approach, given the low numbers of patients with co-infection, patients with HIV mono-infection or HIV/HBV co-infection were categorised together in our model. Consequently, an additional cost for surveillance liver imaging was included for the small number of patients with HIV/HBV co-infection (n = 2). This was a weighted cost. This cost is derived from a study by Kieran *et al* (described in section 4.4.1.3) (173). Table 4.6 shows the mean annual per-patient costs and distributions for HIV mono-infection or HIV/HBV co-infection sub-health states.

Table 4.6: HIV mono-infection or HIV/HBV co-infection: sub-health state mean annual per-patient costs and distributions[a].

HIV mono-infection or HIV/HBV co-infection	Mean annual per-patient health state cost	Distribution	Source
State 1 ($CD4^+$ > 500)	€12,215	Gamma	(156)
State 2 ($CD4^+$ 200 - 500)	€11,403	Gamma	(156)
State 3 ($CD4^+$ < 200)	€13,162	Gamma	(156)
State 4 (Dead)	€0	N/A	N/A

HIV indicates Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a] Distributions informed by standard deviation from source data.

4.4.1.3 HBV Mono-infection or HBV/HCV Co-infection

For the HBV mono-infection or HBC/HCV co-infection health state, mean annual per-patient outpatient non-pharmacological treatment costs were based on a 2015 Irish study by Kieran *et al* of real-world costs of HCV for inpatient and outpatient care (173). While this study by Kieran *et al* analysed HCV outpatient costs, non-pharmacological treatment costs in this study, including staff costs, ultrasound liver costs and laboratory costs, were assumed to be the same for HBV. This assumption was made due to a paucity of national costing studies for HBV treatment (173). This study by Kieran *et al* was performed in the same institution as our study.

Mean annual per-patient pharmacological treatment costs were added to mean annual per-patient non-pharmacological treatment costs for HBV. Mean annual per-patient costs for TDF were €2,700. However, local costs of TDF are likely to be lower because of expected confidential price negotiations then this publicly available listed price (174). While some national centres used ETV as first line pharmacological treatment for HBV, TDF was used as first line pharmacological treatment in this model as per international guidelines (EASL, 2017) (65). Annual per-patient publicly listed costs for ETV are €2,160 (174). Subsequent OWSA indicated that the CEA outputs of this analysis were not sensitive to this cost.

Once patients Linked to Care, if they required pharmacological treatment, it was assumed that patients were treated with TDF. Unless patients transitioned to certain sub-health states that did not require pharmacological treatment as per transition probabilities, they were assumed to remain on lifelong TDF. For patients with HBV/HCV co-infection, an additional cost for HCV treatment with DAA was included for the small number of patients with HBV/HCV co-infection (n = 5). This was a weighted cost. Table 4.7 shows the mean annual per-patient costs and distributions for HBV mono-infection or HBV/HCV co-infection sub-health states.

Table 4.7: HBV mono-infection or HBV/HCV co-infection: sub-health state mean annual per-patient costs and distributions[ab].

HBV mono-infection or HBV/HCV co-infection	Mean annual per-patient cost	Distribution	Source
State 1 (sAg seroconverted)	€0	N/A	N/A
State 2 (eAg – inactive)	€416	Gamma	(173)
State 3 (eAg – active)	€416 (+ TDF)	Gamma	(173)
State 4 (eAg seroconverted)	€416	Gamma	(173)
State 5 (eAg + active)	€416 (+ TDF)	Gamma	(173)
State 6 (CC)	€1,872 (+TDF)	Gamma	(173)
State 7 (DC)	€8,584 (+TDF)	Gamma	(173)
State 8 (HCC)	€23,001 (+TDF)	Gamma	(173)
State 9 (LT)	€5,582[a] (+TDF)	Gamma	(173)
State 10 (Dead)	€0	N/A	N/A

sAg indicates HBV surface antigen; **eAg**: HBV e antigen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **TDF**: tenofovir disoproxil fumarate; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] After one year.
[b] Distributions informed by standard deviation from source data.

4.4.1.4 HCV Mono-infection or HCV/HIV Co-infection

For the HCV mono-infection or HCV/HIV co-infection sub-health state, mean annual per-patient outpatient non-pharmacological treatment costs were based on a 2015 Irish study by Kieran *et al* of real-world costs of inpatient and outpatient care (173). Kieran at al analysed ambulatory costs for patients with HCV and costs were supplemented with inpatient diagnosis-related costs. The costs Kieran *et al* analysed included diagnostic costs (laboratory, radiological, endoscopic, histopathological), staff costs (hepatology, dermatology, oncology, terminal care), therapeutic costs (pharmacological treatment and other including transarterial chemoembolisation for liver cancer/TACE) and pre-transplant workup costs. In this study by Kieran *et al*, 'mild HCV' health state costs represent sub-health state 1 in our model (i.e. patients with non-cirrhotic HCV). This health state cost, inflated to 2020 costs using the Consumer Price Inflation Index, was €416 per annum (95%CI, €343, €503) (157).

Mean annual per-patient pharmacological treatment costs were added to mean annual per-patient non-pharmacological treatment costs for HCV. In our study, the true cost incurred by the institution for all pharmacological treatments costs for HCV are confidential. However, national listed prices lists first line Harvoni®(ledipasvir and sofosbuvir) are €14,835 per month (€44,500 per treatment course) (175). This treatment price was included in our model. This cost assumes 100% compliance and 100% dose intensity. Costs for Harvoni® were used in our model as the majority of patients in the EDVS Programme had HCV genotype 1. The cost of Daklinza® and Sovaldi® (daclatasvir and sofosbuvir), initially used for treatment of genotype 3, is higher at a cost of €25,000 per month (€75,000 per treatment course) (161). These differences in costs are addressed in a OWSA. In our institution, DAAs are supplied by a hospital pharmacy and therefore, fees are included in the outpatient staff costs, as previously described by Kieran *et al* (173).

Local practice in our institution for patients with non-cirrhotic HCV (sub-health state 1) who achieved SVR was to discharge patients from outpatient care after one year follow up. This was also supported by EASL guidelines entitled *Recommendations on the Treatment of Hepatitis C* (2020) (77). Costs incurred include DAA pharmacological treatment cost and a one year annual outpatient non-pharmacological treatment cost. Patients who achieved HCV SVR but were in another sub-health states (i.e. DC, HCC, or LT) remained in the care cascade and did incur an

annual outpatient non-pharmacological treatment cost. For patients with HCV/HIV co-infection, an additional cost for HIV treatment with ART was included for the small number of patients with HCV/HIV co-infection (n = 11). This was a weighted cost. Table 4.8 shows the mean annual per-patient costs and distributions for HCV mono-infection and HCV/HIV co-infection sub-health states.

Table 4.8: HCV mono-infection or HCV/HIV co-infection: sub-health state mean annual per-patient costs and distributions[a].

HCV mono-infection or HCV/HIV co-infection	Mean annual per-patient cost	Distribution	Source
State 1 (NC)	€416[a]	Gamma	(173)
State 2 (CC)	€1,872	Gamma	(173)
State 3 (DC)	€8,584	Gamma	(173)
State 4 (HCC)	€23,001	Gamma	(173)
State 5 (LT)	€5,582 [a]	Gamma	(173)
State 6 (dead)	€0	N/A	N/A
State 7 (SVR)	€0	N/A	N/A

DAA indicates direct-acting antivirals; **NC**: non-cirrhotic; **CC** compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **SVR**: sustained virologic response; **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] Referred to as 'mild HCV' by Kieran *et al*.
[b] After one year.
[c] Distributions informed by standard deviation from source data.

Patients who screened negative only incurred a per-patient EDVS Programme cost and then exited the model.

4.4.1.5 No Emergency Department Viral Screen Strategy

In our model, patients in the No EDVS Screen strategy did not incur a cost until they entered the model 10 years after the EDVS Screen strategy. It was assumed that patients in both arms of the model would continue to visit their General Practitioners at the same rate over this time period; therefore, costs across arms are equal in this respect; thus they can be omitted. This was a conservative approach. Sub-health state costs were the same. Patients in the No EDVS Screen strategy did not incur a per-patient EDVS Programme cost.

4.5 Utilities

4.5.1 Introduction

Utilities are fixed variables. Utility value inputs were applied within our model to calculate outcomes in terms of cost/QALY. Utility values were derived from a targeted search of available international studies. These studies referenced generic HRQOL assessment tools, to include Short Form 12 (SF-12), Short Form 36 (SF-36), EuroQol 5 Dimensions (EQ-5D) and Health Utilities Index Mark 3 questionnaires. The majority of the studies were chosen because the sub-health states were directly comparable to those used in our model.

4.5.1.1 HIV Mono-infection or HIV/HBV Co-infection

For HIV mono-infection or HIV/HBV co-infection sub-health states, utility values were derived from a 2020 review by Whitham *et al* (176). The authors examined peer-reviewed literature to assess the appropriateness of commonly referenced utility studies for HIV-related CEAs. One of these studies examined by Whitham *et al* was a post-ART utility study from the CDC's MMP (2018) (145). MMP was a multisite surveillance system of 3,922 PLHIV receiving medical care in the US. The perspective was that of the community, with participant surveys used to gather data. The median age of PLHIV was 45 years and 85% were on ART. Mode of HIV acquisition was not recorded. Co-infection status was not recorded. Of all respondents, 72% were male. The data collection period was from 2010 to 2015 inclusive. Utilities were collected using a SF-12 HRQOL assessment tool with the same $CD4^+$ count strata for sub-health states used in our study. Table 4.9 shows the mean utility values and distributions for HIV mono-infection and HIV/HBV co-infection sub-health states.

Table 4.9: HIV mono-infection and HIV/HBV co-infection: sub-health state mean utility values and distributions[b].

HIV mono-infection or HIV/HBV co-infection	Mean utility	Distribution	Source
State 1 ($CD4^+$ > 500)	0.73	Beta	(145, 176)
State 2 ($CD4^+$ 200-500)[a]	0.7	Beta	(145, 176)
State 3 ($CD4^+$ < 200)	0.67	Beta	(145, 176)
State 4 (dead)	0	N/A	N/A

HIV indicates Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus.

[a]MMP reported $CD4^+$ strata as 200-349 utility = 0.7, and $CD4^+$ 350-500 utility 0.71. utility of 0.7 chosen (145).
[b] Distributions +/- 10%.

4.5.1.2 HBV Mono-infection or HBV/HCV Co-infection

For HBV mono-infection or HBV/HCV co-infection sub-health states, utilities for all sub-health states were derived from a 2020 CEA of ED screening for HBV and HCV in the UK by Williams *et al* (114). Williams *et al* derived utility values for non-cirrhotic sub-health states from two studies. The first study was a commonly referenced 2006 systematic review and economic analysis by Shepherd *et al* (146). This study by Shepherd *et al* analysed electronic databases from 1995 to 2005 inclusive for studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history of the treatment of chronic HBV. A total of 1,086 references of clinical effectiveness studies were identified, of which seven fully published RCTs and one systematic review met the inclusion criteria. Many of the studies reviewed reported HRQOL as measured by SF-36 questionnaire. The second study referenced by Williams *et al* for utility values for the non-cirrhotic health states is a study by Wong *et al* (2011) (177). In this study, Wong *et al* performed an EE of screening immigrants for HBV in Canada. Data was obtained from over 400 patients with directly comparable sub-health states to our study. HRQOL was measured by Health Utilities Index Mark 3 questionnaire.

The same study by Williams *et al* derived utility values for cirrhotic and advanced liver disease sub-health states (state 6 to state 9 inclusive) from studies by Wright *et al* (2006) and Ratcliffe *et al* (2002) (164, 178). Wright *et al* used EQ-5D data derived from patients in a multicentre

National Health Service (NHS) setting in the UK. The authors sent EQ-5D questionnaires to over 300 patients with moderate disease from HBV and advanced cirrhosis.

For patients in the post LT sub-health state (state 9), Wright *et al* referenced utilities from a 2002 study by Ratcliffe *et al* (178) commissioned by the Department of Health in the UK. This study by Ratcliffe *et al* was a prospective multicentre study of 455 patients in a pre and post LT state in the NHS in the UK over a two year period from 1996 to 1998. Ratcliffe *et al* used SF-36 and EQ-5D data derived from these patients. Sub-health states in this multicentre study were directly comparable to our study. The study by Ratcliffe *et al* reported on utilities for patients who were less than one year post LT (0.45) and for patients who were one year post LT (0.66). This model used utility values for patients less than one year post LT. Table 4.10 describes mean utility values for HBV mono-infection and HBV/HCV co-infection sub-health states.

Table 4.10: HBV mono-infection or HBV/HCV co-infection: sub-health state mean utility values and distributions[c].

HBV mono-infection or HBV/HCV co-infection	Mean utility	Distribution	Source
State 1 (sAg seroconverted)	0.91	Beta	(114, 116, 146)
State 2 (eAg – inactive)	0.87 [a]	Beta	(114, 116, 146)
State 3 (eAg – active)	0.87 [a]	Beta	(114, 116, 146)
State 4 (eAg seroconverted)	0.91	Beta	(114, 116, 146)
State 5 (eAg + active)	0.87 [a]	Beta	(114, 116, 146)
State 6 (CC)	0.55	Beta	(164)
State 7 (DC)	0.45	Beta	(178)
State 8 (HCC)	0.45	Beta	(178)
State 9 (LT)	0.45 [b]	Beta	(178)
State 10 (Dead)	0	N/A	N/A

sAg indicates HBV surface antigen; **eAg**: HBV e antigen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **TDF**: tenofovir disoproxil fumarate; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

[a] Mean utility decrement of 0.04 from general population at age 43 years. As an example, state 2 at 43 years of age, utility of 0.91-0.04 = 0.87.
[b] Utility for patients who are less than one year post liver transplantation.
[c] Distributions +/- 10%.

4.5.1.3 HCV Mono-infection or HCV/HIV Co-infection

Utility values for non-cirrhotic and cirrhotic sub-health states (state 1 to state 3 inclusive) were derived from the study by Williams *et al* (2020) (114). Williams *et al* reference studies by Wright *et al* (2006) (164) and Ratcliffe *et al* (2002) (178). For cirrhotic and advanced liver disease sub-health states, utilities were also derived from a study by Ratcliffe *et al* (178) as described above. Table 4.11 shows the mean utility values for HCV mono-infection or HCV/HIV co-infection sub-health states.

Table 4.11: HCV mono-infection or HCV/HIV co-infection: sub-health state mean utility values and distributions[b].

HCV mono-infection or HCV/HIV co-infection	Mean utility	Distribution	Source
State 1 (NC)	0.77	Beta	(114, 164)
State 2 (CC)	0.55	Beta	(114, 164, 178)
State 3 (DC)	0.45	Beta	(114, 164, 178)
State 4 (HCC)	0.45	Beta	(114, 164, 178)
State 5 (LT)	0.45[a]	Beta	(114, 164, 178)
State 6 (dead)	0	N/A	N/A
State 7 (SVR)	0.91	Beta	(114, 164, 178)
State 1 (NC) SVR	0.91	Beta	(114, 164, 178)
State 2 (CC) SVR	0.82	Beta	(114, 164, 178)
State 3 (DC) SVR	0.61	Beta	(114, 164, 178)

DAA indicates direct-acting antivirals; **NC**: non-cirrhotic; **CC** compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **LT**: liver transplantation; **SVR**: sustained virologic response; **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] Utility for patients who are less than one year post liver transplantation.
[b] Distributions +/- 10%.

4.5.1.4 No Emergency Department Viral Screen Strategy

In our model, patients in the No Screen strategy presented 10 years after the EDVS Screen strategy. During that 10 year period, the model assumed that patients accrued utilities. Therefore, the model applied a utility increment for the model's first 10 years of the No EDVS Screen strategy.

In HIV mono-infection or HIV/HBV co-infection health state, a 0.1 increment was applied to patients in sub-health state 2 ($CD4^+$ 200 - 500). A utility increment of 0.01 was applied to patient in sub-health state 3 ($CD4^+ < 200$). This was based on a study by Wolbers *et al* (2010) (149). This study analysed 23 cohort studies and assessed $CD4^+$ cell slope and progression to AIDS and death

amongst pre-treatment PLHIV. Table 4.12 shows the mean utility increment for the No EDVS Screen strategy.

