國立臺灣大學共同教育中心國際學院
智慧醫療與健康資訊碩士學位學程
碩士論文

Master's Program in Smart Medicine and Health Informatics
Center of General Education, International College
National Taiwan University
Master's Thesis

Investigation on Hepatitis C Virus Reinfection in HCV/HIV Coinfected Individuals

Nicola Marino

指導教授：林亮宇 博士
Advisor: Lian-Yu Lin PhD

共同指導 ： 劉振驊 博士
Co-Advisor: Chen-Hua Liu PhD

中華民國 114 年 6 月
June, 2025

doi:10.6342/NTU202501025

Dedica

A Mamma e Papà.

E che non si dica che abbia nominato prima l'uno e poi l'altro perché amo e voglio bene ad entrambi in ugual maniera, per quanto umanamente possibile.

Grazie per avermi reso la persona che sono io oggi. Senza di voi non sarei nessuno e per quanto uno possa sognare di vivere e crescere sotto soli, mura, odori o fortune altrui io sarò sempre orgoglioso d'appartenervi.

致我在台灣的家人，感謝你們一路以來的支持。雖然我的中文進步不大，但你們的愛一直溫暖著我。

Ai brothers che conosco ormai da un decennio o più, grazie anche a voi.

A chi mi ha mai avuto o m'avrà mai in cuore e mente.

Ce l'abbiamo fatta anche stavolta.

doi:10.6342/NTU202501025

Abstract

The aim of this thesis is to reconcile the disconnected and sparse, but ever growing, information being published on the phenomenon of reinfection of Hepatitis C in HCV/HIV coinfected individuals, as well as providing a purely theoretical and a functional mathematical model that can be expanded upon with future research.

The thesis can be divided into 2 parts. The first half focuses on providing the essential context, starting from the disease, how it was and currently is treated to then tackle the call to action by international organizations and what is impeding the eradication objectives set: reinfection.

From exploring the context, starting from the main protagonists being the virus and the cures of pre-DAA and post-DAA. Regarding the eradication goals for 2030, the Sustainable Development Goals of the United Nations Agenda and the World Health Organization's many handbooks and strategy guidelines. To highlight the world recognized importance of what appears to be a major obstacle in achieving the eradication goals, the reinfection and the micro-elimination of the virus in these target populations.

There we find the argument for why this thesis is written.

The second part instead focuses on the mathematical study of how prediction can be performed for this reinfection phenomena through compartmental models. Three models are constructed, one purely theoretical, a second simplified version as a bridge between the first, and the third being the functional model. In view of the possibility of application in a future where more data is available, with de-escalation of complexity in its second iteration as well as a practical application of said model in a third iteration constructed with one the co-advisor's studies in mind: "Hepatitis C Virus Reinfection in People with HIV in Taiwan After Achieving Sustained Virologic Response with Antiviral Treatment: The RECUR Study." (Liu et al., 2022)

doi:10.6342/NTU202501025

Contents

Dedica i
Abstract ii
Contents iii
1. Introduction 1
2. The Treatments for HCV over the years 5
2. Genotype Distribution 12
3. The Global Burden and the Eradication Goals 15
4. Micro-Elimination of High-Risk Populations 21
5. Reinfection 23
6. HCV/HIV co-infection 27
7. Modelling 38
8. Proposed Model v01 46
9. Proposed Model v02 – A bridging the gap, using available data 52
10. On the applications of this model and Proposal of ModelV03 56
11. Results: 72
12. Discussion, Limitations and Conclusion 89
Bibliography 95

doi:10.6342/NTU202501025

1. Introduction

Hepatitis

Hepatitis describes the inflammation of the liver, it can be brought forth by a number of causes, from infectious to noninfectious agents[1]. Hepatitis in fact can be caused by autoimmune diseases (autoimmune hepatitis) where the host own immune cells target the liver, damage from alcohol, poison or toxins to the liver such as the ingestion of toxic mushrooms[2]. From medications as well as their abuse e.g. acetaminophen[2]. To fatty liver and infections from parasites, bacteria and hepatitis virus (viral hepatitis) A, B or C[2]. Essentially almost any liver disease will cause hepatitis[3]. Including inherited disorders e.g. cystic fibrosis or hemochromatosis[2]. The duration as well as the health hazards of such condition are a spectrum ranging from temporary and non-severe to chronic and fatal[1,3]. Therefore, the distinction between acute hepatitis, for immediate responses and short-term inflammation of the liver and chronic hepatitis for long-term liver inflammation[3]. With chronic hepatitis, it is to be noted that initial symptoms are not obvious and that the patient can even be asymptomatic until progressive liver damage is severe[4].

Viral Hepatitis

The interest of this dissertation is that of viral hepatitis, which is mediated by 5 different strains of viruses identified as hepatitis A, B, C, D and E[4]. With common denominators being that of causing liver damage, they however differ in a variety of modes starting from transmission, severity, geographical distribution as well as in methods of prevention and or of treatment[1]. A first major differentiation characteristic can be made for severity and longevity: hepatitis B and C can cause chronic liver disease, whereas A and E cannot and are found to cause only acute liver disease[1].

Hepatitis A

Hepatitis A, caused by Hepatitis A Virus (HAV), with transmission primarily being that of faecal-oral route[5]: that of ingestion of contaminated, by faeces of infected person, food or water and therefore is associated with inadequate sanitation, poor personal hygiene and oral-anal sex [5]. With symptoms ranging from mild to severe with correlation with older age, fatal outcomes are

doi:10.6342/NTU202501025

higher in number in older age groups as well as number and general severity of symptoms[5]. Geographically HAV infections are most common in low and middle-income countries, where sanitary condition and hygiene practices are scarce, with 90% of children infected by HAV by the age of 10[5]. In high-income countries while infection rates are low, occurrences are reported in high-risk groups: persons who inject drugs (PWID), men who have sex with men (MSM), persons who travel to high endemicity or isolated populations[5]. Vaccines are available and the treatment is unspecific with aim at maintaining comfort and nutrition balance and not requiring hospitalization unless in presence of acute liver failure with possible death due to fulminant hepatitis[5].

Hepatitis E

Hepatitis E, caused by Hepatitis E Virus (HEV), accounts for an estimated 20 million infections annually[6]. It has at least 4 different genotypes with 1 and 2 being found only in humans whereas 3 and 4 are found in pigs, wild boars and deer without cause of disease but with the possibility of infecting humans through ingestion of undercooked animal meat[6]. The primary infectious pathway is that of the consumption of contaminated, by the feces of infected person, water[6]. Symptoms with their longevity and severity are lesser than HAV while treatment descriptions are the same as HAV[6]. While a vaccine has been developed and licensed in China it has not been made available worldwide[6].

Hepatitis D

Hepatitis D, caused by Hepatitis D Virus (HDV) and necessitates Hepatitis B Virus (HBV) for replication[7]. With transmission of HDV via broken skin e.g. injection and tattooing as well as contact with infected blood or blood products[7]. High-risk population are therefore those of MSM, commercial sex workers and recipients of hemodialysis[7]. Given the necessity of HBV for HDV replication, HBV carriers are more at risk, as well as those who already present Hepatitis C Virus (HCV) or HIV infection[7]. The symptoms for simultaneous infection with HBV and HDV can lead to mild-to severe hepatitis and in it's acute form present symptoms which are non-distinguishable from any other acute hepatitis infection[7]. However, in "superinfection", where HDV infection happens in already HBV infected, acceleration of symptoms and severity occurs in all ages[7]. With cirrhosis progression anticipated by almost 10 years in comparison to

doi:10.6342/NTU202501025

HBV only infected persons[7]. Moreover, for those who are in later stages of HDV infection where cirrhosis is already induced, risk of hepatocellular carcinoma (HCC) is increased alongside a faster progression of fibrosis[7]. Unlike HAV and HEV, HDV albeit rarely (5%) can progress from acute disease to chronic[7]. Of importance is the fact that there is no vaccine for HDV, but there is for HBV[7]. While there is no vaccine, treatment exists in the form of pegylated interferon alpha[7]. However, while it is reported to have as outcome a lower likelihood of disease progression, it also has low successful response rate[7].

Hepatitis B

Hepatitis B, caused by Hepatitis B Virus can be both acute or chronic type[8]. Accounting for 1.2 million annual infections and with 254 million chronic disease living people in 2022[8]. The primary HBV transmission route is that of perinatal transmission and horizontal transmission: mother to child at birth and exposure to infected blood respectively with chronic condition development more prominent when the infection happens before the age of 5[8]. The other infection pathways are that of broken skin, as HDV, and exposure to infected bodily fluids such as blood, saliva, menstrual, vaginal, and seminal fluids[8]. In the fields of health care, with the reuse of contaminated needles, syringes or other sharp objects but also in high-risk groups such as that of PWID and MSM[8]. The coinfection prevalence of HDV in HBV is that of 5% while for HBV-HIV it is that of 1%: 2.7 million people, and globally of 7.4%[8]. With symptoms appearing only in later stages of infection, and treatments being the same for most kind of acute hepatitis with availability of vaccine for prevention. Whereas chronic hepatitis treatment through tenofovir or entecavir with aim of reducing the progression of the disease are available[8].