In HBV mono-infection or HBV/HCV co-infection health, utility increments were applied to sub-health states that represented cirrhosis and HCC. For sub-health state 6 (CC), an increment of 0.1 was applied. For sub-health state 7 (DC), an increment of 0.05 was applied. For sub-health state 8, an increment of 0.05 was applied. These increments were applied for the same sub-health states in the HCV mono-infection or HCV/HIV co-infection health state. These increments were based on three studies of disease progression in patients with HCV (152, 179, 180). These utility increments were assumed for patients with HBV due to lack of 10 year data available on disease progression for patients with HBV. For patients in HCV mono-infection or HCV/HIV co-infection sub-health state 1 (non-cirrhotic), we applied the same utility as patients who screen negative for infection.

The utility value for patients who screened negative was derived from a 1999 study by Kind *et al* (181). Kind *et al* used an EQ-5D HRQOL questionnaire to analyse utility values for the normal UK population. Table 4.12 shows the mean utility increment for the No EDVS Screen strategy.

Table 4.12: No EDVS Screen strategy: mean utility increments for sub-health states of three health states[a].

Health state	Mean utility	Distribution	Source
HIV mono-infection or HIV/HBV co-infection state 2 ($CD4^+$ 200-500)	0.8 (0.1 increment)	Beta	(149)
HIV mono-infection or HIV/HBV co-infection state 3 ($CD4^+$ <200)	0.68 (0.01 increment)	Beta	(149)
HBV mono-infection or HBV/HCV co-infection state 6 (CC)	0.65 (0.1 increment)	Beta	(152, 179, 180)
HBV mono-infection or HBV/HCV co-infection state 7 (DC)	0.5 (0.05 increment)	Beta	(152, 179, 180)
HBV mono-infection or HBV/HCV co-infection state 8 (HCC)	0.5 (0.05 increment)	Beta	(152, 179, 180)
HCV mono-infection or HCV/HIV co-infection state 1 (NC)	0.91	Beta	(152, 179-181)
HCV mono-infection or HCV/HIV co-infection state 2 (CC)	0.65 (0.1 increment)	Beta	(152, 179, 180)
HCV mono-infection or HCV/HIV co-infection state 3 (DC)	0.5 (0.05 increment)	Beta	(152, 179, 180)
HCV mono-infection or HCV/HIV co-infection state 4 (HCC)	0.5 (0.05 increment)	Beta	(152, 179, 180)
Patients who screen negative	0.91	Beta	(181)

EDVS indicates Emergency Department Viral Screen; **CC**: compensated cirrhosis; **DC**: decompensated cirrhosis; **HCC**: hepatocellular carcinoma; **NC**: non-cirrhotic; **HIV**: Human Immunodeficiency Virus; **HCV**: Hepatitis C Virus.

[a] Distributions +/- 10%.

4.6 Prevention of Onward Transmission

Another benefit of a BBV screening programmes is the prevention of onward transmissions. Late diagnoses and presentation to care means that opportunities to prevent onwards transmission, either by reducing high risk behaviours or by reducing an individual's infectivity, are missed (182-184). A number of additional diagnoses of BBVs were assumed to be averted by screening. These assumptions were based on the HPSC national guidelines on post-exposure prophylaxis (PEP) entitled *Emergency Management of Injuries and Post-exposure Prophylaxis* and a study by O'Leary *et al* that analysed community acquired needlestick injuries amongst non-health care workers, and the associated BBV acquisition risk factors (185, 186). The risk of acquisition for each health state was based on the most common risk groups in the EDVS Programme[i].

In the HIV mono-infection or HIV/HBV co-infection health state, it was assumed that one in 72 patients would acquire HIV following unprotected receptive anal intercourse (RAI) (185). There were n = 53 patients in our model with HIV mono-infection or HIV/HBV co-infection, or 0.74 patients estimated to acquire HIV following unprotected RAI. These effects and costs of assumed new diagnoses were incorporated into the cost-effectiveness model.

In the HBV mono-infection or HBV/HCV co-infection health state, it was assumed that following unprotected heterosexual intercourse, 18% of patients would acquire HBV (185). In addition, 10% of HBV infections will become chronic (60). Therefore, 1.8% of patients will develop chronic HBV. There were n = 74 patients in our model with HBV mono-infection or HBV/HCV co-infection, or 1.3 patients estimated to acquire HBV following unprotected heterosexual intercourse.

In the HCV mono-infection of HCV/HIV co-infection health state, it was assumed that following a needlestick injury or use of an infected needle by a PWID, 1.62% of people would develop chronic HCV (186). There were n = 143 people in our model with HCV or HCV/HIV co-infection, or 1.13 patients estimated to acquire HCV amongst PWID.

4.7 Discussion

The input parameters of this cost-effectiveness model of ED screening for HIV, HBV, and HCV in an inner-city ED have been described. These input parameters included prevalence, probability, time dependent variables, and fixed variables. A 2003 report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force entitled *The Principles of Good Practice for Decision Analytic Modelling in Healthcare Evaluation*, highlighted the value a well-designed model in healthcare evaluation. The report also iterated the importance of well-researched, applicable input parameters for the model (132). In addition to relevance, input parameters should also be reported clearly and explicitly (132).

Prevalence (in the form of seroprevalence) and probability were based on data from the EDVS real-world PLD registry database[i]. This large database contained 70,386 unduplicated EDVS. Prevalence and probability in our study reflected real-world seroprevalence of these BBVs. This highlights that the results of this model will be directly applicable not only to our study setting's jurisdiction, but to other jurisdictions with similar seroprevalence. Seroprevalence has been shown to influence results of CEA in the arena of ED screening for HIV, HBV, and HCV (114). This further underscores the importance of real-world applicable and validated data.

Time dependent variables included background mortality using a multiplicative approach. Background mortality should be included in a CEA as per the ISPOR task force on modelling in healthcare evaluations (132) The use of a multiplicative approach is supported in the literature (187). This study used the CSO *National Life Tables, 2015 - 2017* (188) which is directly applicable to our study setting's jurisdiction.

A lifetime time horizon was used, and transitions occurred at the end of each Markov cycle. Therefore, there was no requirement to add half-cycle correction (132). Transition rate probabilities were based on frequently referenced literature for all three health states. Markov models can provide a more compact representation than the decision tree when a repeated set of outcomes is possible through time (138). They are particularly suited to modelling chronic diseases (139).

In our model, costs were based on local and national real-world micro-costing data (156, 173). Outpatient costs for HIV, HBV and HCV used in the model were derived from studies by Brennan *et al* (2015) and Kieran *et al* (2015). The study by Kieran *et al* was performed in the same institution as our study. Thus, costs were directly applicable to the costs in our study's institution (173).

An appreciable cost in the model was per-patient per-treatment cost of DAAs. In our model, per-patient per-treatment costs for DAA may have been overestimated due to confidential price negotiations (174). However, a deterministic SA will address whether a lower cost (which is more likely to reflect practice) of DAAs will impact the ICER of ED screening for HIV, HBV, and HCV. It will also address higher treatment costs associated with treatment regimes for different HCV genotypes.

While utilities in our model were not based on national data, utility studies chosen for this model's input parameters used commonly referenced questionnaire instruments to include SF-12, SF-26, EQ-5D, and Health Utilities Index Mark 3 questionnaires. Utility studies with similar patient populations characteristics were used as recommended by the ISPOR task force on modelling in healthcare evaluations (132). For example, in the EDVS Programme[i], 81.9% of people who tested positive for new or known HCV infection were PWID. Consequently, utilities for PWID were used for the relevant sub-health states in the relevant main health states.

4.8 Limitations

As is expected with Markov modelling, uncertainties and assumptions were made with some of these input parameters (139). The following were the most notable assumptions made in our model:

- The EDVS Screen strategy was compared to a No EDVS Screen strategy. The No EDVS Screen strategy followed the same probabilities and pathway as the EDVS Screen strategy. The analysis did not take-into-account background rates of testing. Therefore, in reality, some patients in the No EDVS Screen strategy may have been diagnosed with HIV, HBV, or HCV prior to entering the model.

- In the EDVS Programme[i], there were low numbers of patients with co-infection. As a pragmatic approach, it was assumed that the mono-infection and respective co-infection health states were comparable. While the extra costs associated with co-infection were accounted for, any potential differences in utility and health state transition probabilities were not.

- Patients in the No EDVS Screen strategy and patients in the EDVS Screen strategy who DNA accrued QALYs over the 10 years prior to entering the model, but potential costs accrued during that time period was not included. For example, these patients could have accrued costs from attending for unscheduled care to manage symptoms of undiagnosed infection.

- In the EDVS Programme[i], tri-infections were diagnosed but none required LTC. While tri-infections were represented in the decision tree (in the form of a positive EDVS), no patients with tri-infection were analysed in the Markov model. This may limit the generalisability of our model outputs.

- In the HIV mono-infection or HIV/HBV co-infection health state, it was assumed that, when patients required an inpatient hospital admission, this was for management of PJP. This was based on data from the EDVS Programme[i]. Consequently, costs for hospital admission were based on a per-patient per-treatment cost of PJP. Many PLHIV may require hospitalisation for other reasons which are likely to be more costly. This assumption therefore may have underestimated the impact of cost-effectiveness of our model. In addition, there was no national data available on inpatient costs for PJP. Costs were based on a study by Farnham *et al* in the US which may not be directly replicable in Irish healthcare settings (117).

- In the HIV mono-infection or HIV/HBV co-infection health state, costing was based on a national micro-costing study from 2015 where first line ART was based on a NNRTI-based regimen (156). Up-to-date treatment guidelines have changed with different and likely more expensive recommendations for first-line treatment (189).

- In the HBV mono-infection or HBV/HCV co-infection health state, it was assumed that all patients received TDF as first-line treatment if they required pharmacological treatment. ETV can also be used first line in the treatment of HBV (65).

- In the HCV mono-infection or HCV/HIV co-infection health state, it was assumed that all patients were treated with Harvoni® (ledipasvir and sofosbuvir) for 12 weeks. While approximately 66% of patients in the EDVS Programme[i] were diagnosed with HCV genotype 1, the majority of the remaining patients were diagnosed with HCV genotype 3 During the life time of this research, the initial treatment for genotype 3 was with Daklinza® and Sovaldi® (daclatasvir and sofosbuvir) for 12 weeks (161). Newer DAAs are now available. Treatment costs are higher than those associated with Harvoni® (ledipasvir and sofosbuvir) .However, this will be assessed in a OWSA. In addition to this, no patients were re-treated. Clinical guidelines recommend retreatment for patients who fail first-line DAAs (77).

- In this model, we only offered HCV treatment in the form of DAAs to patients once. In practice, and according to EASL guidelines, second-line DAA treatment is offered to patients who fail first-line if suitable (77).

- Assumptions were made that patients in the No EDVS Screen strategy were at risk of causing onward transmissions. As a consequence, effects and costs of these assumed new diagnoses were incorporated into the model.

- There was no terminal care cost included in the model for PLHIV. Terminal care costs, if included for PLHIV, would have been higher for patients in the No EDVS Screen strategy as they were likely to enter the model in a sub-health state that may have required terminal care. Therefore, the exclusion of terminal care costs from the model was likely to favour the No EDVS Screen strategy, and consequently support a more conservative result from the CEA. Terminal care costs were included for patients with HBV and HCV. Costs were derived from a study by Kieran *et al* that included terminal care costs (173).

4.9 Conclusion

In this chapter, input parameters for our model were presented. Prevalence and parameters were derived from the EDVS real-world PLD registry database[i], national and international data. Costs were predominantly derived from national micro-costing studies, and international data was used where necessary (with costs inflated to 2020 prices and converted to Euro). Due to a paucity of national data, utilities were derived from international literature. PSA distributions have also been included. Necessary assumptions have been described and the model's limitations have been made explicit.

CHAPTER 5 RESULTS OF THE COST-EFFECTIVENESS ANALYSIS

5.1 Introduction

In this CEA, the EDVS Screen strategy, was the intervention being evaluated in this CEA. The EDVS Screen strategy was compared to the No EDVS Screen strategy.

The main CEA output was the ICER. The outcome was cost/QALY.

5.1.1 Incremental Cost-effectiveness Ratio

The ICER was calculated using the following equation (128):

- $ICER = \frac{cost\ intervention - cost\ comparator}{effect\ intervention - effect\ comparator}$

Where: *ICER = Incremental cost-effectiveness ratio.*

If the ICER of the CEA is less than the defined willingness-to-pay (WTP) threshold, the intervention under consideration is deemed to be cost-effective under standard decision rules (130).

5.1.2 Net Monetary Benefit

The net monetary benefit (NMB) result for the base-case analysis was reported. NMB is a summary statistic that represents the value of an intervention in monetary terms when a fixed WTP threshold is known (190). The strategy with the highest NMB represents the strategy that is more cost-effective at this WTP threshold. NMB is calculated using the following equation:

- $NMB = (expected\ effect \times WTP\ threshold) - expected\ cost$

Where: *NMB = net monetary benefit; Expected effect = expected QALYs associated with the intervention; WTP = willingness-to-pay threshold; Expected cost = expected cost associated with the intervention.*

The incremental NMB measures the difference in NMBs between the comparator interventions (190). Incremental NMB is calculated using the following equation:

- *Incremental NMB = NMB of intervention 1 – NMB of intervention 2*

Where: *NMB = net monetary benefit.*

5.1.3 Discounting

The time horizon used in this study was a lifetime time horizon. Most analysts agree a uniform discount rate should be applied to a CEA after year one (191). A discount rate of 4% per annum was applied to costs and effect. This discount rate was set by the Department of Finance in Ireland (192). *National guidelines recommend* this discount rate for both cost and effect (12).

There is ongoing debate around the use of uniform discounting versus nonuniform, or differential, discounting (193). Whether or not discount rates for costs and effects should be equal remains unclear (194, 195). Differential discounting is being advocated for more frequently, whereby health effects are discounted at a different (typically lower) rate than costs (194, 196, 197). In our study, this is of particular importance as time undiagnosed is associated with clinical deterioration and worse outcome for all three infections (39, 198, 199). Differential discounting was reported in this analysis.

5.1.4 Willingness-to-pay Threshold

A WTP threshold is defined as an cost/QALY below which a technology would be considered cost-effective, according to standard decision rules (12). *National guidelines* recommend

reporting the probability of cost-effectiveness at thresholds of €45,000/QALY and €20,000/QALY (12).

5.1.5 Base-case Analysis

The base-case cost-effectiveness of the EDVS Screen strategy was reported using the ICERs in relation to the health payer WTP thresholds, according to standard decision rules (200). In addition, NMB at WTP thresholds of €45,000/QALY and €20,000/QALY were reported.

5.1.6 Sensitivity Analysis

Deterministic SA and PSA were performed. SA is used to inform decision makers about the sensitivity of the outcomes of the cost-effectiveness model (201). Both the ISPOR and the Society for Medical Decision Making (SMDM) advocate deterministic SA and PSA for all CEA (202, 203). *National guidelines in Ireland* recommend performing both deterministic and PSA (12).

Deterministic SA can be undertaken as a OWSA. A series of OWSA can be presented via a tornado diagram. A tornado diagram summarises the individual impacts on the ICER of changes made to individual parameters in the cost-effectiveness model (204). OWSA has several limitations (205). One limitation is that the range of values chosen are often arbitrary and this can lead to bias (121). However, changes in one particular parameter in the decision model may impact on the expected value of a technology (206).

In this CEA, OWSA investigated the impact on the ICER of extreme variations in key, uncertain parameters (134). The total costs were varied ± 20%. Utilities were varied ± 10%. Additional costs were varied with extreme parameters in order to assess the threshold at which the main conclusions of the cost-effectiveness model might change (207).

National guidelines recommend examining limits of 0% and 10% for the discount rate. The impact of ± 1% of the discount rate on the ICER was also investigated in OWSA (12).

PSA values are randomly sampled from parameter distributions (135). One advantage of PSA is that all uncertain parameters can be simultaneously incorporated into an analysis. PSA results provide an estimation of the total impact of uncertainty in the model, or the confidence that can be placed in the analysis results (136).

A PSA was performed using Monte Carlo simulation. Monte-Carlo PSA recalculates expected values in a model multiple times by making random trial runs of the uncertain parameters from their probability distribution (208). Each Monte-Carlo trial run is called an iteration or microsimulation. The process of resampling from each of the iterations and recalculating the cost-effectiveness from the model was repeated 10,000 times. The running time for the PSA was approximately 25 seconds.

Parameter distributions were sampled from appropriate statistical distributions for each parameter type. Probability parameters were constrained on the 0 - 1 interval and distribution forms that were consistent with this restriction were chosen (11). The Beta distribution was chosen for the probability parameters and utility parameters because of its special relationship with binomial data (Appendix 5) (209). The Dirichlet distribution, which is the multivariate generalisation of the Beta distribution, was adopted for all multibranch nodes of the model (Appendix 6) (210). Gamma distribution was chosen for costs. The distribution of cost data can be typically truncated and positively skewed. Gamma distribution can accommodate skewness (Appendix 7) (211). The PSA parameters are summarised in Chapter 4.

5.2 Base-case Analysis

The cost-effectiveness of the EDVS Screen strategy was investigated. In the base-case analysis, base-case inputs for ED screening for HIV, HBV and HCV was cost-effective with an ICER of €9,130/QALY.

The EDVS Screen strategy was more costly but more effective than the No EDVS Screen strategy. (Table 5.1). The ICER was below the WTP thresholds of €45,000/QALY and €20,000/QALY. This indicates that, according to standard decision rules, the EDVS Screen strategy is cost-effective.

Given a fixed WTP threshold of €45,000/QALY, the NMB of the EDVS screen strategy was €40,867. The NMB of the No EDVS Screen strategy was €40,829. At a WTP threshold of €45,000/QALY, the incremental NMB for the EDVS Screen strategy versus the No EDVS Screen strategy was €38. It is the strategy that has the highest NMB (i.e. the EDVS Screen strategy) that the decision maker should choose (190).

At a WTP threshold of €20,000/QALY, the NMB of the EDVS Screen strategy was €18,187 and the NMB of the No EDVS Screen strategy was €18,176. At a WTP threshold of €20,000/QALY, the incremental NMB for the EDVS Screen strategy versus the No EDVS Screen strategy was €11. Table 5.1 shows the base-case cost-effectiveness report of the EDVS Screen strategy compared to the No EDVS Screen strategy.

Table 5.1: Cost-effectiveness report of the EDVS Screen strategy versus the No EDVS Screen strategy[a].

Strategy	**Cost (€)**	**Incremental cost (€)**	**QALY**	**Incremental QALY**	**ICER (€)**	**NMB (€)**	**Incremental NMB (€)**
No EDVS Screen	37	-	0.9081	-	-	40,829 (at WTP €45,000) 18,176 (at WTP €20,000)	-
EDVS Screen	47	10	0.9092	0.0011	9,130	40,867 (at WTP €45,000) 18,187 (at WTP €20,000)	38 (at WTP €45,000) 11 (at WTP €20,000)

All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **NMB**: net monetary benefit; **WTP**: willingness-to-pay; **EDVS**: Emergency Department Viral Screen.

[a] Figures in the table are rounded so calculations may not be directly replicable.

5.3 Deterministic Sensitivity Analysis

There were 163 parameters in the model. Many of the 163 parameters in this model were transition probabilities. Transition probabilities for health states were varied in a OWSA but had no impact on the ICER. Thus, they were not included in the tornado diagram.

Twenty key, uncertain parameters were identified for inclusion in a tornado diagram (Table 5.2). Utility and cost for the most common health state for each infection were included. Following review of these 20 parameters, seven of these parameters had an impact on the ICER. These seven parameters were included in the tornado diagram (Figure 5.1). Assumptions were made for many ranges of these parameters analysed as there were no SD results available.

Combined seroprevalence was one of the seven parameters included in the tornado diagram. This parameter was considered key in assessing the ongoing utility and cost of ED screening for HIV, HBV, and HCV. Given ongoing changes in demographics and migration patterns, the impact of universal childhood HBV vaccination programme, increased availability of therapeutics including P(R)EP for HIV and DAAs for HCV, and treatment for HBV, there may be a future shift in seroprevalence in this study setting (51, 114, 174, 212). Findings of a five year EDVS Programme report (January 2015 to December 2020 inclusive) indicate that the number of new infections diagnosed are reducing year-on-year, from a rate of 0.62% of EDVS samples taken from 2015 to 2016 inclusive to 0.25% of EDVS samples taken from 2019 to 2020 inclusive. Appendix 8 highlights year-on-year trend of new infection diagnoses over five years of the EDVS Programme (170).

The per-patient cost of the EDVS Programme was included in the tornado diagram. The per-patient cost of the EDVS Programme was €14.89. This was a low cost when compared to other studies. This cost may therefore not be generalisable to ED settings in other jurisdictions that report higher per-patient costs of screening for HIV, HBV, and HCV (114, 213, 214).

Age at ED screening for HIV, HBV, and HCV was included in the tornado diagram. A 2020 CEA of screening for HBV and HCV in the ED in the UK reported cost-effectiveness of screening of

people over 70 years as being uncertain due to lower prevalence and lower life expectancy from the point of treatment (114).

Table 5.2 shows the parameters, their definitions within the model, their base-case value and the parameter range analysed in the OWSA.

Table 5.2: Parameters chosen for one way sensitivity analysis.

Parameter	Base-case	Parameter range
Combined seroprevalence	4.8%	0%-10%
Combined seroprevalence of patients who Require LTC	0.81%	0.5-1%
Discount rate	4%	0%-10%
Per-patient per-treatment cost DAA	€44,500	€5,000-€90,000
Annual per-patient cost TDF	€2,700	€500-€2,700
Per-patient cost EDVS Programme	€14.89	€5-€100
Annual OPD cost HIV State 1 ($CD4^+$>500)	€12,215	± 20%
Annual OPD cost HBV State 2 (HBeAg- inactive)	€416	± 20%
Annual OPD cost HCV State 1 (NC)	€416	± 20%
Cost hospitalisation HIV State 3 ($CD4^+$<200)	€8,240	± 20%
Age at EDVS Screen	43yo	20yo-80yo
Utility HIV State 1 ($CD4^+$>500)	0.73	± 10%
Utility HBV State 2 (HBeAg- inactive)	0.87	± 10%
Utility HCV State 1 (NC)	0.77	± 10%
Utility hospitalisation	-0.1	± 10%
10 yr utility gain HIV State2 ($CD4^+$ 200-500)	0.8	± 10%
10 yr utility gain HBV State 6 (CC)	0.85	± 10%
10 yr utility gain HCV State 2 (CC)	0.65	± 10%
Utility patients already LTC	0.79	± 10%
Utility patients screen negative	0.91	± 10%

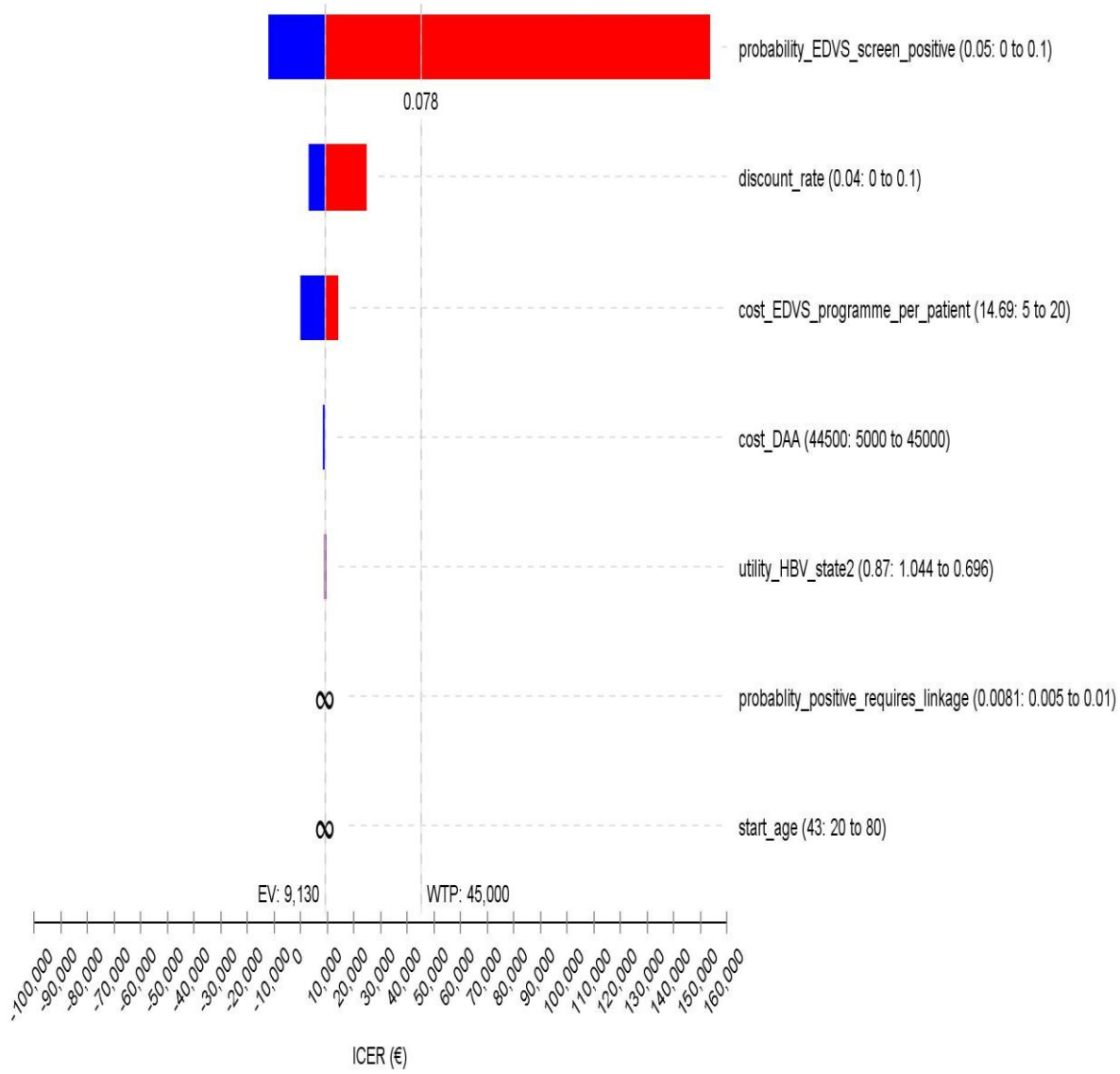
All costs are in €, year 2020 values.

EDVS Emergency Department Viral Screen; **LTC**: linkage to care; **DAA**: direct-acting antiviral; **TDF**: tenofovir disoproxil fumarate; **yo**: years old; **OPD**: outpatient department; NC: non-cirrhotic; **CC**: compensated cirrhosis; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

5.3.1 Tornado Diagram

A tornado diagram for the OWSA of seven key parameters in the model is shown in Figure 5.1. The tornado diagram depicts variation around the base-case ICER (€9,120/QALY) for the EDVS Screen strategy and uses a WTP threshold of €45,000/QALY. The parameter with the greatest impact is at the top of the tornado diagram. The parameter with the greatest impact on the ICER in this OWSA was the combined seroprevalence. This is referred to as *probability_EDVS_screen_positive* in the tornado diagram.

Figure 5.1: A tornado diagram of one way sensitivity analysis of seven parameters around the base-case ICER of €9,130/QALY at a WTP threshold of €45,000; intervals of 10 [abc].



All costs are in €, year 2020 values.

EV indicates the base-case ICER expected value; **ICER**: incremental cost-effectiveness ratio; **DAA**: direct-acting antivirals; **TDF**: tenofovir disoproxil fumarate; **EDVS**: Emergency Department Viral Screen; **DNA**: did-not-attend; **WTP**: willingness to pay; **LTC**: linkage to care; **p_EDVS_screen_positive**: probability patients who underwent and EDVS screened positive; **discount_rate**: discount rate; **cost_EDVS_programme_per-patient**: EDVS Programme cost per patient; **cost_DAA**: cost DAA per-patient; **utility_HBV_state2**: utility HBV state 2; **probability_positive_requires_linkage:** probability patients who screened positive Require LTC; **start_age**: start age at EDVS.

[a] The parameter with the biggest impact on the ICER is at the top of the tornado diagram. The blue portion of the bar represents the ICER range when the parameter value is lower than its base-case value. The red portion of the bar represents the ICER range when the parameter is higher than its base-case value.
[b] The two bottom parameters have an infinity sign rather than a bar. Within the uncertainty range for that parameter, the incremental effectiveness passes through zero, which makes the ICER calculation undefined. Therefore, a bar would be invalid.
[c] The first value in the bracket is the base-case value; the following values are the ranges of the parameter analysed.

5.3.2 Combined Seroprevalence

In this CEA, the parameter with the largest impact on the ICER was combined seroprevalence of HIV, HBV, and HCV (Ab±RNA). At a WTP threshold of €45,000/QALY, ED screening for HIV, HBV, and HCV remained cost-effective at a combined seroprevalence of between 3.5% to 7.8% inclusive (Table 5.3). Beyond these ranges, screening is not cost-effective.

Table 5.3: A one way sensitivity analysis report of combined seroprevalence: EDVS Screen strategy versus No EDVS Screen strategy; base-case combined seroprevalence = 4.8%[ab].

Combined seroprevalence (%)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
0	-22.2387	0.001856	-11,982 (No EDVS Screen strategy dominates[c])
1	-15.848495	0.001698	-9,335 (No EDVS Screen strategy dominates)
2	-9.458287	0.001539	-6,144 (No EDVS Screen strategy dominates)
3	-3.068083	0.001381	-2,222 (No EDVS Screen strategy dominates)
4	3.32212	0.001222	2,728
5	9.712325	0.001064	9,130
6	16.10253	0.000905	17,788
7	22.49273	0.000747	31,021
8	28.88294	0.000588	49,101
9	35.27314	0.00043	82,083
10	41.66335	0.000271	153,616

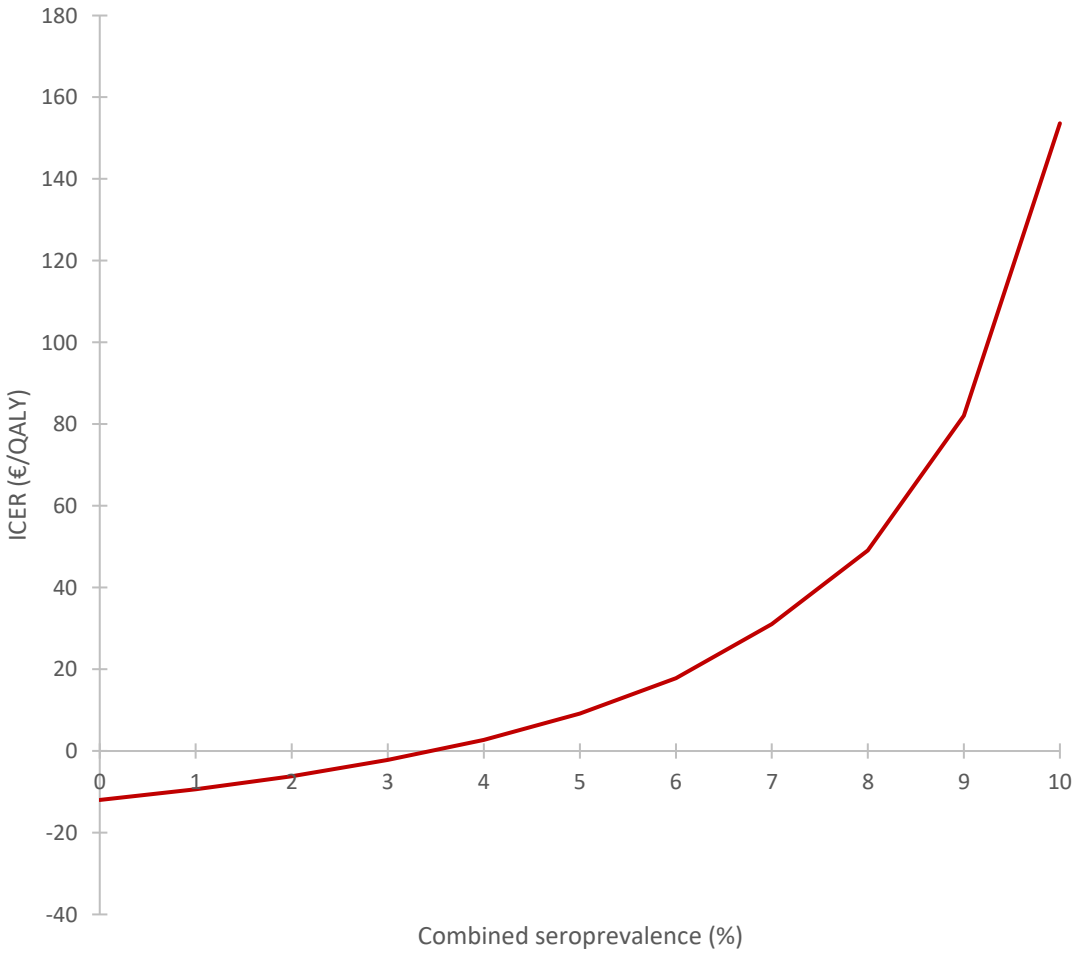
All costs are in €, year 2020 values.