Hepatitis C

Hepatitis C, caused by HCV, like HBV can cause both acute and chronic forms of illness[9]. Infectious pathway is that characterized by HCV being a bloodborne virus, and as such are like HBV, with whom it also shares the characteristics of being initially asymptomatic in most. With a significant difference being that of while in all other cases of hepatitis, the acute form was prominent, in HCV only 30% of infected patients spontaneously clear the virus, while the remaining 70% develops the chronic form of the illness by the 6th month[9]**Error! Bookmark not defined.**. With estimates of 1 million annual new infections and 50 million people living with

doi:10.6342/NTU202501025

chronic hepatitis C infected in 2022[9]. The geographical distribution of HCV infections and their burden can be done with regions as reported by the WHO, with first place for the Eastern Mediterranean with 12 million chronically infected people, following South-East Asia with 9 million, the European with 9 million, the Western Pacific with 7 million, African with 8 million and lastly the Americas with 5 millions[9]. As for prevention, there are no available vaccines[9]. The treatments are instead aimed at curing the disease and prevent long-term damage of the liver, with antivirals: DAA, such as sofosbuvir and daclatasvir[9]. Therapy with direct-acting antivirals (DAAs) is recommended by the WHO due to its efficacy but remains expensive in high and middle income countries, while prices have dropped in low income countries due to the introduction of generic DAAs[9]. Another aspect that needs discussion is that of the diagnosis, which was omitted in the other viral hepatitis. Initial infection is often asymptomatic, as it is the case for all other viral hepatitis, and with a high degree of certainty will go undiagnosed until later, more advanced stages[10]. However HCV differs from the other hepatic viruses as it is more prominent to develop into a chronic stage and as of consequence, in a timespan of decades, liver damage[10]. The WHO describes the general procedure for testing for diagnosis[10]. A two-step method that starts with serological testing for anti-HCV antibodies, after which in the should the test return positive, confirmation is done through HCV's RNA nucleic acid test[10]. With the advents of technology, newer diagnostic tests allowing for one-step diagnosis are in the making such, an example being the HCV core antigen test[10]. Liver conditions, for fibrosis or cirrhosis, should then be assessed through invasive or noninvasive tests which can then guide the treatment prescriptions[10]. Similarly to HBV, HCV presents a coinfection argument, that with HIV, in fact, as reported by the WHO, about 2.3 million people of the estimated 39 million living with HIV globally have serological evidence of past or present HCV infection[10]. It is important to highlight that chronic liver disease represents a major cause of morbidity and mortality among people living with HIV globally[10].

doi:10.6342/NTU202501025

Table 1: Summary of Viral Hepatitis types with Chronic Potential

	Hepatitis B	Hepatitis C	Hepatitis D
Transmission	Perinatal and bloodborne (exposure to infected blood and bodily fluids)	Bloodborne (e.g., via contaminated needles, transfusions)	Parenteral (requires coinfection with HBV)
Risk groups	Newborns; PWID, MSM, healthcare settings	PWID, MSM, unsafe medical environments	HBV carriers; MSM, hemodialysis patients
Geographical Prevalence	Globally distributed; particularly high in parts of Asia and Africa	Worldwide, with a significant chronic burden	Generally follows the HBV endemicity pattern
Vaccine	Yes	No	No (HBV vaccine indirectly protects)
Treatment	Antivirals (e.g., tenofovir, entecavir)	Direct-acting antivirals (DAAs)	Pegylated interferon α (with limited success)
Chronic Stage	Yes	Yes (approximately 70% progress to chronicity)	Rare (approximately 5%)

Table 2: Summary of Viral Hepatitis types without Chronic Potential

	Hepatitis A	Hepatitis E
Transmission	Fecal–oral route (ingestion of contaminated food or water)	Fecal–oral route (typically via contaminated water; sometimes undercooked meat)
Risk groups	Mainly children in endemic regions; also PWID, MSM, travelers	Populations in areas with poor sanitation
Geographical Prevalence	Primarily in low- and middle-income countries	Common in developing regions
Vaccine	Yes	Limited availability (licensed in some countries)
Treatment	Supportive care	Supportive care
Chronic Stage	No	No

Table 1, Summary Table for Viral Hepatitis Strain Types differentiated by Chronic Stage Potential

2. The Treatments for HCV over the years

HCV is described as a spherical, enveloped, positive-sense single-stranded RNA virus of the Flaviviridae family[10, 11]. Its discovery dates back to the year 1989 with its antibody assay being developed just the following year in 1990 for screening the donor's blood[11]. The immediate realization that followed was that 3% of adults presented chronic HCV infection[10]. The first HCV curative cocktail was approved by FDA in 2014[10]. But since 2014, multiple other treatments have been approved to be used against HCV, in particular oral soluble direct acting anti-viral or DAAs. Before the FDA approval of DAAs in 2014, antiviral therapies principally relied on interferon-based regimes[12]. We can therefore determine 2 "eras" one preceding and the one following the introduction to the public of DAAs.

Pre-DAAs

As already mentioned in the introductory segment of this paragraph, interferon-based regiments were the main weapon utilized in antiviral therapies. However, not only poorly tolerated, in the required longevity of the treatment and administration methodology (i.e. patient compliance), but also poor in performance as infective in majority of patients[12]. Interferon-alpha (IFN-α) was the first compound used to fight the infection[13]. The addition of Ribavirin to IFN- α then enhanced the compound[13]. Nowadays they are obsolete, but it is fundamental to briefly review them.

The Underwhelming Performance of IFN- α and Ribavirin

doi:10.6342/NTU202501025

It is to be noted that before 1975 HCV was described as non-A, non-B hepatitis (NANBH)[10,13,14]. As observed by titles of the papers illustrating the performance of the compound in treating this newly discovered disease, even after 1975, as far as 1990[13,14]. Initial preliminary reports coming from studies compromised of cohorts of size no bigger than 10 subjects, observed excellent results, especially in therapies lasting 12 months[14]. The extensive studies that followed published a decade after the preliminary ones went against their positive findings[15]. With emphasis on the scarce performance of IFN, with a decrease of HCV RNA in only 40% to 60% of patients during the treatment[15]. But of much more importance is what was neglected by preliminary tests: that of relapse after treatment withdrawal with catastrophic numbers in those patients that achieves sustained virological response (SVR) to treatment: no more than 15% to 25%[15]. Re-treatment was observed to be ineffective as well[15]. With the best results needing therapies of 12 months, with three times per week administration of higher than 3 Million Units (MU): 43% SVR achieved[15]. And the worst results for those who did not respond to initial treatment and were retreated with 3 MU three times weekly for 6 months, with none achieving SVR[15]. A crucial point that was then understood from these randomized controlled trials was that non-responders should not be re-treated with IFN by itself[15]. In here lies the addition of Ribavirin to IFN and that of Pegylated (PEG) IFN. However, the results obtained were far from acceptable[16,17,18,19]. As they only brought the median SVR achieving rate from 12% to 23%[16,18,20]. With the SVR rates in any of the combinatory treatments not reaching above 56% in cohorts subject to the highest dosage of PEG-IFN+Ribavirin[16,18,19,20], furthermore requiring prolonged treatment, exposure to side effects even if PEG-IFN was more tolerated given the weekly and not thrice a week administration[10,17,19,20,]. With a withdrawal rate parallel to that of standard IFN, in the ranges of 15% to 27%[18,19].

Patient Adherence

As already briefly mentioned in the introduction to this section regarding Pre-DAA treatment methodologies. One of the issues with this treatment aside from the therapeutical performance was that of patient compliance. Poor adherence to chronic diseases is a frequent phenomenon per se. Coupled with the poor performance of achieving SVR, good adherence was in the recommended guidelines for the treatment of HCV[19]. It is observed that for the treatment

doi:10.6342/NTU202501025

of HCV the percentage of population of interest with an adherence of >=80% ranges from 27 to 96%[19]. An incredible spectrum derived from a systematic study that analyzed the results of the at the time available literature. The reason for such a result can be originated from the studies that were chosen to perform this analysis which for HCV are 13[19]. Which included studies whose results were obtained from pharmacy claims utilizing medication possession ratio[19] as well as patient self-report[19]. The highest adherence was obtained from patient self-reports studies, with the lowest obtained from pharmacy refill claims[19]. An important observation to be made is that in this systematic review it is noted that in the majority of the HCV adherence studies predictors for non-adherence were assessed[19]. With illicit drug-use and psychiatric diagnoses being most frequent identifiers, HIV co-infection happens to be in 2 studies an indicator for highest adherence[19]. A topic that will be discussed further and in more detail in the following chapters, but with considerations the following factors: ease of administration and access to DAAs, persons who inject drugs (PWID), men who have sex with men (MSM) and HIV-HCV coinfection.

DAA-Era

The discovery of the first direct-acting antiviral agents (DAAs) and their approvement dates to 2011[13]. With NS3/A4 protease inhibitors Telaprevir and Boceprevir[13]. Initially their administration was coupled with that of IFN and Ribavirin administrations[13], and while they provided a significant increase in response rate, the side effects they brought along were not negligible[13]. In 2013 a polymerase inhibitor for NS5B was developed that did not require coupling with IFN: Sofosbuvir[13]. It was only in 2014 when the first all-DAA regiment was approved[13]. That is Ledipasvir/Sofosbuvir in a single tablet[20]. Few months after and then again in 2015 two combinations of multiple DAAs where approved to be treatment for patients of genotype 1 and later for genotype 4 HCV infections[20], however for genotype 4 it would only be until 2016 when ribavirin would not be necessarily coupled with the DAAs[20]. Then in July of 2016 sofosbuvir combined with Velpatsvir was approved as treatment in adult patients in all genotypes, a pan-genomic treatment[20]. Not only is administration oral, once a day, but the duration of treatment is that of 8 to 12 weeks only[13,21] up to 16 and 24 weeks[21]. With most

doi:10.6342/NTU202501025

important point being the incredibly high SVR rate that is achieved of overall >90%[21] as well as being very well tolerated[21].

First Generation DAAs & Genotype Specific DAAs Treatment

Of the first generation of DAA's against HCV, the first to be released is Boceprevir: HCV NS3/4A protease inhibitor, to be administered in combination with PEG-IFN and Ribavirin, for the treatment of CHC genotype 1[20,22]. Initially released in 2012, it was withdrawn in 2015 due to more effective and better tolerated DAAs[22]. Low-tolerance was observed due to acute liver injury during therapy, caused when combined with PEG-IFN and Ribavirin[22]. The reason for combinatory treatment was that monotherapy resulted in rapid inhibition of HCV RNA levels but followed by a rapid resistance development in the majority of patients[22]. In combinatory treatment, it was demonstrated that in genotype 1 patients, from the PEG-IFN + Ribavirin treatment SVR achieving rate of 40% to 50%, 65% to 75% of patients would achieve SVR[22]. Administration was thrice daily, which was also believed to be a factor in the development of undesirable side effects in 5% to 20% of patients who then discontinued treatment[22]. Telaprevir (TPV), another first-generation DAA protease-inhibitor also brought fort adverse effects in almost 50% of patients[23], with no clearly established pathogenesis[23]. With the underwhelming results of these DAAs and their requirement of a "triple-therapy" based on the combination of DAA together with IFN and Ribavirin alongside the adverse effects and several drug-drug interaction[20]. A "second wave" followed and was comprised of 1) Inhibitors: Simeprevir; Paritraprevir; Grazoprevir[20]. 2) NS4A inhibitors Daclatasvir, Ledipasvir; Ombitasvir; Elbasvir; Velpatasvir[20]. 3) NS5B inhibitors: Sofosbuvir and Dasabuvir[20]. While some of them will be discussed in further paragraphs detailing Fixed Dose Combinations for pangenotypic treatment, with first generation we can indicate also the genotype restriction of some of these agents.