EDVS indicates Emergency Department Viral Screen; ICER indicates incremental cost-effectiveness ratio.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4.8; low value = 0; high value = 10; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.
[c] A dominant treatment option is one that is both less costly and results in better health outcomes (134).

Figure 5.2 shows the ICER variation in a OWSA of combined seroprevalence using limits of 0% to 10% inclusive.

Figure 5.2: A one way sensitivity analysis of combined seroprevalence: EDVS Screen strategy versus No EDVS Screen strategy; base-case combined seroprevalence = 4.8% [a].



All costs are in €, year 2020 values.

EDVS indicates Emergency Department Viral Screen**; ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4.8; low value = 0; high value = 10; intervals of 10.

5.3.3 Age at Emergency Department Viral Screen

When considering ED screening for HIV, HBV, and HCV by age, at a WTP threshold of €45,000/QALY, screening was cost-effective for those aged between 20 years to 61 years inclusive. It was most cost-effective for those aged between 20 years to 44 years inclusive, with ICERs below €10,000/QALY. For those aged between 63 years to 65 years inclusive, screening

was over the WTP threshold of €45,000/QALY. For those aged 66 years and older, this CEA suggests that it is not cost-effective to screen (Table 5.4).

Table 5.4: A one way sensitivity analysis report of age at EDVS Screen: EDVS Screen strategy versus No EDVS Screen strategy; base-case age at EDVS Screen = 43 years[ab].

Age at EDVS Screen (years)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
20	10.44109	0.001598	6,532
26	10.31993	0.0015	6,880
32	10.15851	0.001376	7,383
38	9.944417	0.001221	8,144
44	9.658909	0.001029	9,387
50	9.280683	0.000794	11,684
56	8.785291	0.000513	17,123
62	8.143197	0.000183	44,534
66	7.545783	-0.00010	-77,654 (No EDVS Screen strategy dominates[c])
68	7.326154	-0.00019	-37,629 (No EDVS Screen strategy dominates)
74	6.326254	-0.00061	-10,401 (No EDVS Screen strategy dominates)
80	5.193961	-0.00103	-5,048 (No EDVS Screen strategy dominates)

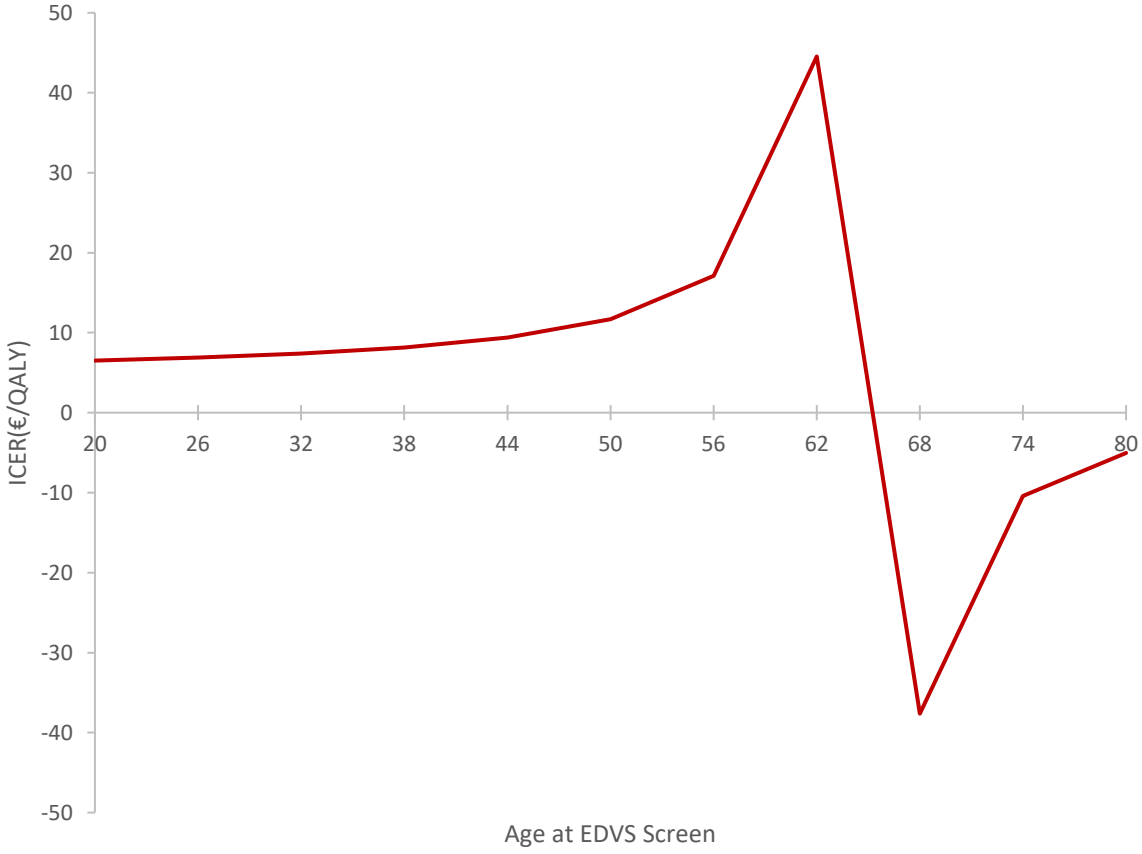
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 43; low value = 20; high value = 80; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.
[c] A dominant treatment option is one that is both less costly and results in better health outcomes (134).

Figure 5.3 shows the ICER variation in a OWSA of age at EDVS Screen.

Figure 5.3: A one way sensitivity analysis of age at EDVS Screen: EDVS Screen strategy versus No EDVS Screen strategy; base-case age at EDVS Screen = 43 years[ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **EDVS**: Emergency Department Viral Screen; **QALY**: quality-adjusted life-year.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 43; low value = 20; high value = 80; intervals of 10.
[b] X axis begins at 20 years as this was the lowest age analysed in OWSA.

5.3.4 Per-patient Cost Emergency Department Viral Screen Programme

The ICER was sensitive to the per-patient cost of the EDVS Programme. At a WTP threshold of €45,000/QALY, ED screening for HIV, HBV, and HCV remained cost-effective when the per-patient cost of the EDVS Programme was under €52.50 (Table 5.5).

Table 5.5: A one way sensitivity analysis report of per-patient cost of EDVS Programme: EDVS Screen strategy versus No EDVS Screen strategy; base-case per-patient cost EDVS Programme = €14.89[ab].

Per-patient cost EDVS Programme (€)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
5	0.022998	0.001064	21.62
14.5	9.522338	0.001064	8,952
24	19.02168	0.001064	17,881
33.5	28.52102	0.001064	26,811
43	38.02036	0.001064	35,741
52.5	47.5197	0.001064	44,671
62	57.01904	0.001064	53,601
71.5	66.51838	0.001064	62,531
81	76.01772	0.001064	71,461
90.5	85.51706	0.001064	80,391
100	95.0164	0.001064	89,321

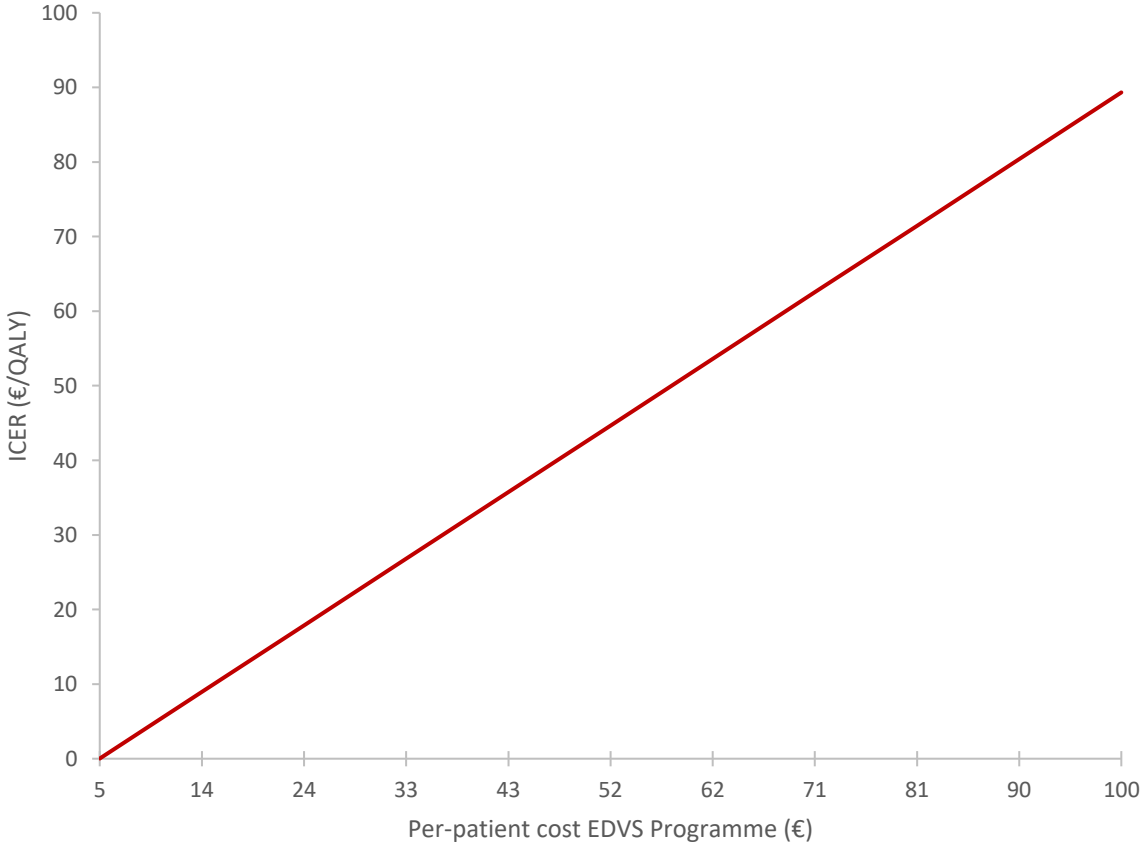
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 14.89; low value = 5; high value = 100; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.

Figure 5.4 shows the ICER variation in a OWSA of per-patient cost of EDVS Programme.

Figure 5.4: A one way sensitivity analysis of per-patient cost EDVS Programme: EDVS Screen strategy versus No EDVS Screen strategy; base-case per-patient cost EDVS Programme = €14.89[ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 14.89; low value = 5; high value = 100; intervals of 10.
[b] X axis commences at €5 as this was the lowest value analysed in OWSA.

5.3.5 Discount Rate

The ICER was sensitive to variations in the discount rate. Table 5.6 shows a OWSA of discount rate. Ranges from 0% per annum to 10% per annum inclusive were examined with the assumption was that a uniform rate across costs and effects was appropriate. BBV panel screening remained cost-effective under all these ranges. The ICER remained below a WTP threshold of €45,000/QALY and €20,000/QALY with a discount rate for both cost and effect between 0% per annum to 4% per annum inclusive.

Table 5.6: A one way sensitivity analysis report of discount rate: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate = 4%[ab].

Discount rate (%)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
0	7.979932	0.002667	2,992
1	8.444839	0.002051	4,118
2	8.89786	0.001613	5,516
3	9.322591	0.001296	7,191
4	9.712325	0.001064	9,130
5	10.06564	0.00089	11,311
6	10.38387	0.000758	13,704
7	10.66964	0.000656	16,275
8	10.92607	0.000575	18,988
9	11.15635	0.000511	21,811
10	11.36352	0.00046	24,714

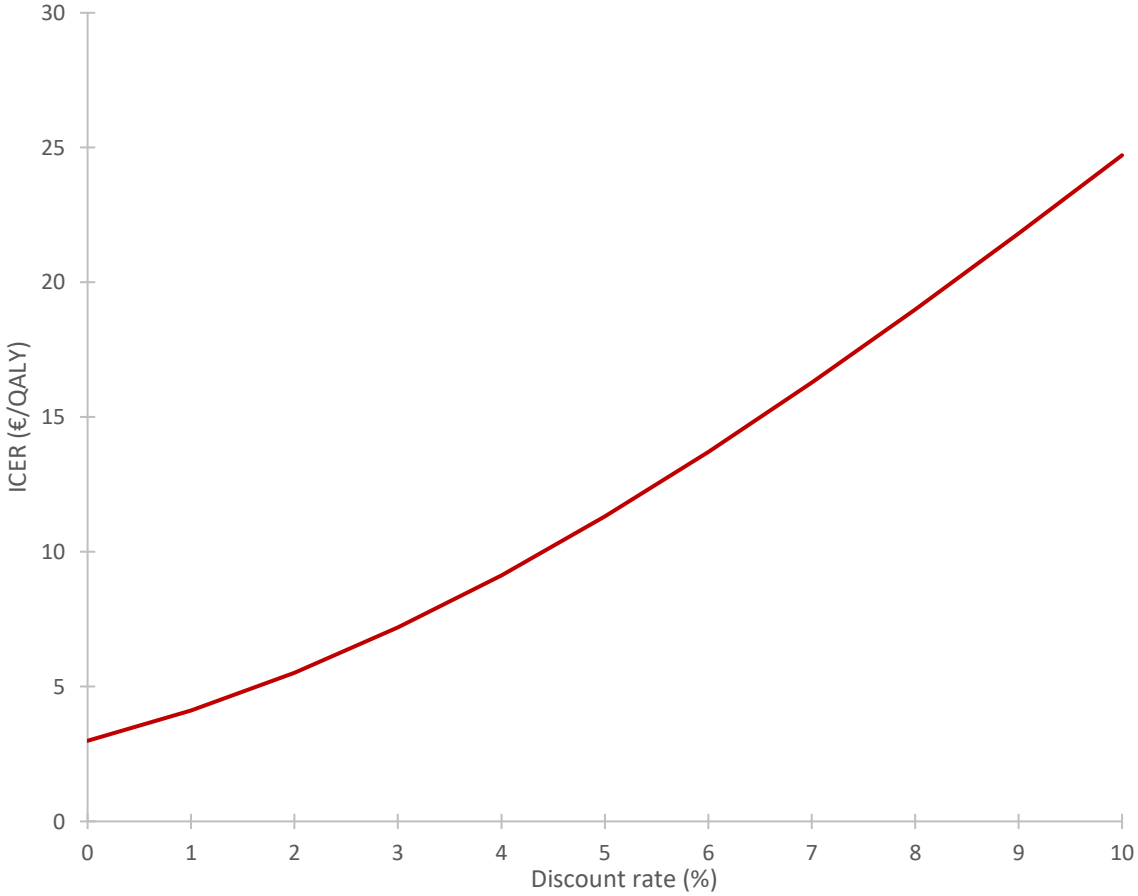
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.

Figure 5.5 shows the ICER variation in a OWSA of discount rate.

Figure 5.5: A one way sensitivity analysis of discount rate: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate = 4%[ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **EDVS:** Emergency Department Viral Screen**.**

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Discount rate applied to both cost and effect.