FIXED DOSE-COMBINATION (FDC): MODERN CARE OF HCV: SOF VEL, SOF VEL XOV, GLE PIB

Sofosbuvir (SOF)

doi:10.6342/NTU202501025

Approved as Sovaldi since 2014[24], it is an inhibitor of NS5B polymerase, it is a pyrimidine nucleotide analog[20]. Indicated for the treatment for all genotypes of HCV in combinatory antiviral therapy regiments[20]. Offering a great alternative to the patients who are contraindicated to IFN therapy or who have dropped out due to side effects or for being non-responsive or even for reinfection[20]. It is to be noted that the reported side effects were observed when SOF was administered in combination with IFN, RBV and during longer treatments of 24 weeks rather than 12[20],[21]. Resistance to SOF were observed only in 1 patient during monotherapy regiment[20],[21].

The Current first-line antiviral treatment: Epclusa, Mavyret and Voxevi

It is observed through EASL, WHO and APASL recommendation guidelines on the treatment of HCV, that there are recurring agents prescribed in this fight. According to the WHO Global Hepatitis Report of 2024, the guideline treatment for HCV shall be done mainly through DAAs with: SOF/VEL, SOF/DAC, GLE/PIB and SOF/LED indicated as non-pangenotypic to be used in particular GT3 infections[45]. Similarly, the European Association for the Study of the Liver (EASL) and Asian Pacific Agency for the Study of the Liver (APASL) latest guidelines for the treatment of HCV, recommend similar treatment agents[25,26]. With APASL still profoundly rooted in a genotype-based approach even while utilizing pangenotypic DAAs[26]. It also to be noted that Ribavirin is still present in the WHO "Model List of Essential Medicines" of the same report[45].

Velpatasvir/Sofosbuvir (SOF/VEL)

Approved in 2017 as Epclusa[27], a combination of: Velpatasvir, an inhibitor of NS5A, and SOF, was approved for the treatment of all genotypes of HCV infection in adult patients[20]. Allowing for prescription without performing genotype testing[20]. Another important aspect is that with respect to the stage of CHC, ribavirin will be included in the regiments for patients with decompensated cirrhosis[20,25,45]. Administration mode is of daily single FDC tablet for 12 weeks[28]. It's presence is notable in many studies, that have appeared after the proclamation of the eradication goal by the WHO, targeting high-risk vulnerable populations in closed settings especially in prisons[28,29]. This agent also introduces the concept of "panfibrotic" meaning that aside from "pangenotypic" agents that can be administered to all genotypes of HCV, these can be

doi:10.6342/NTU202501025

administered to all stages of fibrosis[28], further increasing the simplicity of treatment administration[28,45]. With its efficacy proven over the ASTRAL 1 through 5 clinical trials, it was demonstrated that the SVR rate varied from 83% to 99%[30]. With 99% reached in all genotypes except for GT3 which was the subject of ASTRAL-3 where SVR was achieved in 95%[30]. While ASTRAL-4 studies highlighted the performance in "difficult-to-treat"[30] HCV infected, with SVR achieved in 83%[30] after 12 weeks of treatment and 86% after 24 weeks where one the challenges was GT3 cirrhotic patients[30]. Such results have been then contested in an Italian nationwide study where GT3 cirrhotic patients treated with SOF/VEL had an SVR rate of 97.6%[31]. It was noted that combining SOF/VEL with Ribavirin would bring the SVR rate to 94% after 12 weeks. Furthermore ASTRAL-5 study demonstrated efficacy in HCV/HIV co-infected population with SVR reached in 95% in the cohort[30]. During the ASTRAL studies the tolerability of Epclusa was also observed was high[30]. With most common side effects being headache, fatigue, nausea and cold-like symptoms, with incidence similar to the placebo patients[30]. Lastly it can be administered with a certain degree of freedom to renal impairment, with only exclusion to those who have severe impairment, denoted as:" eGFR\30 mL/min/1.73 m"[30].

Glecaprevir/Pibrentasvir(GLE/PIB)

Approved as Mavyret in 2017[32], Glecaprevir (GLE) and pibrentasvir (PIB), respectively, are HCV's NS3/4A and NS5A inhibitors[33]. Co-formulated as a FDC with pangenotypic activity[33]. Differentiating from other treatments as it provides the shortest standard treatment duration of 8 weeks, against the standard 12[25,32]. Trials such as the ENDURANCE-1 & 4, SURVEYOR-2 and EXPEDITION-1 demonstrated that the SVR12 rate were of 95%-99% in the genotype 1 through 6 when treatment was 8 to 16 weeks long[33]. Of further importance are the MAGELLAN-2 trials aimed at specific populations, such as HIV coinfected, or that presented other forms of impairment in liver or renal functions such as transplant, with SVR12 rates of 98-99%[33]. Further studies have been conducted on CHC patients with severe renal impairment demonstrating the effectiveness and toleration of the drug[34] Moreover, other clinical trials demonstrated efficacy and excellent SVR12 rates in patients whose initial treatment with NS3A or NS5A DAA agents failed[33]. In 2018, GLE/PIB was reimbursed by Taiwan National Health Insurance (NHI) for patients with chronic HCV infection who had a hepatic fibrosis stage of

doi:10.6342/NTU202501025

≥F3. In 2019, Taiwan NHI cancelled reimbursement restrictions and approved physicians to treat all HCV viremic patients by GLE/PIB. Administration of the FDC is thrice daily orally for 8 weeks in non-cirrhotic patients, in naïve or PEG-INF+Ribavirin and SOF (PRS)-experienced patients of all 6 genotypes[33]. 12 weeks for all genotypes cirrhotic patients in naïve, but for PRS-experienced, genotype limitation for type 3 who instead required 16 weeks, regardless of cirrhosis status[33]. By subgroup, stratified analysis it was observed that SVR12 rates were of 90.5% in GT3 patients, and 60% in GT3 patients with cirrhosis[33]. Lastly safety of treatment is described as 99.7% of the 658 patients in the study, therefore 656, having completed the scheduled treatment without discontinuation due to severe adverse effects[33]. With minor side effects such as pruritus, fatigue, nausea/anorexia, insomnia and headache only occurring in a percentage <8.7% for the duration of all treatments with exception of 16-week where the cohort was of 6 patients[33].

Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX: Voxevi)

Voxevi is another FDC, composed of SOF, VEL and VOX which are agents respectively for the inhibition of HCV's NS5B, NS5A and NS3[35]. Administered for pangenotypic treatment in once a day, daily oral administration[36]. Particular usage of Voxevi is in the indication for retreatment of patients whose failed initial treatment was of NS5A inhibitors DAAs (DCV/ASV, ProD, EBR/GZR, SOF/LDV, SOF/DCV, GLE/PIB, SOF/VEL)[36]. Recommended in fact by international guidelines as "first-line salvage therapy for DAA-experienced patients with HCV"[36]. SVR12 rates have been observed to be at 97%.2 for 12 weeks treatment during the POLARIS-1 trial[36], with real-world studies reporting back similar results for DAA-experienced patients[35]. Tolerance was observed in 16.8% of the cohort of the study, reporting at least one adverse effect, with 1.9% having a non-fatal serious adverse effect[36]. While the cohort of this study was composed of about 1/6 of the patients of the GLE/PIB study, none withdrew from the treatment of SOF/VEL/VOX[36]. Furthermore no significant alterations persisted in bilirubin, ALT or eGFR values during and post-treatment[36], indicating the usage in conditions similar to those studies in GLE/PIB MAGELLAN-2 trial[33]. The reason for placing Voxevi on the end of the list of the current FDC's DAAs utilized to treat HCV infections, is to highlight it's major role. That while first-line DAA, NS5A inhibitors, treatment is reported to be highly effective with SVR12

doi:10.6342/NTU202501025

rates at >95%, there are, even if a minority, patients who are unresponsive[36]. Therefore, the need of a therapy that can target his subpopulation is necessary and this role is covered by Voxevi which SVR12 are proven throughout clinical trials and real-world implementation[36].

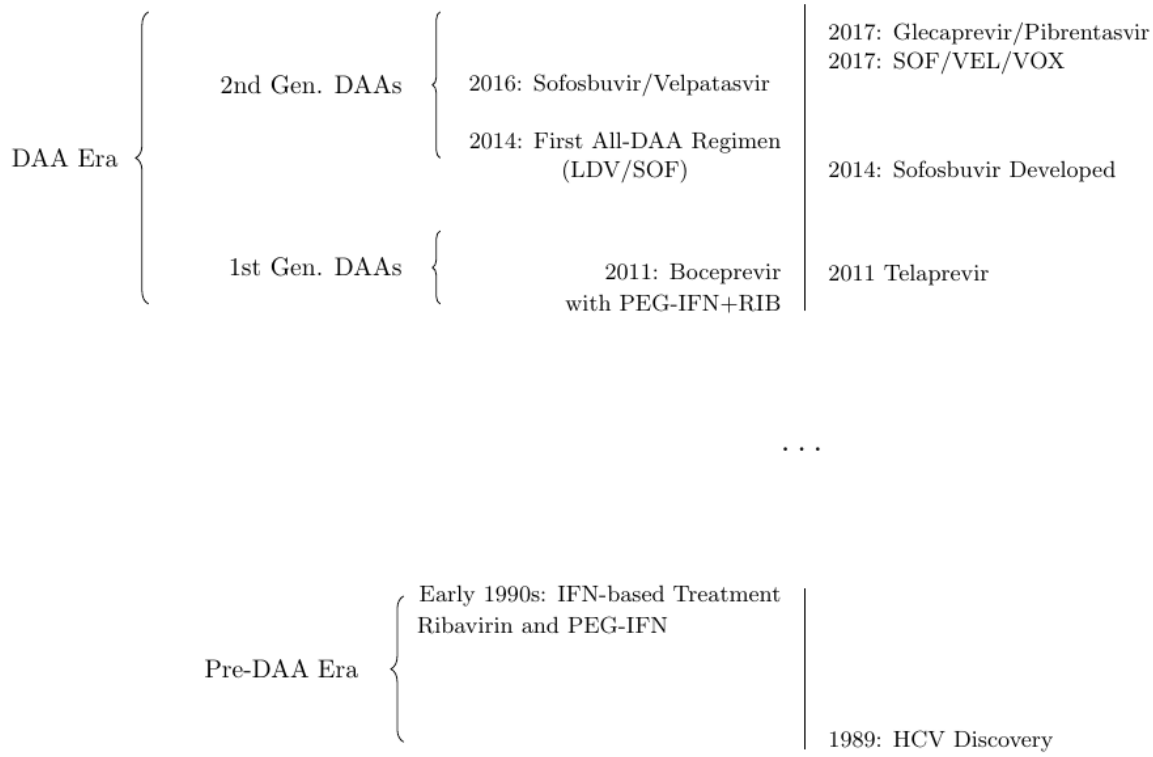


Figure 1, Summative timeline of treatment eras

2. Genotype Distribution

A topic that was neglected when discussing HCV and was then mentioned when discussing the DAA treatments is that of the 8 genotypes in which HCV can be found[37]. Due to the development of the pan-genotype DAA cocktail which has reduced the importance and interest in the subject[37]. All other treatments were prescribed based on the results of the genotype testing with particular importance during the pre-DAA era. In accordance with the Lancet report of 2023 on HCV, 8 genotypes have been identified, with the latest being identified in India in 2018[38]. The geographical distribution follows the HCV genotype 1 in North and South America,

doi:10.6342/NTU202501025

Europe, Australia and central and east Asia[38]. Genotype 3 is most prevalent in India and Pakistan, genotype 4 instead in Egypt and Central and Sub-Saharan Africa[38].

Resistance-Associated Substitutions, Viral Resistance and Virological Failure in the Treatment of HCV with DAAs

Virological resistance is one of the main reasons for obtaining a virological failure during the treatment of a patient with DAAs for CHC[39]. On the agenda of main items that need consideration regarding this are the regiment of DAAs the patient is administered and the genotype of HCV of the infected patient[39]. With other causes being adherence, drug-drug interactions, insufficient concentration due to impaired uptake or assimilation observed in decompensated liver and host immune response genetic variantions[39]. It needs to be explicit that resistance-associated substitution (RAS) leading to resistance-associated viral variants (RAVs) are an important reason for the virological failure during DAA treatment[39]. In previous paragraphs the current indicated medications introduced by international liver associations guidelines were introduced. Section 1.4 restating a loss of particular interest and attention to all genotypes following the DAAs-Era. As DAAs now indicated as front-line or first line[39,45]: SOF/VEL and GLE/PIB have high antiviral activity and high barrier of resistance therefore, they generally do not require testing for resistance[39]. With resistance testing instead promoted to optimize therapy in subgroups who are overrepresented in DAA treatment failure, e.g. HCV GT 3[39]. With resistance testing being of more interest in the retreatment, or second-line treatment when the previous DAA treatment fails, and RAS or RAV can be present[39]. Furthermore, it is reported that not all RASs detected by sequencing for genotypic resistance analysis are relevant for prediction of response to DAA therapies[39]. With RAV frequency withing HCV quasispecies, or it's behavior as a mix of variants derived from RNA replication errors, seemingly being of more importance than RAS[39]. With the prevalence of naturally occurring RASs being diverse on accounts of the genotype and subtype of HCV, allowing also for a geographical variation[39].

In coinfection with HIV, RAS highlighted during the DAA therapy can remain in the quasispecies in a limit undetectable by sequencing assays[39]. During retreatment, these variants can reappear quickly and lead to the development of resistance[39]. As already stated in the

doi:10.6342/NTU202501025

previous section, the salvage treatment or rescue treatment for failures in first treatment with DAAs is that of VOX/VEL/SOF[39]. While this rescue treatment covers multiple failed treatments, there are differences in the RAS profiles in different generations and typologies of DAA used, detectable in the target regions of the respective DAA[39]. While in general, different NS3 and NS5A inhibitors have partially overlapping RAS patterns[39]. There are certain RAS patterns which are not overlapping and that present importance when discussing the selection of salvage treatments, while there is no evidence that known RAS impact on VOX/VEL/SOF multiple targeted therapy in rescue treatment[39]. With regards of countries not being able to access DAA past the first generation (e.g.: 1st gen. protease inhibitors: grazoprevir and 1st gen. NS5A inhibitors: daclatasvir) in ample manner, the recommended optimized retreatment is that of a newer DAA class[39]. With NS5A RAS associated to the reduced SVR rates[39]. And where the patient was not exposed to NS5A inhibitors, 1st gen. DAA retreatment is reported as possible but with reduced efficacy[39]. Again, newer DAA class is suggested but with resistance analysis recommended for optimized salvage therapy[39]. Whereas for virological failure on NS5A inhibitors such velpatasvir in combination with sofosbuvir, NS5A RAS presence has been observed leading to 33-67% v 88% of SVR achievement, against its absence[39]. Retreatment in this case seemed to benefit, aside from the switching of DAAs, from the addition of ribavirin, especially in genotype 3 patients[39]. Reportedly, given the rarity of NS5A resistances after virological failure on NS5A inhibitors with further problematic being the limited efficacy of alternative inhibitors[39]. The standard rescue treatment for patients with failure on previous DAA regiments is that of VOX/VEL/SOF for 12 weeks[39]. Such salvage treatment brings those previously exposed to NS5A inhibitors to an SVR of 96% with or without ribavirin[39]. With genotype 3 and cirrhosis being a negative, although weak, negative predictor of response, with SVR rates of 81-92% and 81-90% respectively[39]. Therefore, the addition of ribavirin can be considered for these subpopulations, and other difficult to treat patients[39]. It is then necessary to understand the possibility of retreatment should the rescue treatment of VOX/VEL/SOF fail. It is observed how resistance analysis brought only minor changes in the RAS profiles or frequencies[39]. Moreover, as already brought forwards as negative predictors of response, patients infected with genotype 3 and those presenting cirrhosis consisted of 45% and 70%, respectively, of the population who failed treatment[39]. In such cases retreatment with VOX/VEL/SOF with or

doi:10.6342/NTU202501025

without ribavirin for 12 to 24 weeks was demonstrated effective as rescue treatment but given the lack of data no specific recommendation in provided by the review paper[39].

Table 1: Summary of Hepatitis C Treatments: IFN-Based vs. DAA-Based

Name (Generic)	Commercial Name	Date of Release	Median SVR Rate	Brief Description
IFN-Based Treatments				
Interferon-α (monotherapy)	–	Early 1990s	10–20%	Significant flu-like side effects; low efficacy
Pegylated IFN + Ribavirin	–	Late 1990s	40–50%	High side-effect burden (e.g., anemia, depression), lengthy treatment
DAA-Based Treatments				
Boceprevir	Victrelis	2011	∼70%	Still required IFN+RBV; risk of anemia
Telaprevir	Incivek	2011	∼75%	Skin rash, anemia; required IFN+RBV
Sofosbuvir	Sovaldi	2013	80–90%	High initial cost; generally fewer side effects
Ledipasvir/Sofosbuvir	Harvoni	2014	90–99%	Well-tolerated; cost constraints
Sofosbuvir/Velpatasvir	Epclusa	2016	>95%	Generally well-tolerated
Glecaprevir/Pibrentasvir	Mavyret	2017	>95%	Shorter treatment duration; generally well-tolerated
Sofosbuvir/Velpatasvir/Voxilaprevir	Voxevi	2017	∼97%	Used as salvage therapy; effective with few adverse effects

Figure 2, Summative table of treatments

3. The Global Burden and the Eradication Goals

The 2030 Agenda for Sustainable Development and WHO Handbooks

On the 25th of September 2015, the United Nations adopted the resolution for 2030 Sustainable Development Goals (SDGs)[40]. Of particular interest is SDG 3: "Ensure healthy lives and promote well-being for all at all ages"[40]. In its subpoint 3.3, "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases"[40]. From this we can understand that there was already a worldwide interest in combatting viral hepatitis. To contribute to this interest and resolution, approved by the World Health Assembly[42], the WHO published in 2016, the first Global Health Sector Strategy on viral hepatitis[41] for its elimination by 2030[42]. For the time period of 2016 to 2021[41]. Taking act of the frameworks that have been established through the "Prevention and Control of Viral Hepatitis Infection: Framework for Global Action" of 2012 and the 2 resolutions adopted by same organization in 2010 and 2014[41]. A strong argument to the reason why this 2012 framework was a result of can be attributed to the World Hepatitis Day established in 2011 and celebrated on the 28th of July[43]. A celebration for the development and approval of DAAs, and the declaration by the WHO that "for the first time in history, hepatitis C is curable"[43]. It is important to underline that already in 2012, geographical distribution differences, as well as the transmission and diagnosis means were taken into consideration when discussing a "tailored prevention"[43]. With the understanding that there are populations more at risk than others[43]. Furthermore, awareness was already placed as a pedestal in the guidelines and

doi:10.6342/NTU202501025

as a remaining challenge. Given the success that was underlined in the 2012 framework towards and already global progress and work done against viral hepatitis[43]. The 2016 WHO's strategy highlights and reiterates the SDG goal with the word "elimination": "A goal of eliminating viral hepatitis as a major public health threat by 2030"[41]. As described by the organizations in 2016, the targets to meet are a reduction in incidence of viral hepatitis by 90% with a 95% decline in HBV and a 80% decline in HCV[42], a rate of diagnosis at 90% for all viral hepatitis infections[42] and having treatment for 80% of the eligible population by 2030[42]. With projected reduction of mortality by 65%[42]. From the Global Health Sector Strategy of 2022[44], by 2030 the target is to reduce the at the time 6 to 10 million infections of HCV[44] to less than 1 million by 2030[44] and reduce the deaths from 1.4 million to 500 000 by 2030[44]. The delineated 2020 and 2030 targets in 2016[41], respectively are a 30% reduction in incidence[41], 10% in mortality[41] and 90% reduction in incidence[41] and 65% reduction in mortality[41]. With a service coverage that targets blood safety, through blood donation screening from 89% to 95% and then 100%[41]. Then safe injection practices through usage of "safety-engineered devices"[41] from 5% to 50% and then 90%[41]. Follows indications to increase the numbers of sterile needs for PWID, from 20 to 200 and then 300[41], and lastly the treatment for HCV, from a baseline of less than 1% to 3 million in 2020 then to 80% of eligible in 2030[41]. Through the 5 strategic directions illustrated, pursuing once again how "information for focused action"[41] is fundamental, as well as the universal health coverage, depending on: aimed interventions, equity and financing for sustainability[41]. Lastly, an interest in the keeping the interest alive and further increase the speed in development and innovation[41]. In 2022 the WHO then published the "Global Health sector strategies on, respectively, HIV, Viral Hepatitis and sexually transmitted infections for the period of 2022-2030"[44]. Interestingly the first chapter is titled: "Ending epidemics in a new global health era"[44]. The handbook describes the importance of adaptation to the "contextual shift of recent years"[44]. With importance once again in the difference between countries and the necessity of each country to define the populations most affected[44]. And the same 5 strategic directions that were presented on the 2016 sector strategies handbook. However, this time, these 5 strategic directions are relocated to have as center the people[44]. Recognizing the achievements that were made in the 2016 to 2021 period such as a 10-fold increase from 2015 on treatment for HCV patients with consequence of reduced HCV mortality[44]. The handbook recognizes the lack of diagnosis and affordable