5.3.5.1 Differential Discounting: Cost

In a OWSA, changes in differential discounting for cost (0% per annum to 10% per annum inclusive) were analysed (Table 5.7). The discount rate for effects remained at 4% per annum. At a discount rate for cost of 0% per annum, the ICER was €7,502/QALY. At a discount rate for cost of 10% per annum, the ICER was €10,682/QALY. Neither WTP thresholds were broken across this OWSA.

Table 5.7: A one way sensitivity analysis report of discount rate for cost: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate for cost = 4% [abc].

Discount rate for cost (%)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
0	7.98	0.001064	7,502
1	8.44	0.001064	7,939
2	8.90	0.001064	8,364
3	9.32	0.001064	8,764
4	9.71	0.001064	9,130
5	10.06	0.001064	9,462
6	10.38	0.001064	9,761
7	10.67	0.001064	10,030
8	10.93	0.001064	10,271
9	11.16	0.001064	10,488
10	11.36	0.001064	10,682

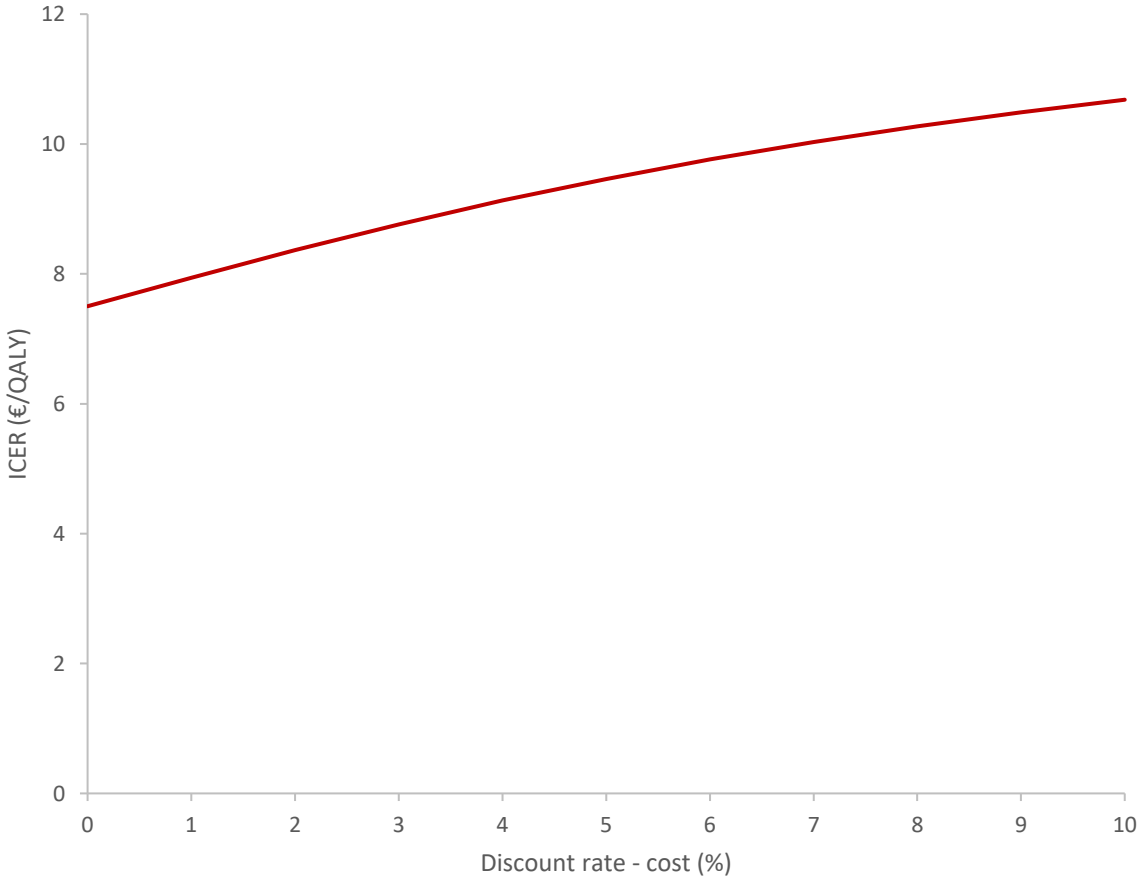
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.
[c] Discount rate for effect remained at 4% in all analyses.

Figure 5.6 shows the ICER variation in a OWSA of discount rate for cost.

Figure 5.6: A one way sensitivity analysis of discount rate for cost: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate for cost = 4% [ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **EDVS:** Emergency Department Viral Screen**.**

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Discount rate for effect remained at 4% in all analyses.

5.3.5.2 Differential Discounting: Effect

In a OWSA, changes in differential discounting for effect (0% per annum to 10% per annum inclusive) were analysed. The discount rate for cost remained at 4% per annum. The ICER ranged from €3,641/QALY at a discount rate for effect of 0% per annum to an ICER of €21,123/QALY at a discount rate of 10% per annum (Table 5.8). In differential discounting, changes to the discount rate for effect had a greater impact on the ICER than changes in discount rate for cost. All limits assessed in the OWSA remained cost-effective with an ICER below a WTP threshold of €45,000/QALY.

Table 5.8: A one way sensitivity analysis report of discount rate for effect: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate for effect = 4%[abc].

Discount rate for utility (%)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
0	9.71	0.002667	3,641
1	9.71	0.002051	4,736
2	9.71	0.001613	6,022
3	9.71	0.001296	7,492
4	9.71	0.001064	9,130
5	9.71	0.00089	10,914
6	9.71	0.000758	12,818
7	9.71	0.000656	14,815
8	9.71	0.000575	16,879
9	9.71	0.000511	18,988
10	9.71	0.00046	21,123

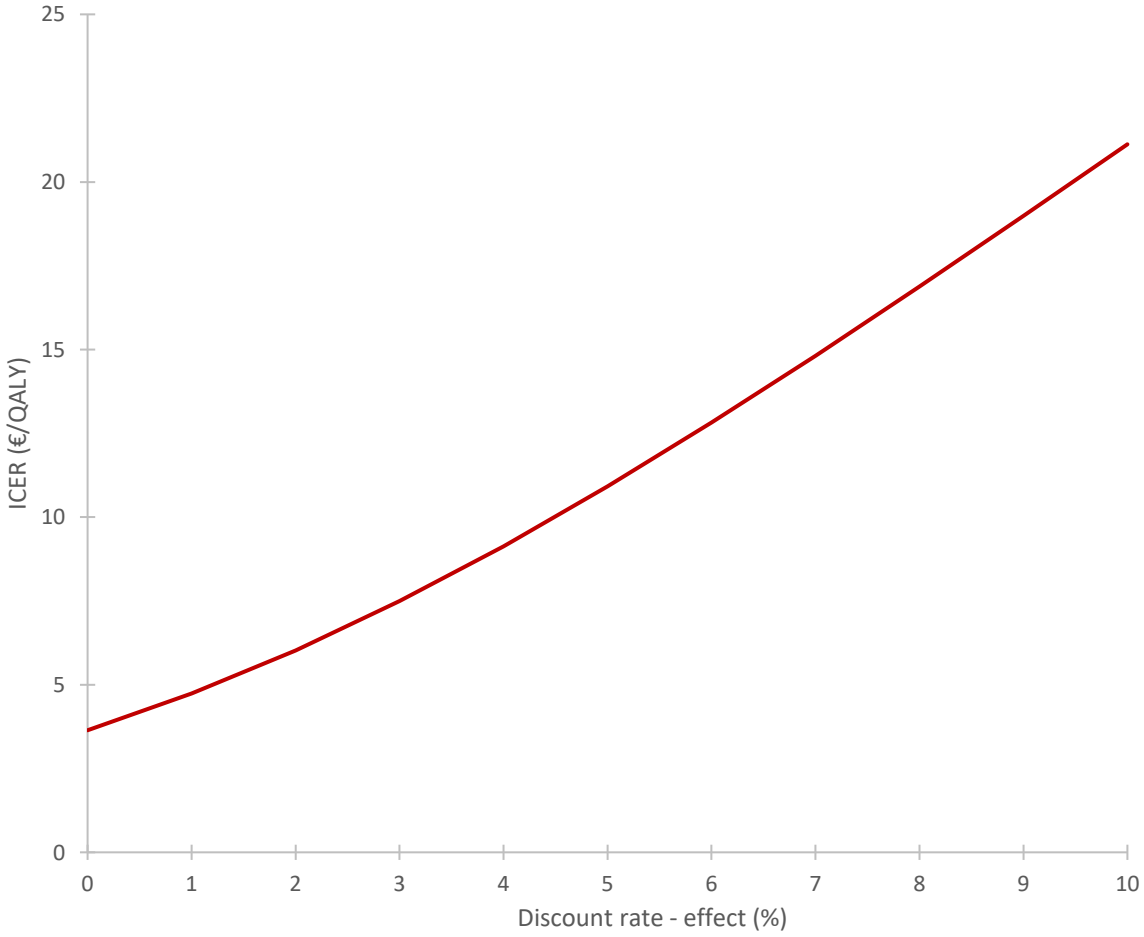
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **EDVS:** Emergency Department Viral Screen**.**

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.
[c] Discount rate for effect remained at 4% in all analyses.

Figure 5.7 shows the ICER variation in a OWSA of discount rate for effect.

Figure 5.7: A one way sensitivity analysis of discount rate for effect: EDVS Screen strategy versus No EDVS Screen strategy; base-case discount rate for effect = 4%[ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **EDVS:** Emergency Department Viral Screen**.**

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 4; low value = 0; high value = 10; intervals of 10.
[b] Discount rate for cost remained at 4% for all analyses.

5.3.6 Per-patient Per-treatment Cost Direct-Acting Antivirals

Variations in per-patient per-treatment cost of DAA had a minimal impact on the ICER (Table 5.9). The ICER remained under €20,000/QALY for all variations to per-patient cost of DAA, including per-patient per-treatment costs of DAA from €5,000 to €90,000 inclusive.

Table 5.9: A one way sensitivity analysis report of per-patient per-treatment cost DAA: EDVS Screen strategy versus No EDVS Screen strategy; base-case per-patient per-treatment cost DAA = €44,500[ab].

Per-patient EDVS cost (€)	Incremental cost (€)	Incremental effect (QALY)	ICER (€)
5,000	8.749596	0.001064	8,225
13,500	8.956765	0.001064	8,420
22,000	9.163935	0.001064	8,615
30,500	9.371105	0.001064	8,809
39,000	9.578274	0.001064	9,004
47,500	9.785444	0.001064	9,199
56,000	9.992614	0.001064	9,394
64,500	10.19978	0.001064	9,588
73,000	10.40695	0.001064	9,783
81,500	10.61412	0.001064	9,978
90,000	10.82129	0.001064	10,173

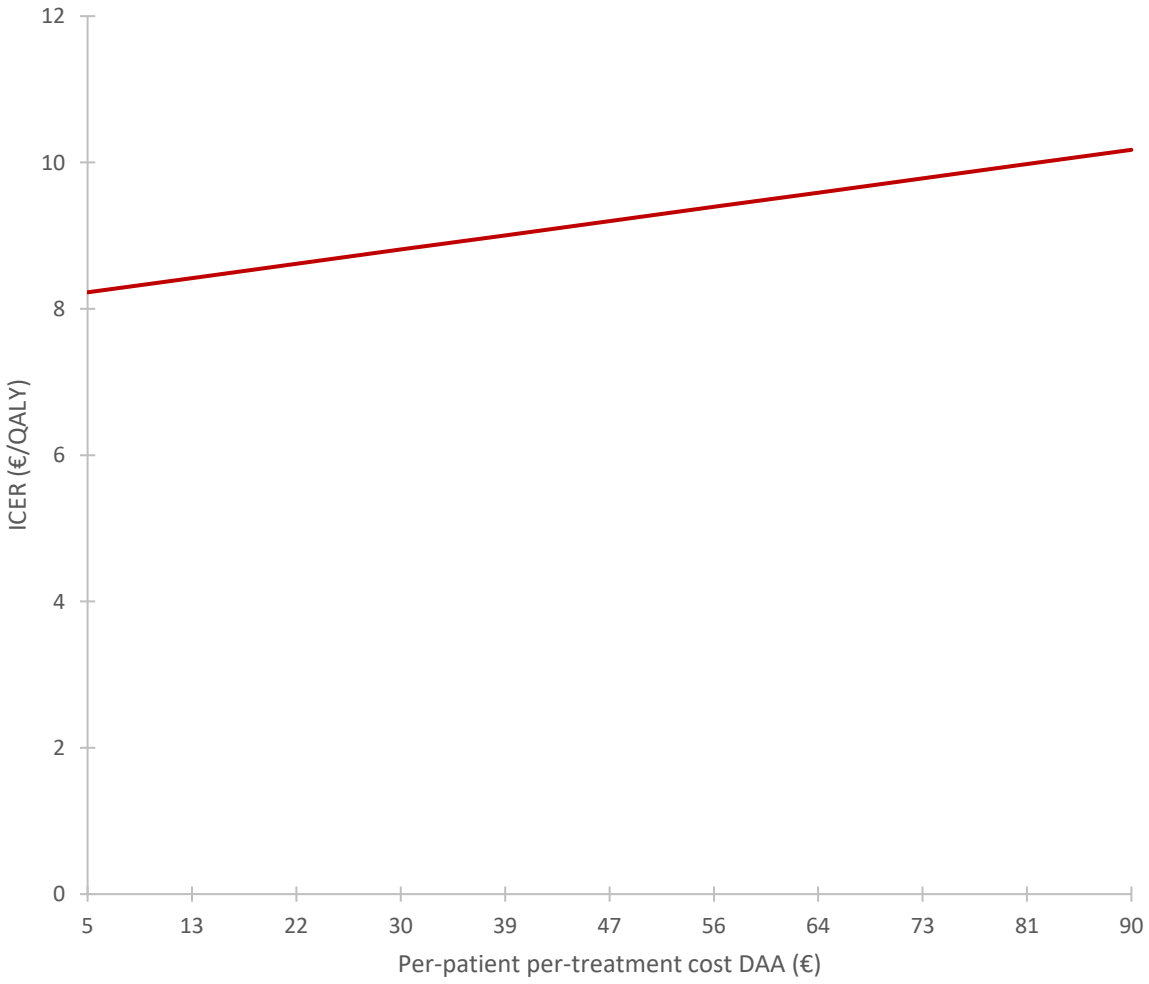
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **DAA:** direct-acting antiviral; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 44,500; low value = 5,000; high value = 90,000; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.

Figure 5.8 shows the ICER variation in a OWSA of per-patient per-treatment cost of DAA.

Figure 5.8: A one way sensitivity analysis of per-patient per-treatment cost DAA: EDVS Screen strategy versus No EDVS Screen strategy; base-case per-patient per-treatment cost DAA = €44,500[ab].



All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **DAA:** direct-acting antiviral; **EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 44,500; low value = 5,000; high value = 90,000; intervals of 10.
[b] X axis begins at €5,000 as this was the lowest value analysed in OWSA.

5.3.7 Prevalence of Patients who Screen Positive who Require Linkage to Care

The ICER was negative (due to greater costs and less effect) in a OWSA for the prevalence of patients who screen positive for infection and Require LTC. In a OWSA, at a WTP threshold of €45,000/QALY, a prevalence of patients who screen positive and Require LTC of 0.7% or more was cost-effective. (Table 5.10).

Table 5.10: A one way sensitivity analysis report of prevalence of patients who screen positive who Require LTC: EDVS Screen strategy versus No EDVS Screen strategy; base-case prevalence of patients who screen positive who Require LTC = 0.81[ab].