doi:10.6342/NTU202501025

treatment accessibility[44]. Furthermore, the handbook promotes a different approach, "joint action with disease focus": that there between diseases and disease areas there are similarities and differences, with a unique response for each but that they are interellated[44]. As a matter of fact, this handbook not only places importance on viral hepatitis but also sexually transmitted diseases such as the Human Immunodeficiency Virus (HIV)[44]. Urging a revitalization of the efforts that have been put in the fight against HIV on a global scale for over 40 years to other SDTs[44]. With the 2030 target of ending HIV as public health threat requiring a reduction from the 1.5 million incidences in 2020 to 335,000 by 2030, then avoiding more than 500,000 annual deaths[44]. The interest in fighting these infectious diseases together, and for the people at the center approach, lies in the common modes of transmission and determinants that are shared by HIV, Viral Hepatitis and STDs, and therefore the population that are affected could present overlap[44]. The populations of interest not only experience an overlap in this field of disease, but also in the many forms of social and structural determinants of health as a result of them[44]. Then illustrating those who are the most at risk populations: people exposed to sexual transmission, which are listed as: young and adolescents, men who have sex with men(MSM), sex workers and clients, transgender people, people in prison or closed settings and those whose sexual behavior is mediated through substances[44]. People who are exposed to unsafe blood, including medical procedures such as injections and PWID[44]. Further attention is then given to those who lack access to health services, and to mother to child transmission[44]. It is lastly urged that each country understand its own demographic distribution and populations[44].

The Global Hepatitis Report 2024

Building on the foundations that have been established through the 2016, 2018 and 2020 reports, that were parallel to the Global Health Sector Strategies described in the previous paragraph[45]. Declared to be "The first consolidated WHO global report on viral hepatitis"[45]. Providing a baseline necessary to monitor the global progress against hepatitis and its eradication, alongside HIV and STDs in the timeframe of 2022 to 2030, fitting closely with the health goals of the 2030 Sustainable Development Agenda[45]. With a greater collection of data, with implied success of the strategic directions towards improved accountability, as of 2022 viral hepatitis is still regarded as a major public health challenge[45]. HCV is the cause for an estimated

doi:10.6342/NTU202501025

244 000 deaths (range of 197 000-288 000)[45], and with an estimated 50 million people living with CHC[45]. An estimated decline from 1.03 million (in range of 0.76 to 1.32) to 0.98 million (ranging from 0.76 to 1.34) new annual HCV infections from 2019 to 2022[45]. Lastly it is estimated that only 36% of CHC patients have been diagnosed between 2015 and 2022[45] an increase from the 21% in 2020[32] and goal of 30%. With only 20% or 12.5 million in 2022, of them having received treatment[45]. That is in comparison to the 13% baseline for 2020 and against the pre-existing target of 30%[45]. Other target goals not reached included those of diagnosis, which during 2020 was at 21% against 30%, and as of 2022 reached 36.4%[45]. Needles and syringes for PWID remained at 33 during 2020, against the 200 target and are at 35 as of 2022[45]. While blood safety, and safe injections have surpassed the target set at 95% in 2020 by reaching 97% and 96% coverage respectively but have not changed as of 2022[45]. The report once again, as it has been done in the Strategies handbooks, states the importance of glocalization efforts[45], describing how the burden is carried differently across countries in the globe, with 10 accounting for almost 60% of the global viral hepatitis burden[45]. Lastly, it provides economical reasoning necessary to motivate the investment into such health crisis, providing estimates based on case studies of the return on investment of 2 to 3 US Dollars for every invested one[45]. Because of the high cost that results in cancer treatment and care, against that of continued care for hepatitis patients[45]. The cumulative number of saved lives is estimated at 2.85 million if the goals are reached by 2030 and 23 million going forwards in 2050[45]. The report also provides insight into those who are the 3 major transmission routes: 1) Injecting drug use; 2) Unsafe medical and non-medical practices; 3) injections[45]. Accordingly, the sharing of equipment among PWID results in the largest number of new HCV infections in the world[45]. Estimating that unsafe drug injection use contributes to 43.6% (33.9 to 52.5%) of new HCV infections globally[45]. Reiterating by region, it is noticeable that by descending order, the Americas, with 92.4% and the Western Pacific with 90.4% regions are those most impacted in the new hepatitis C infections due to injecting drug use[45].

Forecasts of the Global Hepatitis Report 2024

With an indicated “window of opportunity in 2024-2026”[45]. The report indicates that to meet the SDGs, an estimated 30 million people need to be treated from HCV by the end of

doi:10.6342/NTU202501025

2026[45]. Projections of the coverage and services to increase on exponential matter until 2028 to then sharply decline by 2030, with resulting decline in incidence and mortality by 2030[45].

As a matter of fact, according to Liver International report of 2021 on the Progress towards Hepatitis C Virus elimination in high income countries[46]. In disease progression modeling study of these 45 high income countries, only 11 were on track with meeting the WHO targets by 2030[46]. With another 5 meeting the objectives by 2040, and 2 by 2050[46]. With the remaining 27 countries having estimated achievement of HCV elimination after 2050[46]. Surprisingly, comparing these results to the 2017 disease progression modeling study performed on the same countries, it was observed that 30 countries out of 45 saw no change in elimination goals[46].

Availability and Access of Diagnosis, Coverage and Medicines

The report indicates that for the availability of hepatitis C testing free of charge in the public sector of 2023, the number of reporting countries indicating that HCV testing was not free charge is allocated in the African Region first, then the Western Pacific Region and lastly the South-East Asia Region[45].

With the development of DAAs and their generics, the cost for the treatment for HCV has been declining through the years[45]. Accordingly, a 12-week course of the pangenotypic regiment for HCV, as for the global pricing agreement is available at 60 US Dollars[45]. However, of 24 reporting countries only Egypt, India, Nigeria and Pakistan are paying prices below or at this baseline[45]. With highest reported price in China where a SOF/DAC, another pangenotypic DAA, fixed dose is found at 10 000 US Dollars[45]. Only about half of the 33 WHO focus countries having included in the national essential medicine list for adults the SOF/DAC or SOF/VEL cocktail for adults and even less for children[45].

Therefore, it is argued that the stagnation of results toward the goal of HCV elimination derive not only in costs of medications which have been decreasing[47]. But also, from costs associated with the diagnostic recommendation and pre-treatment genotype tests[47]. Furthermore monitoring during treatment, can have an economic burden higher than that of the medication itself[47], or not be available at all[47]. Therefore, in consideration of the lack of healthcare infrastructures, especially in the low-income countries, minimal-in-person monitoring

doi:10.6342/NTU202501025

(MINMON) approaches are of particular interest[47]. As both the EASL and the American Association for the Study of Liver Diseases (AASLD) and ISDA have recommended guidelines for the simplification of HCV treatment when using pan-genotypic DAAs such as SOF/VEL and GLE/PIB[48,49]. However, these simplified algorithms are intended with specialist in mind, with non-real-world consistency due to regional HCV care infrastructure variation[47,48,50]. In order to attain the strategy of simplification of treatment delivery, to avoid pre-treatment genotyping, and the vastity of tools used to classify cirrhosis, against simpler and more accessible laboratory ones, or the non-correct representation of the diversity of the HCVs patient populations, as well as proving the non-necessity of repeated clinic visits e.g. for refills[46]. The AIDS Clinical Trials Group(ACTG) A 5360 MINMON trial demonstrates in fact how HCV treatment can be simplified without compromises in the safety and efficacy of DAAs[46], for diverse patients without cirrhosis decompensation[46] through the administration of SOF/VEL. Of interest in this study is the subpopulation characterizing 42% of the cohort, being patients living with HIV as well as HCV and with 99% of these on suppressive antiretroviral therapies[47]. Reporting also that the SVR achieved in HIV-HCV coinfected reached 94.6%[46] on par with what was observed in the ASTRAL-5 trial[47]. And that of currently on substances population, with regards to the size of the subpopulation not being optimal, achieved SVR rate was that of 94.6%[47]. Overall, the SVR achieved in this trial is that of 95%[47], comparable to that of other meta-analysis studies and registration trials in which SOF/VEL was delivered through extensive in person monitoring[47]. A similar study was performed utilizing GLE/PIB treatment for a duration of 8 weeks[47,50]. Also demonstrating SVR similar to those of the registration trials of GLE/PIB, overall, at 92%[50]. The SMART-C trial[51], with differences in comparison to the MINMON trial being in the methodology used for cirrhosis and fibrosis status, using a more sophisticated and less common transient elastography[50]. Also failing to acquire large representation of vulnerable subpopulation of PWID and HIV/HCV coinfections[50]. Nevertheless, establishing another model for simplifying the delivery of treatment of HCV[47,50,51]. Further help could be provided as reported in a meta-analysis study by the WHO, by decentralizing and integrating HCV care, to harm-reduction centers or primary care for PWID, closed settings and prisons which are part of the vulnerable populations[52]. Allowing for improved access to treatment and testing, with task-shifting to non-specialists who have been associated with high cure rates of care on par with specialist across

doi:10.6342/NTU202501025

populations and settings[48,52]. Such concept can be categorized in the linkage to care (LTC), regarding both uptake in treatment as well as continuum of treatment, which has been studied for both urban environments as well as rural areas[53,54].

Evolution of HCV Eradication Goals

Year	Document/Strategy	Key Eradication Goals/Targets
2015	2030 Agenda for Sustainable Development	• SDG 3.3: End the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases, and combat hepatitis. • Establishes a global framework for reducing communicable diseases by 2030.
2016	WHO Global Health Sector Strategy on Viral Hepatitis	• Target elimination of viral hepatitis by 2030. • Aims for a 90% reduction in incidence and a 65% reduction in mortality. • Sets goals of 90% diagnosis and treatment of 80% of eligible cases. • Interim targets: 30% reduction in incidence and 10% reduction in mortality by 2020.
2024	Global Hepatitis Report 2024	• Consolidates recent progress and updates the strategic roadmap toward elimination. • Emphasizes micro-elimination approaches, refining targets based on new data. • Highlights challenges such as low diagnosis rates (e.g., only 36% of chronic cases diagnosed in some regions) and coverage gaps. • Projects potential reductions in new infections and mortality if 2030 targets are met.

Table 2, Summary of HCV's eradication framework

4. Micro-Elimination of High-Risk Populations

By utilizing PubMed's advanced search function, by setting the search box to the following: "((Hepatitis C) OR (HCV)) AND ((Micro-Elimination) OR (microelimination))". It is possible to identify that the first article regarding micro-elimination as a strategy to fight HCV is published in 2017. Direct consequence and possible answer to the UN and WHO's 2030 elimination goal set in the 2016 SDG[55]. Consisting in promoting a more pragmatic approach in which the scale of the target is reduced to smaller objectives, which in this case are individual populations or specific sub-populatation[55]. Population who would benefit in terms of efficiency of treatment through targeted or tailored methods[55]. Examples of such populations are: "people living with

doi:10.6342/NTU202501025

HIV, prisoners, people with haemophilia"[55], including where such people live, such as closed settings, prisons, hospitals or addiction centers, and geographical areas, urban or rural, city or region[55]. As described in the 2017 issue, a micro-elimination target was already being pursued in high income countries as the prioritized patient population for treatment was that of advanced liver disease[55]. However, there are certain high-risk populations whose LTC is compromised by social margination which example can be people who inject drugs[55]. The issue puts emphasis on one of the points which have been repeated in the strategies, frameworks and even the 2024 report by the WHO on the importance of data collection[55]. Without which it is not possible to understand the necessary information to bring forth successful micro-elimination[55]. That is to understand the epidemiological situation of HCV in a country[55]. For a successful micro-elimination strategy, there are defined criteria which are to be applied and shaped on accounts of the application for determined epidemiological profiles and settings[56]. First, a plan on tailoring the LTC and achieving high levels of HCV diagnosis and treatment in well-defined populations of interest[56]. Secondly the targeted achievement and progress timeframes need to be feasible and relevant based on mathematical modelling[56]. Thirdly the set targets are to be implemented through multiple stakeholders, including government officials, health service providers and civil service representatives[56]. Lastly, there should be monitoring of the progress and transparency with the public reporting the information through indicators which were previously identified and selected[56]. These 4 criteria and scoring methodology for micro-elimination were first defined in 2018 by Lazarus et al, and in the 2022 review the first to provide a quantitative analysis on their utility[56]. In said review, it was determined low-scoring groups, according to the criteria, had as commonly unreported components: "multi-stakeholder involvement and defined targets"[56]. Furthermore, the review gives attention to the lack of interest defined by the number of papers

doi:10.6342/NTU202501025

that have analyzed regarding micro-elimination targeting specific populations[56]. With PWID, or PWUD, having the greatest number of papers and therefore most common population in this review[56]. Incarcerated individuals are defined as another key population, considering that they are exposed to multiple HCV risk factors, example being the use of injection drugs[56]. Quantifying the risk of HCV among recently incarcerated PWID to be 62% higher than those not incarcerated[56]. Moreover, globally 58% of PWID have reported a history of incarceration[56]. While treatment success measured in the rate of achievement of SVR equal to general population cohorts, the report indicates that not all in this population initiate treatment, and that SVR is achieved in <80%[56]. Furthermore, indicating the existence of barriers in the LTC, from initiation to follow up, for PWID and in closed settings, specifically in prisons[56]. In contrast, the review advices on the low number of studies reporting the elimination efforts in people living HIV(PLHIV) with co-infection[56]. Highlighting how there is a viable engagement point due to the high co-infection prevalence and how about 67% of PLHIV are on antiretroviral therapy on a global scale[56]. In other words, their supposed already present connection to the healthcare system[56]. With further supporting statements of micro-elimination by the British HIV association[56]. Having set target of treating all HIV/HCV co-infected individuals in the UK by 2021[56]. Another point is brought forward in discussing the few studies which account for re-infection, stipulated as a critical threat to a sustainable elimination[56,57]. Particularly when considering the high risk of re-infection for population such as PWID and PLWH[56,57].

5. Reinfection

When discussing treatment for HCV infection it is important to repeat the concept of immunity acquisition, which isn't acquired after the infection[58]. Individuals who have cleared HCV

doi:10.6342/NTU202501025

infection from treatment or through spontaneous clearing remain at risk of recurrence of HCV viremia, of reinfection[58]. There can be identified 3 different perspectives through which analyze this issue: from a patient, provider and population[58]. The concern of reinfection itself can be an obstacle to providers and health care systems to persons perceived to be at high risk for reinfection of HCV[58]. Therefore, such treatment might be thought as unworthwhile, for such population by the providers given the costs[58,60]. From a population perspective it represents a major obstacle to control, given the necessity and dependence to treat enough infected people to reduce overall prevalence and therefore those who can sustain the epidemic by transmission[58]. If we are to analyze high income countries, HCV transmission occurs primarily in a different manner than it does in low-income countries as introduced in earlier sections. Interestingly, such same individuals and their subpopulations are also the ones who are principally referenced when discussing reinfection[59,60]. In particular for PLWH and of those who identify themselves in PWID and those who are MSM[59,60].

In understanding the characteristics of individuals with reinfection, we are presented with observational studies such as the REACH-C(real-world effectiveness of antiviral therapy in chronic hepatitis C) evaluating the treatment outcome following DAA initiation across multiple health services in Australia spanning 2016 to 2019[60]. With baseline characteristics of those found with reinfection being of male sex 84% and median age of 37[60]. 83% had recent injection drug usage, 8% had HIV and 38% were incarcerated[60]. Another retrospective study, using the InCHEHC: International Collaboration on Hepatitis C Elimination in HIV Cohorts, found that of the people with HIV at risk for HCV reinfection, the median age was higher at 49 years and in line with male overexpression[61]. Furthermore 46% reported being MSM, and 38% reported being PWID[61]. One more important aspect is that the most common reinfection genotype was that of

doi:10.6342/NTU202501025

GT3 at 44% and GT1 at 40%[60]. The study allowed for retreatment history in secondary reinfection, reporting that of the 99 who were subject to reinfection, 53 were successfully treated[60]. Of these 53, 5 underwent retreatment for a secondary reinfection, and among them, all reported recent injection drug use while 3 were in prison setting[60].

Reinfection poses a threat to elimination, with estimates of post-treatment HCV reinfection incidence at 4-6% per person years among PLWH, gay and bisexual man (GBM) with HIV and PWID[62]. With studies such as the REACT: Recently Acquired HCV Infection Trial, evaluating efficacy of standardly adopted treatment, SOF/VEL for recent infections, defined as infection in the past 12 months, with main outcome of interest being reinfection following treatment[62]. The characteristics of the REACT cohort, have as vast majority male set as 96% of 196, GBM at 87% and with HIV infection at 71%[62] from 6 western high income countries[62]. Having consideration of already defined key populations which are already disproportionally represented in HCV epidemic and reinfection being PWID and HIV infected men who have sex with men (MSM)[63]. With a good proportion of PWID, discriminating between recent and all-time: 20 v 53%[62]. Injection of drug was reported following treatment by 40% of the cohort[62]. Among the GBM, unprotected or unsafe sexual activities such as condomless anal intercourse and group sex were reported at 82% and 63% prior and 87% and 58% during follow up respectively[62]. Sexualized drug use here renamed as "chemsex"[62], was reported in 30% with 19% involving injection prior to enrollment and 47% with 34% involving injection in follow-up[62].

Recent infection participants had higher reinfection incidence, with 25.6 per 100 person-years, compared to primary infections at 7.8 per 100 person-years[62]. Participants who are PWID post-treatment also had a higher incidence compared to those are not[58]: 21.1 per 100 person-years v

doi:10.6342/NTU202501025

9.4 per 100 persons-years[62]. Of the participants with reinfection: 27 out of the 196 cohort, which is composed of 89% GBM and 85% of PLWH, 44% reported injection of drugs, 59% reported use of "chemsex", and 63% reported unprotected anal intercourse with casual male partners during follow-up[62]. Injection and sexual unsafe/risk behaviors were reported in 30%[62].

An important detail is that of the median time to retreatment from reinfection diagnosis being 17 weeks, ranging from 2 to 33 weeks[62]. Furthermore of 10 reinfection cases that remained untreated, with PLWH consisting of 7 of them, none were subject to spontaneous clearning[62].

Of the factors associated with reinfection of HCV, prior HCV reinfection, injection of drug post treatment, unprotected sexual intercourse including condomless anal intercourse with casual male partners and "chemsex" as well as geographical location[62], with variance according to the main group of interest: GMB or PWID[62]. In other reviews it is in fact highlighted that there is a presence of overlap of sexual and injection drug use risk factors in increasing the risk of HCV infections[58]. While traditionally, individuals at risk of infections are categorized or grouped as HIV infected MSM and PWID, there must exists also a subpopulation of men living with HIV that use injection of drugs and have sex with men[58]. It is believed that the transmission between PLWH/MSM happens during intercourse through high-risk practices, in which blood contact is more likely[58]. Furthermore, such high-risk practices are also more frequent in a setting where PWID, or recreation drug use, for chemsex[58]. Studies such as that of the V-HICS cohort have demonstrated that HIV coinfection by itself isn't a major component in leading to reinfection, rather a moderate factor[59]. With the high-risk behaviors more prominent in said subpopulation being a more likely major fact in the reinfection overrepresentation[59].

doi:10.6342/NTU202501025

It must be noted that these events seldom occur in isolation, rather in cluster of HCV infection[58]. These clusters have been identified among networks of high risk PLWH/MSM[58], which are observed to overlap with the reported injection relationships among PWID[58].

Leading once again to discussing the importance of a tailored treatment plan, rather than a generalized one[58], discussed in the micro-elimination section. Given for example the existing variance in PWID populations[62]. BGM who engage in "chemsex" or sexualized drug, be injecting or non, traditional harm reduction interventions known to reduce risk could present an obstacle presented as the majority of the participants or focus on injection of opiods[62]. Furthermore, while discrimination against GBM in high-income countries is rare, it is believed that disclosure of behaviors associated with transmission of HCV is limited and an obstacle given the fear of stigma[62]. Therefore, it is suggested that an individual risk for HCV reinfection post-treatment should not be a deterrent. Instead, be considered in the treatment process itself for such individuals[58].