Prevalence of patients who screen positive who Require LTC	**Incremental cost (€)**	**Incremental effect (QALY)**	**ICER (€)**
0.5%	0	0	0
0.55%	0	0	0
0.6%	1.428727	-0.00029	-4,990 (No EDVS Screen strategy dominates [c])
0.65%	3.40101	0.000035	96,818
0.7%	5.373297	0.000356	15,069
0.75%	7.345	0.00067	10,834
0.8%	9.31786	0.00099	9,323
0.85%	11.29	0.00132	8,547
0.9%	13.262	0.001642	8,075
0.95%	15.23	0.001963	7,758
1%	17.207	0.002285	7,529

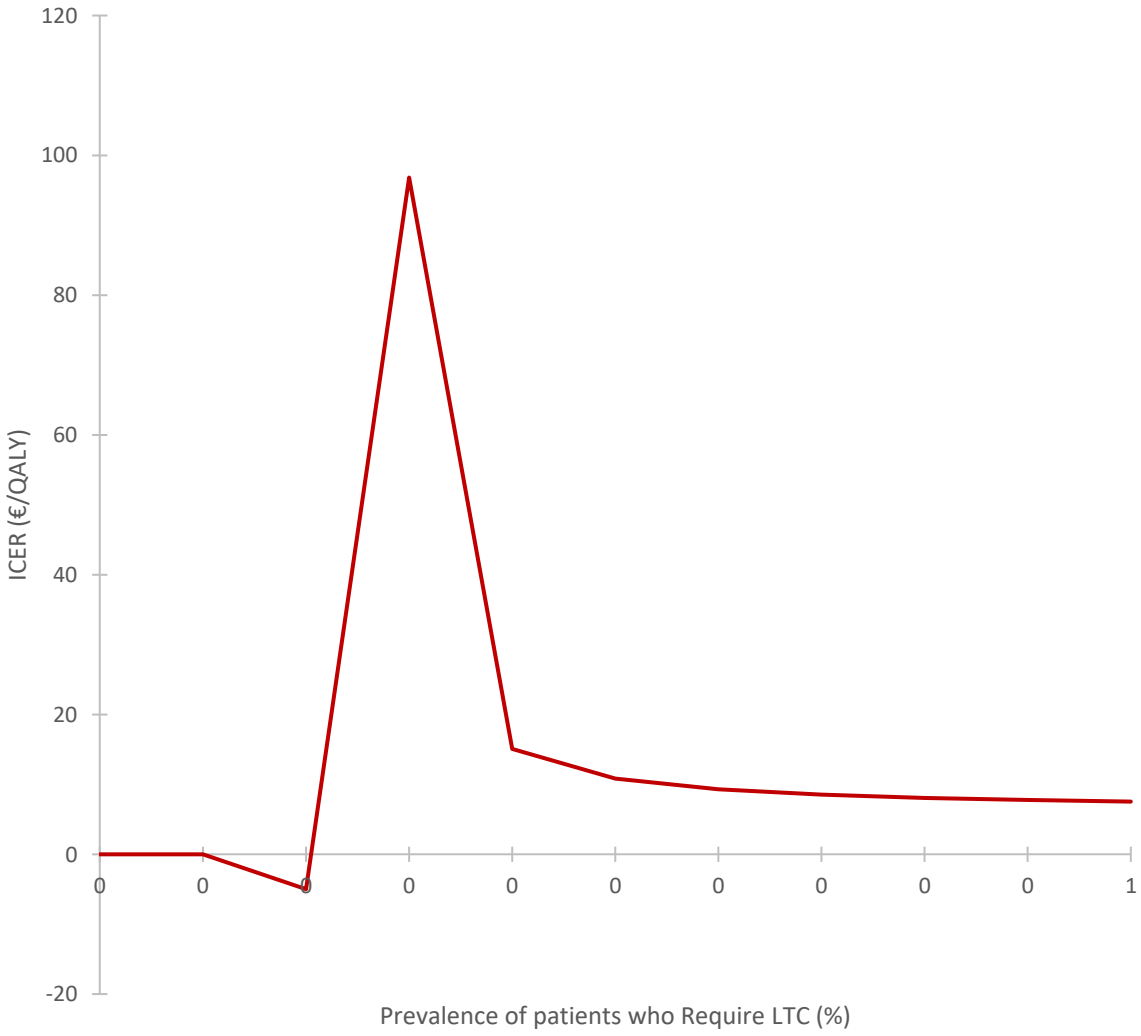
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **LTC:** linkage to care**; EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 0.81; low value = 0.5; high value = 1; intervals of 10.
[b] Figures in the table are rounded so calculations may not be directly replicable.
[c] A dominant treatment option is one that is both less costly and results in better health outcomes (134).

Figure 5.9 shows the ICER variation in a OWSA of prevalence of patients who screen positive who Require LTC.

Figure 5.9: A one way sensitivity analysis of prevalence of patients who screened positive who Require LTC: EDVS Screen strategy versus No EDVS Screen strategy; base-case prevalence = 0.81[ab].



All costs are in €, year 2020 values.

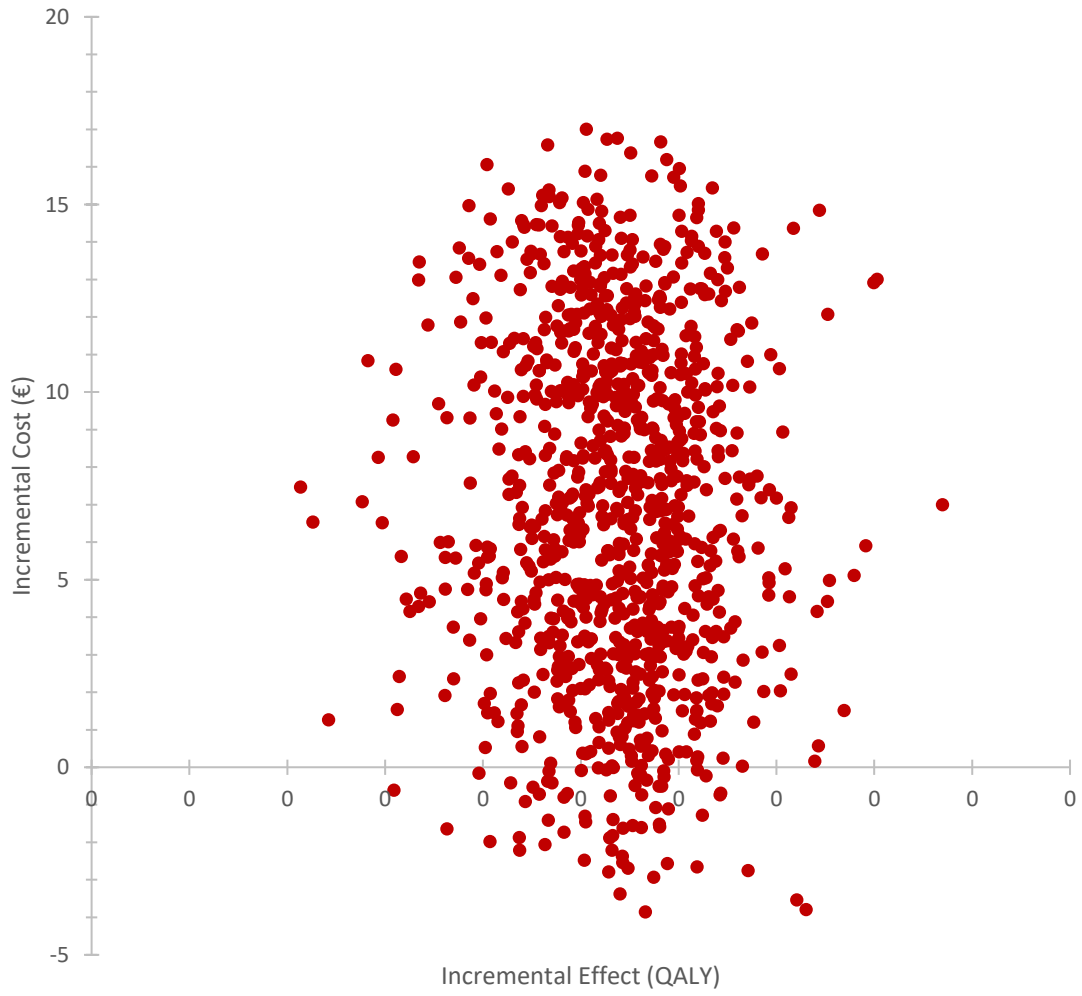
ICER indicates incremental cost-effectiveness ratio; **LTC:** linkage to care**; EDVS**: Emergency Department Viral Screen.

[a] Sensitivity analysis metadata: model evaluation method used expected value calculation; base-case value = 0.81; low value = 0.5; high value = 1; intervals of 10.
[b] X axis begins at 0.5 as this was the lowest value examined in the OWSA.

5.4 Probabilistic Sensitivity Analysis

In the base-case analysis, base-case inputs for ED screening for HIV, HBV, and HCV was cost-effective with an ICER of €9,130/QALY. Figure 5.10 shows the cost-effectiveness plane for ED screening for HIV, HBV, and HCV.

Figure 5.10: Cost-effectiveness plane for ED screening for HIV, HBV, and HCV. The base-case ICER is €9,130/QALY; 10,000 iterations were analysed; base-case incremental cost = €10, base-case incremental effect = 0.0011 QALY.



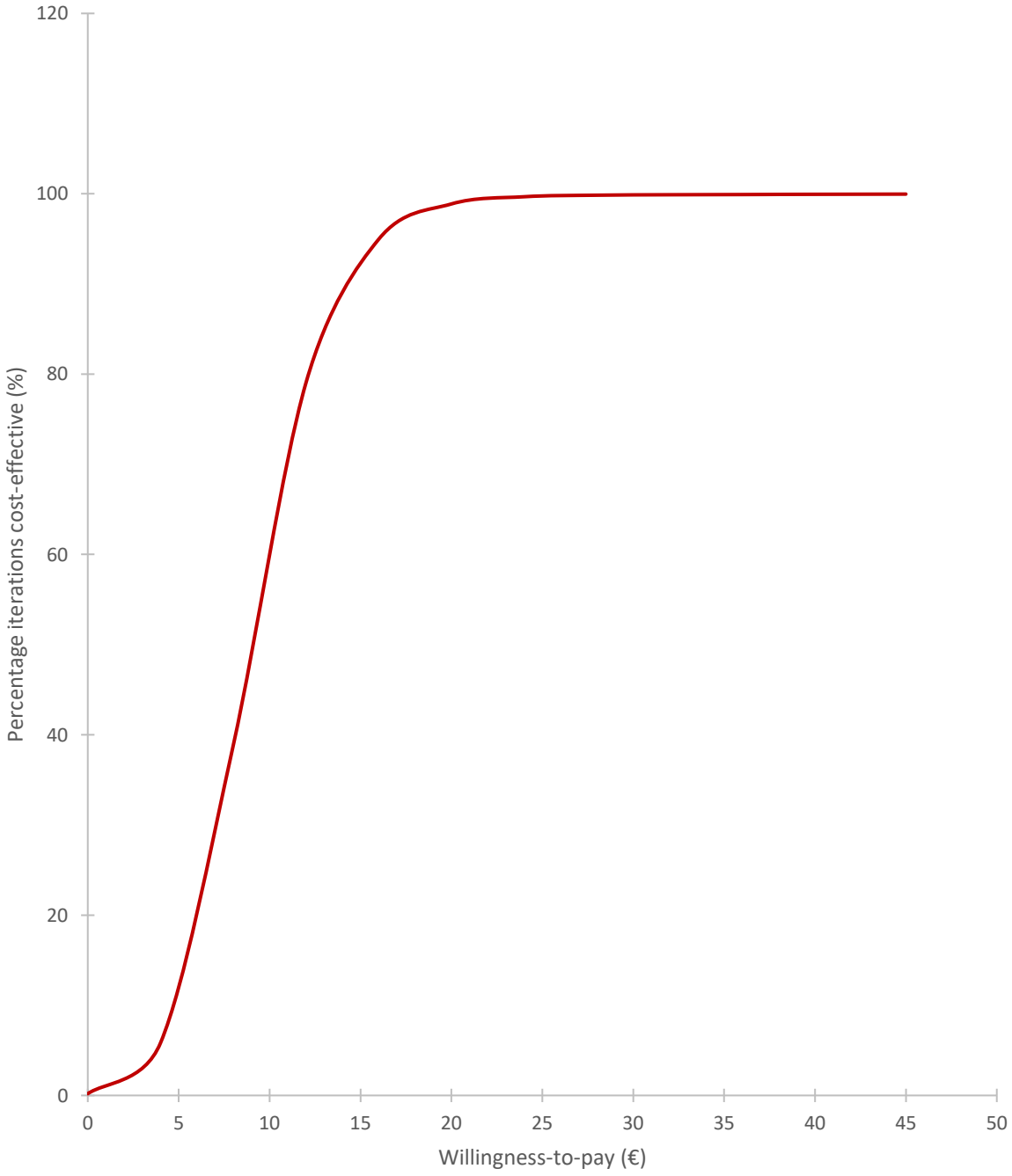
All costs are in €, year 2020 values.

ICER indicates incremental cost-effectiveness ratio; **QALY**: quality-adjusted life-year; **ED**: Emergency Department; **HIV**: Human Immunodeficiency Virus; **HBV**: Hepatitis B Virus; **HCV**: Hepatitis C Virus.

A cost-effectiveness acceptability curve presents the relative cost-effectiveness as a function of the WTP threshold (215). For each WTP threshold, the graph uses net benefits to determine the percentage of simulation iterations that favour each strategy. The percentages will increase for more effective strategies as the WTP threshold increases. The graph value at a particular WTP threshold represents the probability that it is cost-effective, based on the uncertainties included in the cost-effectiveness model (215).

In the base-case analysis, ED screening for HIV, HBV, and HCV was 98.8% likely to be cost-effective at a WTP of €20,000/QALY. At a WTP of €45,000/QALY, ED screening for HIV, HBV, and HCV was 99.96% likely to be cost-effective (Figure 5.11).

Figure 5.11: A Monte Carlo cost-effectiveness acceptability curve: EDVS Screen strategy versus No EDVS Screen strategy[a].



EDVS indicates Emergency Department Viral Screen**.**

[a] This graph demonstrates the percentage of model calculations/ iterations that favour each strategy.

5.5 Discussion

With an ICER of €9,130/QALY, ED screening for HIV, HBV and HCV represents a cost-effective strategy for diagnosing patients who Require LTC, including patients with new infection diagnoses, patients with known infection who disengaged from care, and patients who tested positive who were uncontactable and therefore their infection status history was unknown. PSA confirms confidence in these results at both WTP thresholds of €45,000/QALY and €20,000/QALY.

While previous studies have reported cost-effectiveness of either mono-infection for HIV screening or co-infection for HBV and HCV screening in the ED, to our knowledge, this is the first CEA of ED screening for HIV, HBV, and HCV not only in Ireland, but also internationally. This study adds to the body of available literature on the the acceptability and cost-effectiveness of screening for HIV, HBV, and HCV in the ED setting. It also increases the available evidence of the benefit of screening for all three infections, of which there is very little available data (114, 143, 216, 217).

A key strength of this study was that the model and many of the input parameters that were used were analysed from the EDVS real-world PLD registry database[i]. For the majority of the remaining input parameters, national data was used (156, 173). Following that, where necessary, international data was used.

The CEA has also conformed *to* national guidelines (12). Another strength was that the model adopts the Markov modelling technique. Markov modelling is a commonly used approach in CEA. It allows analysts to handle the complexity of modelling options with multiple possible consequences (218).

Several key findings in the OWSA warrant discussion. The parameter with the biggest impact on the ICER was combined seroprevalence. This includes patients who test positive for one or more of HIV, HBV and HCV (Ab±RNA). This study determined that ED screening for HIV, HBV, and HCV was cost-effective at a combined seroprevalence of between 3.5% to 7.8% inclusive. In our study, the base-case seroprevalence of HIV, HBV and HCV respectively were 1.07%, 0.5% and

3.63% (1.4% for HCV RNA). This represents a cost-effectiveness threshold for HIV seroprevalence of between 0.78% to 1.74% inclusive, HBV seroprevalence of between 0.36% to 0.8% inclusive, and HCV seroprevalence of between 2.65% to 5.9% with an RNA seroprevalence of between 1.02% to 2.3% inclusive.

With respect to combined seroprevalence, our study compares favourably to other studies in the ED setting that have reported similar seroprevalence (114, 216, 217, 219, 220). Williams *et al* (114) reported a seroprevalence in a UK ED setting of 0.8% and 1.4% for HBV and HCV (RNA) respectively. Parry *et al* (216) reported a combined seroprevalence of 4.1% in a London ED. Evans *et al* (217) reported a seroprevalence of 0.5% and 2% for HBV and HCV (Ab±RNA) respectively. Cieply *et al* (219) reported seroprevalence from two London EDs. In the two EDs studied, they repored a HIV seroprevalence of 1.3% and 2.2%, a HBV seroprevalence of 1.1% and 1.0%, and a HCV seroprevalence of 1.6 and 2.3% with an RNA seroprevalence of 0.9% and 1.6%. A combined seroprevalence of 3.5% was reported during BBV testing week in nine UK EDs (220). This study suggests that ED screening for all three infections was cost-effective in the ED setting and potentially in other settings with similar combined seroprevalence.