6. HCV/HIV co-infection

The AIDS epidemic has been a global public health issue that has persisted for more 4 decades, with burden in deaths accounting for approximately 40 million deaths[64]. The agent causing AIDS is the Human Immunodeficiency Virus (HIV), a retrovirus, transmitted through body fluids and secretions[64]. HIV targets as host T cells, with consequence to untreated individuals an increased vulnerability to opportunistic infections as well as cancers[64]. With fatal outcome in the time range of 2 to 10 years from infection[64]. Rapid diagnostics and effective antiretroviral therapy have led to a dramatic reduction in mortality and morbidity, once on a worldwide effect[64]. HIV-infection is nowadays a chronic but manageable condition[64]. However, it is necessary to report

doi:10.6342/NTU202501025

on the still present discrimination, stigmatization and other structural barriers that may be present in blocking this population to seek prevention, testing or treatment as well as its upkeep[64,65]. The treatment for HIV is that of an antiretroviral therapy (ART), allowing for a restoration of the compromised immune system through suppression of viral replication[64]. Effectively requiring LTC[65], prevention and treatment to be made available at an affordable and accessible means for all[64]. Given that focus on the continuum of care in multimorbidity scenarios especially and good quality of life in long term[64]. Necessitating an early intervention and continued care or maintained viral suppression[64]. Given the threat of patient attrition and loss of follow-up, similar to what has been discussed in the patient adherence section, they are a threat to the eradication goal[65]. This is highlighted as this infectious disease is included and explicitly called out for eradication in the SDG goal 3, as previously reported in the 2030 Agenda section[40]. As well as the multiple global strategy handbooks that have been published, and mentioned before, regarding infectious disease and have as interest both HIV and HCV. With affirmation from organization such as the USAID (United States Agency for International Development) and plans such as the PEPFAR (US President's Emergency Plan for AIDS Relief) launched in 2022 and lasting 5 years, aiming at achieving and sustaining a control on the HIV epidemic and an end to the public health threat posed by HIV/AIDS by 2030[66]. With an extended strategy of the targets of UNAIDS from the by 2020 goals to the by 2030 promoting a 90 diagnosis-90 ART -90 achieve viral suppression to 95-95-95 as illustrated in the "Fast-Track Targets" strategy[67]. With a new sustainability approach launched in early 2024, by UNAIDS as a global HIV response for beyond 2030[68].

Therefore, in what can be described as an impaired or less-effective immune system[69], a reinfection event of HCV, is a common occurrence among certain population, given that

doi:10.6342/NTU202501025

treatment to HCV does not grant immunity. In fact, HIV/HCV coinfection accelerated hepatic decompensation as well as other liver conditions, promoting a negative effect on the immune system against HCV[69]. With argument that a reduced level of anti-HCV antibodies may facilitate reinfection[69].

Of interest is the consequence of highly effective, accessible and untaken ART therapy that life expectancy of HIV-infected patients is comparable with that of the general population[70]. With PLWH ever more experiencing health problems unrelated or indirectly associated with HIV infection[70]. As a matter of fact, HCV infection and its associated liver diseases remain one of the principal causes of morbidity and a factor that affect quality of life as well as length of life for PLWH[70].

However, this was not always the case. As historically the HCV/HIV coinfected were labeled by the FDA as "a special population with unmet medical needs" given that the treatment of HCV in HIV coinfected was reporting lower SVR rates when compared to those without HIV infection[71]. With the upscaling of DAA and the affirmation that the treatment itself is when compared to the IFN treatments of improved safety, tolerability and efficacy[71], such label should be reconsidered since reviews have demonstrated the comparable results achievable in both coinfected and monoinfected[71]. What has been mentioned before, returns in view of the continuation of treatment, and other negative predictors or barriers that may impair the SVR more commonly in the coinfected population[71].

In such population such as HIV/HCV coinfected, given the need of administering multiple drugs, interest in drug-drug interaction must also be addressed. A retrospective study has observed how anti-HCV-nAbs, antibodies against HCV infection as well as anti-E2-Abs exhibit rapid decay in

doi:10.6342/NTU202501025

coinfected individuals post SVR achievement[69]. While this study is principally interested in the understanding of anti-HCV-nAbs for their role in protection and clearance of HCV, as a late or weak anti-HCV-nAbs response is a factor in the progression from acute to chronic HCV infection[69]. Other studies have reported the same phenomenon of HCV elimination leading to a lowering of the count of anti-HCV antibodies[69]. With attributed cause being the loss of antigenic stimulation post clearance[69]. Of the six main genotypes taken into consideration, it was observed that GT3 presented the most pronounced loss of anti-HCV-nAbs[69].

On accounts of phylogenetic clustering, with interest in the increasing number of studies of molecular epidemiology on the transmission of HCV[72]. Reportedly have found that the phylogenetic clustering of HCV is associated with HIV coinfection and sexual acquisition of HCV in recent infections[72]. With understanding that phylogenetic clustering of HCV is associated with social injecting networks in PWID living in urban environments living with HCV infection[72]. With corollary argument that closely related viruses can indicate a possible transmission link between the hosts[72]. Moreover, coinfection studies have shown that phylogenetic clustering of HCV is observed among homosexual and bisexual men living with coinfection[72]. With an important point being multiple introductions of HCV into networks gay and bisexual (men) people living with HIV indicated by the observance of many unrelated clusters of multiple HCV genotypes and subtypes[72]. Therefore, we find the utility of studying patterns of phylogenetic clustering on a population level on a population level in revealing information on the direction of transmission[72]. By observing the results of the CEASE trial: Control and Elimination of HCV from HIV infected individuals in Australia[72]. Looking at the adjusted analysis by mixed-effect model with random intercept for site where participants were

doi:10.6342/NTU202501025

recruited from, there was no considerable variation between subjects[72]. Among gay and bisexual men, of age 40 or younger, having completed higher education and reporting high-risk sexual behaviors, were associated with phylogenetic clustering[72]. A high-risk that is defined in this study as condomless anal intercourse with one or more casual male partners including group sex[72]. With results indicating that one out of three participants were infected by HCV subtypes variants highly related to each other, mainly 1a or 3a[72]. While phylogenetic clustering provides an indication on how closely related the networks through which HCV is being transmitted in a community, it is not a direct marker of transmission[72]. Having as findings that the proportion of phylogenetic clustering found in the CEASE trial are consistent with what has been observed in previous molecular epidemiological studies of CHC coinfected with HIV[72]. Further supporting the evidence in Australia that HCV is transmitted within networks of people living with HIV, particularly among gay and bisexual man[72].

An interesting result of the study done with the InCHECH of Australia, Canada, France, the Netherlands, Spain and Switzerland between 2010 and 2019[61]. Is that HCV incidence in PLWH, declined during the initial DAA introduction when compared to the pre-DAA era[61]. However, the incidence due to reinfection was the highest overall during broad access to DAA[61].

Moreover HCV-HIV coinfection is associated with an increased risk of death[73]. 3 times as great when compared to HIV monoinfected and 12 times higher when compared to general population[73]. While End-Stage-Liver-Disease (ESLD) were the primary cause of death in Co-Infected cohorts, with the upscaling of HCV treatment, ESLD mortality is observed to be have been in decline[73]. However, HCV infection has been linked with biological extrahepatic

doi:10.6342/NTU202501025

morbidities as well as compartmental or high-risk behaviours[73]. Such as cardiovascular, renal, insulin resistance and cancers or substance abuse and drug overdose[73].

It has been observed that DAA treatment for HCV-infected patients, in a multi-cohort France nationwide study, leads to similar SVR rates for HCV-monoinfected and HIV/HCV coinfected[74].

With coinfection of HIV however being responsible for an increased risk of all-cause death after the initiation of treatment, when compared to monoinfected patients[74]. Risk of death deriving from extrahepatic cause, or non-liver-related deaths[74], but also increasing the risk of extrahepatic cancer development[74]. With note to be taken accounting for the higher-risk of non-liver-related cancer in HIV/HCV coinfected deriving from both from a biological disease standpoint and from social behavior[74]. As the coinfected patients have been noted to partake in high-risk behaviors with tobacco and alcohol consumption in more than half of the subpopulation[74].

HIV coinfection is also reported in reducing the spontaneous clearing event of HCV infections as well as a higher HCV viral load accounting for a possible circumstantial greater infectivity[75].

Returning to what had been discussed in the Reinfection section, while there is a disproportionate dominance of HIV infected MSM subpopulation accounting for the HCV burden, biological factors alone do not justify this[75]. While a higher HCV viral load and consequent increased infectivity as well as a lower spontaneous clearing rate, high risk behavior combined with preferential mixing by HIV status are reported to greatly contribute to the phenomena[75]. Therefore, proposing that HCV infection and co-infection to be "seen as a marker of high sexual risk behaviours"[75]. With further damage done by the "treatment optimism"[75] born with the scaling up of efficacious treatment of HIV[75] as well as that of HCV.

doi:10.6342/NTU202501025

Zeroing on Taiwan, The RECUR Study

The Reinfection of hEpatitis C in patients with immuUodeficiency viRus (RECUR) study, published in 2022, prospectively asserted the risk of HCV reinfection in multiple academic centers in Taiwan[76]. Reporting the trend of incidence of HCV reinfection in the time period of 2005 to 2021 in chronically HCV monoinfected as well as HIV/HCV coinfected patients[76]. Compared to previously illustrated studies in past sections, similarities in the characteristics are once again found. With HIV positive patients being younger, being predominantly of male sex, having higher eGFR and lower BMI and ALT levels[76]. Furthermore, it is reported that of this HIV positive subgroup, the vast majority: 92.6%, were MSM[76].With reinfection being reported in 14.4% of the HIV-positive patients who had achieved SVR12, and with 96.8%: 30 out of 31 HCV reinfections being attributed to high-risk sexual behavior and 3.2% or 1 out of 31 attributed to injection drug use[76]. For the reference patients, monoinfected chronically infected HCV patients, 0.9% had reinfection with the most common route of transmission being unsafe medical injections, accounting for about half of the reinfections at 53.3%[76]. It is possible to report therefore how cumulative incidence rate of HCV reinfection is higher in HIV-positive patients against reference patients[76]. Of high importance if the reported secular trend of HCV reinfection by calendar year which results are in line with what has been reported by a newer study conducted on different cohort set and that was previously illustrated: InCHECH. It is reported in RECUR how while during the 2005 to 2014 timeframe, when IFN was the only available treatment the incidence for HCV reinfection remained at 0 per 100 PYFU[76]. Since 2015, with the public market release in Taiwan of DAAs, especially of out-of-pocket brand and generic DAAs, an increase of the PYFU is reported. 2.82 per 100 PYFU in 2015[76]. With reimbursement, albeit

doi:10.6342/NTU202501025

restricted, policies were established in 2017 and 2018 an increase of PYFU were observed at 3.85 to 4.30 per 100 PYFU respectively[76]. In 2019 the restriction of brand-name DAA reimbursement was lifted to unlimited and further increase progression is reported all the way to 2021, from 4.39, 5,74 to 6.42 per 100 PYFU[76]. While no baseline factors predicted HCV reinfection, characteristics which were listed multiple times previous sections are once again reported as being highly associated with HCV reinfection in the HIV infected, with consideration of the interpolation of HIV/PWID population as well as the contribution of other STI during post SVR or in its follow up stages[76].