In the UK, NICE recommends widespread screening in the ED for HIV at a seroprevalence of 2% or greater (115). Our study suggests that screening for HIV in the ED is cost-effective at a HIV seroprevalence of between 0.78% to 1.74% inclusive. In a NICE 2017 review of screening in the ED for HCV and HBV, they recommend screening at risk groups only for HBV and HCV, unlike HIV. The review does comment that there was a lack of cost-effectiveness data available on screening in the ED for BBV infections (105). Our study adds to the lack of available data in this arena.

This analysis confirms the cost-effectiveness of screening for tri-infections. The ECDC advocates an integrated approach for screening for tri-infections (1). The ECDC comments that the three viruses have common modes of transmission. There tends to be significant overlaps in affected population groups and high levels of co-infection. Integrated screening also reflects existing patterns of service delivery (1). The ECDC recommends ED screening for tri infections when seroprevalence for HIV is 1% or greater and HBV and HCV combined seroprevalence is 5% or greater. These guidelines do not cite cost-effectiveness data . Our study suggests screening for tri-infection was cost-effective at a combined seroprevalence of between 3.5% to 7.8% inclusive.

We are aware that seroprevalence in this study setting may change in the future. As a result of ongoing changes in demographics and migration patterns, the introduction of universal childhood HBV vaccination programme, the increased availability of therapeutics including P(R)EP for HIV and DAAs for HCV, and increasing use of HBV treatment, there may be a future shift in seroprevalence in this study setting (51, 114, 174, 212). Given that the ICER was sensitive to a change in combined seroprevalence, a re-evaluation of ED screening for HIV, HBV, and HCV may be warranted in the future.

In addition to this point regarding potential future changes in seroprevalence, as an example, the National Hepatitis C Treatment Programme has seen an expansion in treatment initiatives, to include community-based screening and treatment (221). In the EDVS Programme, year-on-year, numbers of new HCV diagnoses are decreasing (170). In 2015, 8.6% of patients who underwent an EDVS and who screened positive for HCV were new diagnosis. In 2016, 2017, 2018 and 2019, this number decreased to 6.7%, 5.7%, 6.2% and 3.5% respectively. This year-on-year downward trend would indicate that seroprevalence rates are likely to continue to decrese over the next number of years.

Outside the setting of the ED, Allen et al report seroprevalence of these infections in an acute medical unit in Ireland (222). The authors offered opt-out screening to patients attending an acute medical unit setting in a tertiary referral hospital in Galway, Ireland. They concluded that of the 1,936 patients screened (with an opt-out rate of 44.4%), diagnosed prevalence rates for HIV, HBV and HCV were 0.5 per 1000, 2 per 1000 and 1.5 per 1000, respectively. This combined seroprevalence of 0.4% suggests that screening for tri-infection is not cost-effective in an acute medical unit setting. More study is required in this area however.

In the OWSA, variations to age at time of screening impacted the ICER. Our study suggests that the cost-effectiveness of screening those aged 66 years or older is not cost-effective in this age group. Of all patients screened with a positive EDVS[i] (n = 3,360), 5% (n = 172) of people were aged 66 years or older. There is a paucity of data available on this age at OWSA. Nonetheless, our results are similar to results from a study by Williams *et al* (114). This study reported the uncertainty of cost-effectiveness for screening those aged 70 years or older. This could potentially be due to lower life expectancy and therefore health gains from point of treatment

for patients aged 66 years or older. Our analysis reported that the incremental effect of ED screening for HIV, HBV, and HCV decreases with age. Further study is required to assess this the results of this OWSA in more detail.

Per-patient cost of the EDVS Programme had an impact on ICER in the OWSA. In our study, per-patient cost of the EDVS Programme was relatively low at €14.89 per-patient compared to other studies (114, 213, 214, 220). As described in Chapter four (Table 4.3), this cost was a mean cost over all patients tested and included the screening test, consumables, laboratory and EDVS Programme staff costs and VAT @ 23%. Williams *et al* (114) reported costs of up to €60 for screening for HBV and HCV; this cost does not include confirmatory testing. During BBV testing week in nine UK EDs , Orkin *et al* (220) reported a per-patient cost of €8.40 for screening for all three infections. The breakdown of this cost is unclear however. Mendlowitz *et al* (213) reported a per-patient screening cost of €109 in a Canadian ED for HCV alone. This cost does not include confirmatory testing.

In our study, ED screening for HIV, HBV, and HCV remained cost-effective when the per-patient cost remained below €52.50. The low per-patient cost of the EDVS Programme is potentially unrealistic and unreproducable in other settings and jurisdictions. In addition to this, with the advent of new molecular diagnostic techniques, per-patient cost of the EDVS Programme may increase in the future.

A uniform discount rate of 4% per annum for both cost and effect was applied to the base-case analysis. In a OWSA, the ICER remained below a WTP threshold of €45,000/QALY when extremes in discount rates of between 0% to 10% inclusive for both cost and effect were examined. In differential discounting, while changes to the discount rate for effect resulted in a greater variation in ICER, the ICER remained below a WTP threshold of €45,000/QALY.

Uniform discounting is generally the standard approach to applying discount rates in CEA (193). Screening programmes such as the EDVS Programme is a health technology characterised by early investment and late health outcomes, similar to vaccination programmes (223). Some analysts debate that discounting discriminates against these types of health technologies,

argueing that future benefits of such programmes should not be discounted (224, 225). In the OWSA, while the ICER remained below a WTP threshold of €45,000/QALY for both uniform and differential discounting, further study in this area is warrented given the nature of screening programmes.

While DAA costs are currently static in Ireland, per-patient per-treatment cost of DAAs were previously much higher. In the OWSA, extremes of per-patient per-treatment DAA costs were examined; the limits examined had little to no impact on the ICER. Per-patient treatment costs of between €5,000 to €90,000 inclusive were analysed. The ICER remained below a WTP threshold of €45,000/QALY and €20,000/QALY for the upper and lower limits of this parameter.

In summary, this analysis of ED screening for HIV, HBV, and HCV reported the cost-effectiveness, with an ICER of €9,130/QALY. The combined seroprevalence of this study was 4.8%. The ICER was sensitive to combined seroprevalence and remained cost-effective at a combined seroprevalence of 3.5% to 7.8% inclusive. Beyond these thresholds, screening was not cost-effective. The reason for cost-effectiveness not being shown above 7.8% remains unclear, and is likely multifactorial. The model uses a lifetime time horizon, and does not take-into-account background rates of testing. These likely contribute to this finding. Further resreach in this area however is required.

While no data is available for Ireland, nearly one quarter of the population in England use the ED every year (226). It has proven to be an acceptable setting to introduce opportunistic screening for BBV (92, 143, 227-229). The ED is disproportionately used by marginalised and underserved groups (including people who are homeless and PWID) in whom BBVs are known to be more prevalent (230-233).

5.6 Limitations

Limitations for the bespoke cost-effectiveness model and the input parameters have been listed and discussed in Chapter 3 and Chapter 4. In addition to these limitations, this CEA used a Markov modelling technique. Markov modelling has limitations. Markov cycle time may force the analyst to make simplifying assumptions regarding transition probabilities (234). In addition,

cost-effectiveness evaluations are sensitive to choice of distribution, and choice of distribution can make a difference to the conclusions drawn (211).

An important limitation of this study is that the EDVS was an opt-out screen. During this study period[i], 62.9% of all patients who attended the ED were phlebotomised and 66.6% of these patients underwent an EDVS. This may result in selection bias. Screening was also only offered to patients who were being phlebotomised for other reasons. Non-phlebotomised patients were not included in the screening programme and therefore not included in the analysis. This may falsely alter seroprevalence if a high risk population was over-represented in the phlebotomised cohort. In addition to this, in the phlebotomised group, as per previous studies, we were unable to distinguish between EDVS not being offered to patients, and patients' refusal to screen amongst those who did not undergo an EDVS (216). This could result in further selection bias. Further study is required in this area. Offering ED screening for HIV, HBV, and HCV to the non-phlebotomised cohort may also represent a future area of interest. An analysis of non-phlebotomised patient characteristics in the ED in our institution is being planned for 2022/2023.

The modelling technique also required assumptions to be made. Several assumptions were made in this model. These assumptions are listed in Chapter 4. One important assumption to discuss was an assumption about patients with co-infection. The number of patients with co-infection was small in our analysis and as a result, these patients were grouped with patients with mono-infection in a pragmatic approach to modelling. However, it is known that patients with co-infection have faster rates of progression of disease associated with that infection and more complications (23, 24). While some additional costs were accounted for in the analysis, it is likely these costs were under-represented. Transition probabilities and utilities of patients with mono-infection were used. These would likely under-represent the impact of ED screening for HIV, HBV, and HCV.

Another important assumption made was that we categorised patients diagnosed with infection but uncontactable as patients who Require LTC. Some of these uncontactable patients may have been known or Linked to Care (Chapter 3, Table 3.1). Patients were only classified as a new infection or known to Require LTC if we could contact them. This would result in an

overestimation in the model of patients who Require LTC as a result of ED screening for HIV, HBV, and HCV.

This analysis assessed cost-effectiveness of screening for three infections. While tri-infection was diagnosed, (n = 2), no patient was identified as a new diagnosis or categorised as patient who Require LTC. Therefore, while tri-infections were represented in the decision tree, no tri-infections were represented in the Markov model. This may limit the generalisability of our results.

The CEA was that of the perspective of the health payer in Ireland. It did not take-into-account a societal view. It did not assess the indirect costs and effects associated with not diagnosing infection and consequently not linking to care patients with these infections. These costs can be considerable. Additionally, costs can be reversed, and effects gained as a result of diagnosis and LTC, taking as an example work presenteeism amongst patients (235, 236). Further study in this area is warranted.

5.7 Conclusion

Cost-effectiveness model-based evaluations are a valuable resource for health care decision makers. The results of this CEA suggest that ED screening for HIV, HBV, and HCV is cost-effective at our base-case combined seroprevalence of 4.8%. The results are robust to SA.

This CEA will provide further data for decision makers with regard implementing screening for HIV, HBV, and HCV not just in an ED setting, but other settings with similar seroprevalence. Moreover, the SA highlights that there is an upper and lower threshold at which ED screening for HIV, HBV, and HCV is cost-effective. By performing this CEA analysis, we can better reflect medical practice and provide better quality evidence for decision makers making difficult trade-offs between funding screening interventions or other health technologies.

CHAPTER 6 SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

6.1 Summary

HIV, HBV, and HCV are three BBVs with common modes of transmission. There are appreciable overlaps in affected population groups and high levels of co-infection. Integrated screening reflects existing patterns of service delivery (1). Treatment targets have been established by the WHO and UNAIDS, and are aimed at eliminating these infections. A key strategy to reaching these targets is by screening for infection (2, 3).

Screening for BBV is a well established healthcare intervention (4-6). More data is required to analyse cost-effectiveness of screening for HIV, HBV, and HCV amongst the general population and in an ED setting. CEAs can provide this cost-effectiveness data. CEAs can inform health care decision makers about which healthcare interventions to fund from available resources (10). Given the need for most healthcare systems to make resource allocation decisions across a whole range of disease areas, CEAs are increasingly being used. CEAs require decision modelling, and with that can come a degree of uncertainty. However, uncertainty within a model can be measured with SA (11).

In this CEA, we have developed a bespoke cost-effectiveness model that reflects the lifetime pathways of patients attending an Irish healthcare setting. In the model, patients were either screened or not screened for HIV, HBV, and HCV. The model was informed by applicable and validated real-world practice in the form of the EDVS Programme. Data was derived from the EDVS real-world PLD registry database[i]. The model was also informed by applicable data from national and international studies. The structure was clearly described, and necessary assumptions highlighted. Limitations to the model design and input parameters were also highlighted.

Many of the limitations of this CEA were related to assumptions in the model, as described in Chapter 3 and Chapter 4. Other limitations, as discussed in Chapter 5, discuss limitations around the use of a Markov modelling technique. Amongst ither limitations discussed in Chapter 5 included how the screen was an opt-out screen, and how this may have led to selection bias. It also highlighted how the perspective used is that of the healthcare provider.

The results of this CEA suggest that the ED setting is a high risk setting. The CEA confirms that screening for HIV, HBV, and HCV is cost-effective at our base-case combined seroprevalence of 4.8%. The ICER was €9,130/QALY. The results are robust to SA. In addition, a OWSA confirms the cost-effectiveness of screening when the combined seroprevalence (HIV, HBV, and HCV) ranges between 3.5% to 7.8% inclusive.

6.2 Conclusion

This CEA will provide further data for decision makers with regard implementing screening for HIV, HBV, and HCV not just in a high risk ED setting, but other settings with similar seroprevalence. It also highlights the role for general population screening as opposed to high risk screening in this high risk setting. Moreover, the SA highlighted that there is an upper and lower threshold at which ED screening for HIV, HBV, and HCV is cost-effective. By performing this CEA, we can better reflect medical practice and provide better quality evidence for decision makers who are required to make difficult trade-offs between funding screening interventions or other health technologies.

6.3 Recommendations

This research informs a number of recommendations for changes to healthcare policy, public health policy, and has highlighted areas for future research.

6.3.1 Healthcare Policy

This research identified recommendations for changes in healthcare policy for HIV, HBV, and HCV screening. These recommendations include:

1. General population BBV screening should be offered to all patients attending a setting where combined seroprevalence of HIV, HBV, and HCV is between 3.5% to 7.8% inclusive. The ED setting should be considered a high risk setting. Healthcare systems should be informed that this intervention is deemed to be cost-effective in this setting.

2. Given common modes of transmission, common risk demography, and common patterns of service delivery, panel screening for tri-infections is recommended as opposed to screening for mono-infection or co-infection.

3. Ongoing assessment of seroprevalence is required due to changing migration patterns, increased availability of pharmacological treatment for HIV, HBV, and HCV, high cure rates with DAAs for HCV, the effect of PrEP on risk acquisition, and the availability highly effective ART. In the future, seroprevalence may be lower than the seroprevalence threshold for cost-effectiveness. High risk screening could be considered if that seroprevalence threshold is reached.

4. Specific to the EDVS Programme that offers an opt-out screen for HIV, HBV, and HCV for patients who are phlebotomised, screening should now be offered to non-phlebotomised patients. Pilot studies will be needed to address local feasibility of screening non-phlebotomised ED attendees (e.g. point of care screening).

5. Continuous education of health care providers with respect to BBV screening is recommended. This includes education on epidemiology, natural history of infection, disease states, and treatments available. It also should include education on seroprevalence within that healthcare setting.

6. Education of health care providers with respect to CEA is recommended, particularly in a third-level education setting. Of particular importance is how health care providers can assess data arising from a CEA, and how to apply that data to their healthcare setting.

7. Quality improvement tools should be used to continuously assess the EDVS Programme. In particular, tools to improve LTC amongst patients who are lost to follow up, and tools to reduce duplicate EDVS screening would be beneficial, except in settings of ongoing reported high risk behaviours.

8. The analysis of the EDVS Programme identified a service and patient-level issue around HCV diagnoses amongst PWID In the EDVS Programme[i], 81.9% of people who tested positive for new or known HCV infection were PWID. In addition to screening for HIV,

HBV, and HCV, the service must ensure high rates of engagement in care amongst this group of patients.

6.3.2 Research

This research highlighted particular research gaps. It is suggested that further research be undertaken to close these research gaps, and include the following:

1. Studies examining the feasibility and acceptability of offering BBV screening to non-phlebotomised patients attending the ED should be considered.

2. A pilot study of molecular-based point-of-care screening for HIV, HBV, and HCV in the ED should be considered.

3. Other settings outside the ED should be explored. As an example, Allen et al performed an analysis of seroprevalence in an acute medical unit setting over a 44 week period. In this way, cost-effectiveness of BBV outside the ED setting could be explored.

4. A detailed semi-structured interview is necessary to further understand reasons for frequent attendance to the ED amongst a small group of patients who have been identified as frequent attenders as part of the EDVS Programme.

5. A detailed semi-structured interview is recommended to better understand BBV screening opt-out rates of patients who are being phlebotomised in the ED and service providers who are performing the EDVS.

6. A detailed semi-structured interview is necessary to further understand reasons for higher rates of disengagement to care amongst, in particular, non-Irish European patients with HBV and PWID with HCV.

6.3.3 Public Health Policy

In the area of public health policy, this research makes the following recommendations:

1. The cost-effectiveness of screening the general population for tri-infections in other settings with a combined seroprevalence between 3.5% to 7.8% inclusive should be explored.

2. In healthcare settings where guidelines recommend screening for mono-infection or co-infection, consideration to screening for tri-infection should be analysed.

3. A National Unique Patient Identifier and resourced disease registries are required to trace patients with BBV infection, to avoid duplication, and to track patient care provision. It would also support the ability 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 the EDVS real-world PLD registry database[i] will be a valuable resource to inform policy and to generate funding in required areas.

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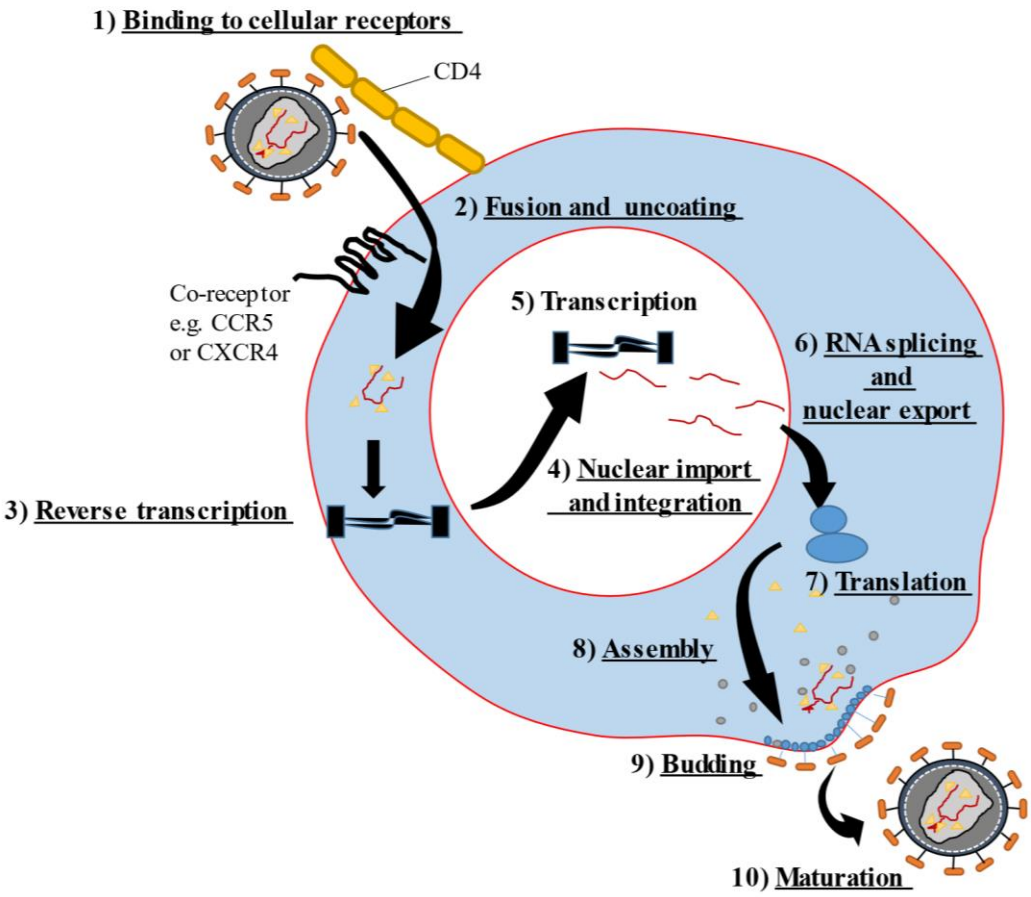
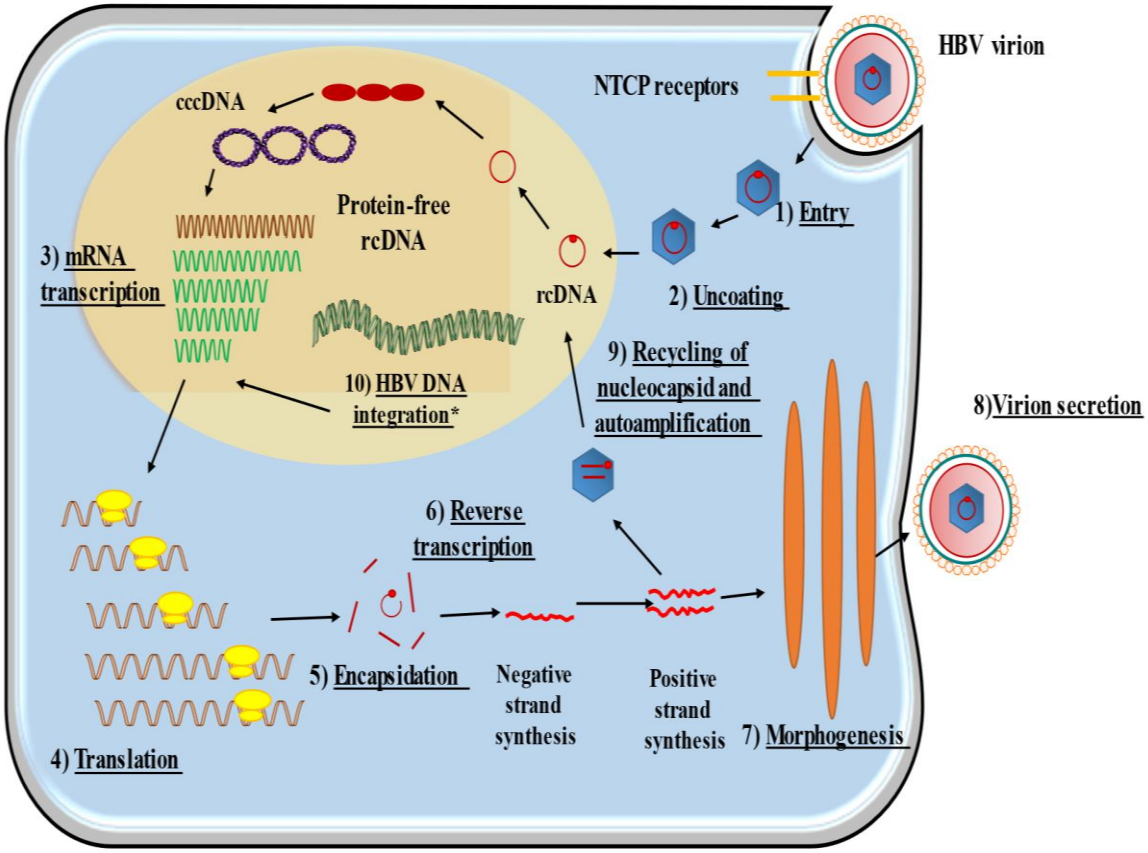
Appendix 1: Life cycle of HIV.



HIV indicates Human Immunodeficiency Virus; **RNA**; ribonucleic acid; **DNA**: deoxyribonucleic acid.

Source: Adapted from HIV/AIDS eradication, Marsden *et al* (26).

Appendix 2: Life cycle of HBV.

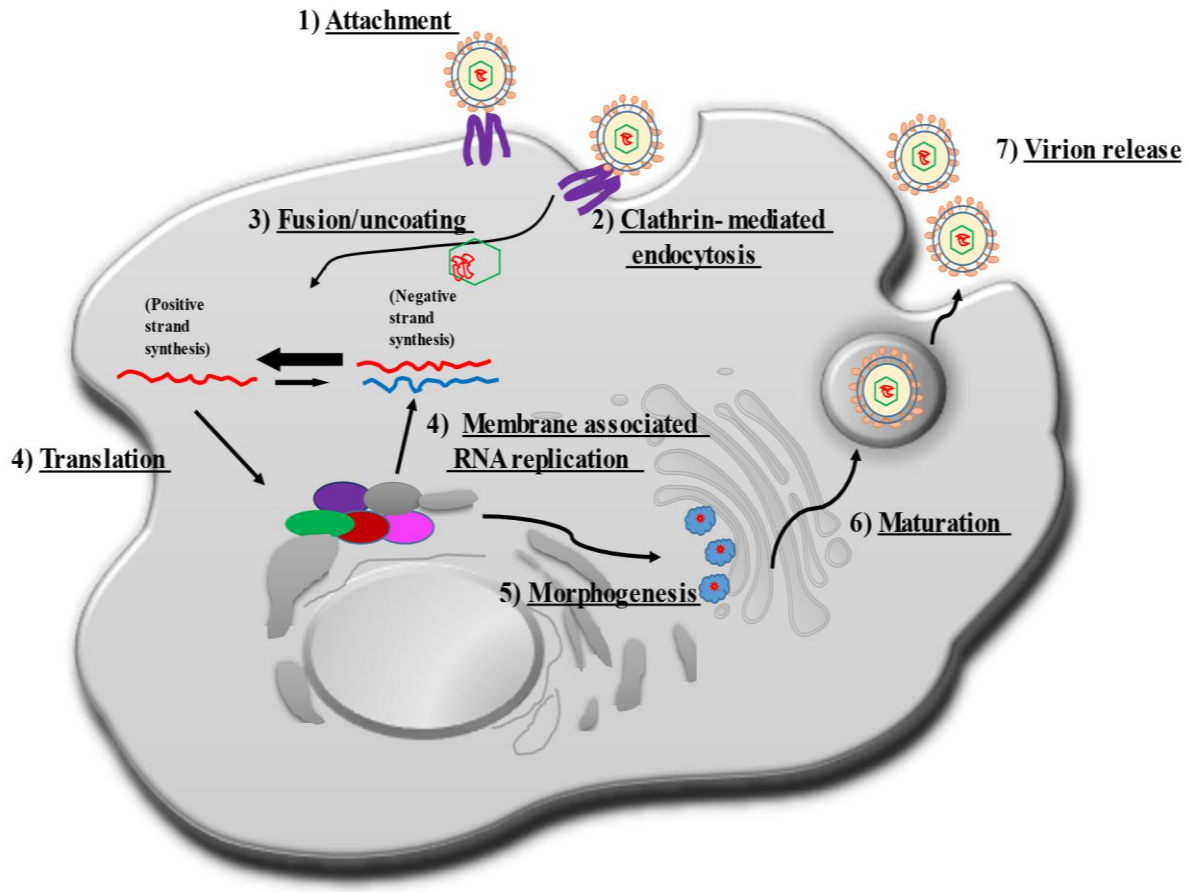


HBV indicates Hepatitis B Virus; **cccDNA**: covalently closed circular DNA; **NTCP**: sodium taurocholate co-transporting polypeptide; **rcDNA**: relaxed circular DNA; **†cccDNA**: the stable form of intrahepatic HBV DNA responsible for the persistence of HBV; **mRNA**: messenger RNA; **DNA**: deoxyribonucleic acid; **RNA**: ribonucleic acid.

*Integrated HBV DNA sequences can produce HBsAg and generate mutant viral proteins that have a role in hepatocarcinogenesis.

Source: Adapted from Chronic Hepatitis B Virus Infection, Seto *et al* (62).

Appendix 3: Life cycle of HCV.



RNA indicates ribonucleic acid.

Source: Adapted from Studying Hepatitis C Virus, Tellinghuisen *et al* (75).

Appendix 4: Calculation of Per-patient cost EDVS.

Per-patient cost EDVS = cost EDVS + 'other' cost

Where: *per-patient cost EDVS = €14.89, cost EDVS = €8, 'other' cost = (total five year EDVS Programme cost (€1,530,935) - five year cost EDVS (€822,696)/total number of EDVS (102,837) = €6.89*

Appendix 5: Beta Distribution Formula (209).

Formula: $$f(x) = x^{(a-1)}(1-x)^{(b-1)}\frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}$$

Domain: $$0 < x < 1$$

Parameters: $$a > 0,\ b > 0$$

Details: $$Mean = \frac{a}{(a+b)}$$

The parameters a and b can be parameterized from a mean μ and standard deviation σ:

$$a = \mu\left(\frac{\mu(1-\mu)}{\sigma^2} - 1\right)$$

$$b = (1-\mu)\left(\frac{\mu}{\sigma^2}(1-\mu) - 1\right)$$

Appendix 6: Dirichlet Distribution Formula (210).

Formula: $$p_j = \frac{x_j}{\sum_{i=1}^{k} x_i}$$

Where x_i *'s are sampled from Gamma distributions:* $x_i \sim Gamma(\alpha_i, 1.0)$

The parameters $\alpha_1, \alpha_2, \ldots \alpha_k$ *are specified in the Alphas list of the Dirichlet distribution dialog using following list statement: List (*$\alpha_1; \alpha_2; \ldots; \alpha_k$)

Domain: $0 \leq p_j \leq 1$ *where* $\sum_{i=1}^{k} p_i = 1.0$

Parameters: $\alpha_1, \alpha_2, \ldots \alpha_k$

Appendix 7: Gamma Distribution Formula (211).

Formula: $$f(x) = \frac{\lambda^{\alpha} x^{(\alpha-1)}}{\Gamma(\alpha)} e^{-\lambda x}$$

Domain: $$x > 0$$

Parameters: $$\alpha > 0,\ \lambda > 0$$

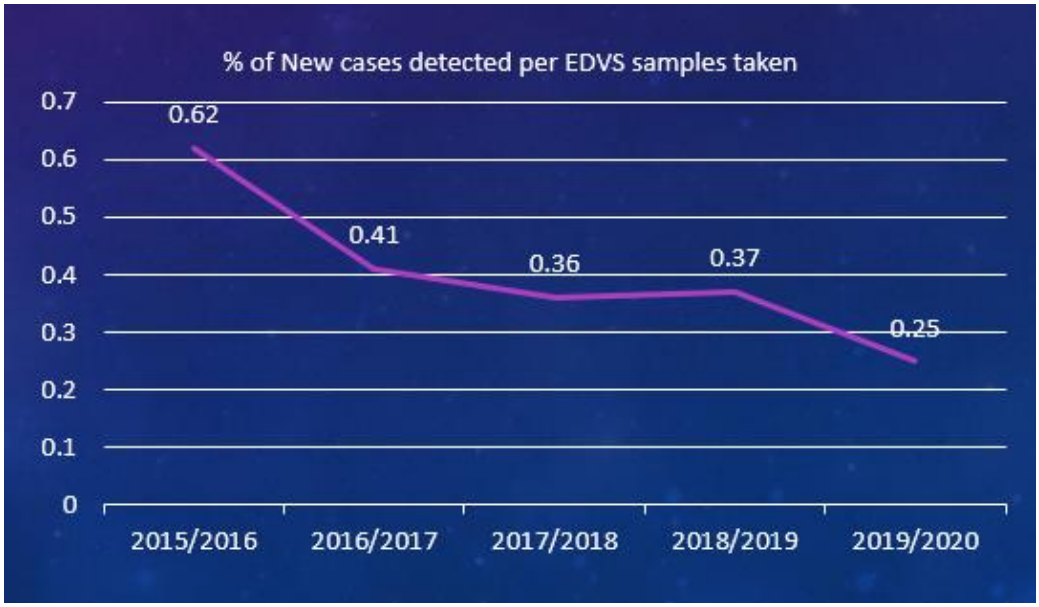
Details: $$Mean = \frac{a}{\lambda}$$

The parameters α and λ can be parameterized from a mean μ and standard deviation σ:

$$a = \frac{\mu^2}{\sigma^2}$$

$$\lambda = \frac{\mu}{\sigma^2}$$

Appendix 8: Percentage of new cases of infection detected year-on-year per EDVS samples taken.



EDVS indicates **Emergency Department Viral Screen.**

Source: Adapted from EDVS Programme 5 year review (170).

[i] *EDVS Programme study period between 1/7/2015 to 30/6/2020 inclusive. Data derived from the EDVS real-world PLD registry database.*