On the change of policies, access to treatment and corollaries

The RECUR study identifies a temporal trend, that HCV reinfection incidence in PLHIV increased after 2015, coinciding with the introduction and availability of DAA in Taiwan[76].

A pattern that appears paradoxical: increased treatment, with increased accessibility, reinfection also increases. A correlation that can potentially arise from several factors:

1) Treatment expanding and reaching more High-Risk individuals who also maintain these behaviors indifferently from treatment.
2) Reduced perception of HCV severity due to treatment availability, affecting risk behavior.
3) Two-speed between integration of preventive services and treatment expansion.
4) Surveillance bias due to increased monitoring, leading to increased detection of reinfections.

However, the consistency of RECUR study's to that of the pan-European survey in overall incidence being of similar value: 4.02 per 100 PYFU v 4.65 per 100 PYFU in PLHIV[76]. Suggesting a common underlying dynamic in policy change and reinfection pattern.

doi:10.6342/NTU202501025

The advent of DAA's transformed HCV treatment by offering high cure rates, shorter treatment durations and fewer side effects in comparison to it's predecessor the IFN based treatments. However, it is important to point out that initial roll-out of these medication presented a high-cost that prompted healthcare systems worldwide to implement restrictions to access and strict criteria for reimbursement.

A question that should arise then is that of how policy changes influence these reinfection dynamics, even if inadvertently.

Globally, similar policy transitions have occurred, although with varying approaches in reimbursement restrictions. In Italy for example, in 2020 Russo et al. conducted a national registry analysis on DAA reimbursement restriction and it's effects on the elimination goals of HCV[77]. With 165,105 patients treated with DAA from 2015 to 2018, with a segmentation of 2 time periods: 2015-2017 where only advanced stage, defined as cirrhosis, and making up 62% of the cohort had access to the therapy[77]. After 2017, the reimbursement criteria was extended to include F0-F1 and F2, respectively composing 43,2% and 22.9% of the patients treated, with cirrhotic patients making up only 18.5%[77]. However, the conclusion reached is that even in light of a "no-limit" reimbursement policy for DAA prescriptions, HCV's elimination progress was not significant[77].

In Canada, a descriptive study reviewing 16 publicly funded drug plans by Snell et al. in 2022 reported that despite the elimination of disease-stage restrictions for DAA reimbursement, other barriers persist[78]. Out of the 16, 15 plans maintained at least one policy limiting simplified HCV treatment, with requirements on genotype, fibrosis staging, eligible prescribers and approval processes lengthy, with one case explicitly discouraging treatment of reinfections[78].

doi:10.6342/NTU202501025

While we have pointed out the existence of consistency across the pan-European survey and RECUR's study observations, there also exist contrasting trends across studies. Such as those of Western studies documenting a decrease in incidence of HCV reinfection following widespread DAA use[76]. Highlighting the importance of localization of implemented factors, healthcare system structures, prevention strategies as well as patients' specific factors e.g. risk profiles, follow-up and surveillance methods. Specifically, the 0 to 17% per 100 PYFU across studies reinforces how context specific factors define the relationship between policy changes and reinfection dynamics[76].

Another example of temporal correlation regarding PLHIV, Salazar-Vizcaya et Al. mathematical modelling observed how unsafe sex practices among HIV-infected MSM after HIV diagnosis rose throughout the years, from 5% in 2000 to 13% in 2013[88], and estimated value at 14% in 2016[79]. In parallel with the increase of treatment rates rising from 11% in 2006 and 42% in 2013[88]. With predictions that despite an increase of treatment uptake and efficacy, the continuous increase of high-risk behavior, seen at exponential level, would have as consequence an increase in incidence and prevalence[88]. Likewise in a follow-up paper published by the same authors in 2017, with regards to the increase administration of DAAs, failure to target high-risk behavior group, with assumption that the fraction of population remains stable, also leads to an increase in prevalence[79].

Against the local policy contexts, specific population vulnerabilities lead back to a consistency, that of the High-Risk target population such as PLHIV MSM and PWID. Therefore, highlighting the need for targeted approaches[85].

doi:10.6342/NTU202501025

The challenge then comes to identifying predictive factors, which were not found nor in RECUR nor in EuroSIDA, including HIV risk group, CD4 count, antiviral treatment or fibrosis status[76,80]. Suggesting that ongoing risk behaviors rather than pre-treatment characteristics may be more important determinants of reinfection risk[85].

1: Summary of Changes in Policies, Access to Treatment, and Corollaries in HCV Management

Year/Period	Policy Change / Intervention	Impact on Treatment Access	Corollaries / Outcomes
2011–2012	• Introduction of first-generation DAAs (Boceprevir, Telaprevir) • Reimbursement restrictions (only for patients with advanced fibrosis)	• Limited eligibility for treatment • High treatment costs and low uptake	• Modest improvements in SVR rates over IFN-based regimens • Significant side effects and treatment discontinuation issues
2014–2015	• Introduction of all-DAA regimens (e.g., LDV/SOF) • Continued use of fibrosis restrictions in many regions	• Expanded eligibility compared to IFN-based treatments • Improved cure rates (median SVR up to 90%)	• Shorter treatment durations and improved tolerability • Persisting issues with access due to cost constraints
2017	• Policy reforms: removal of fibrosis restrictions in several countries • Introduction of newer regimens (e.g., GLE/PIB, SOF/VEL/VOX) • Availability of generic DAAs in some markets	• Broader patient access including early-stage infections • Increased treatment uptake and decentralization of care	• Significant improvements in SVR rates; (median SVR up to 95%) • Reduction in treatment duration and adverse effects • Emergence of new challenges such as reinfection management
2020–2024	• Implementation of simplified treatment protocols and minimal-monitoring strategies • Integration of HCV care with other services (e.g., HIV clinics, primary care)	• Streamlined and decentralized access to testing and treatment • Improved diagnosis and linkage-to-care rates	• Accelerated progress towards elimination goals • Ongoing challenges with reaching underserved populations and managing reinfections

Table 3, Summary of HCV management changes

doi:10.6342/NTU202501025

7. Modelling

Aside from the discussion, goals and promises made with the eradication or elimination goals, the discovery of highly effective HCV treatment has led to an increased interest in modelling[81]. As discussed in previous sections, HCV disproportionally affects subpopulations based on the country of interest[81]. In high income or developed countries PWID are disproportionately affected by HCV, and models can be used to provide evidence of an intervention current or expected effect[81]. Example being NSP (needle and syringe programs) and OST (opioid substitution therapies)[81]. Investigating the typology of models used is interesting, not only the model utilized but also, its interpretation. With the COVID-19 pandemic, a surge in popularity for mathematical modelling of epidemics occurred[82]. With the initial utilization of forecasting models, also known as weather models and their misinterpretation and misinformation due to the lack of understanding of the uncertainty, being an intrinsic characteristic of such models[83].With data errors, resolution limitation and non-linearity that are taken into account with computation power, albeit ever increasing in availability[83]. It is important therefore to understand the reason why forecast predictions in weather are displayed as percentages e.g. a 20% chance of rain. Furthermore, it has been reported how in the initial stages of the COVID-19 pandemic in the many models that were released, some were flawed in the methodologies and projections[82,84]. Therefore, there have been difficulties in utilizing epidemiological models as a tool to inform outbreak responses[82].

Before expanding on the models that have been released on studying the HCV transmission, it is important to understand what the moving parts are constituting the model and determining its performance.

doi:10.6342/NTU202501025

To start, one of the important drivers for the model's performance is data quality[82]. Having health outcomes, such as infection, recovery or death, to which to increase accuracy in the transmission pattern prediction, human behavioral data may be included for forecasting and scenario analysis[82]. As observed with the COVID-19 pandemics, even in the US the public health infrastructure was neither equipped nor prepared to respond without delay to provide quality health outcome data[82]. Furthermore, behavioral data collection in real-time, to understand the shift in dynamics of transmission patterns, are a challenging issue with reliance to surveys, and even when administration of said surveys is done through social network platforms, cognitive biases are at play such as self-reporting and data sampling biases[82]. From this singular driver we can already understand the many difficulties that arise in the theoretical epidemiological field that has risen[84]. The pseudo-novelty and obstacles of this field can be found with the release in 2020 of the EPIFORGE 2020 Guidelines published by Pollet et al.[85] with support from other publications indicating the guideline to increase the authority of models by improving transparency in epidemiological models[82]. Lamenting the lack of checklist present in other fields of medical research such as CONSORT or PRISMA guidelines in clinical trials or systematic reviews[85]. EPIFORGE is a guideline in the form of checklist proposed to standardize the reporting of epidemic forecasting research[85]. Promoting "consistency, reproducibility, comparability and quality of epidemic forecasting reporting"[85]. Acting as a standard, as a scientific method of epidemiological forecasting and prediction, for reporting criteria when researchers are reporting methodological details of their studies[85]. In similar spirit, Rui et al. have published in 2024 a framework for developing infectious disease models in lieu of plethora of models published with COVID-19 presenting methodological errors[84]. Consisting of 6 steps, the "MODELS" framework, the name being an acronym in order of steps recommended by the

doi:10.6342/NTU202501025

authors to develop an infectious disease model[84]. Beginning with the "Mechanism of occurrence"[84], every step is followed by inclusion of secondary steps as a mean of defining as holistically as possible said steps. Taking as example the Mechanism of occurrence step, this includes as secondary steps: "Disease natural history"; "Transmission process"; "Risk factors"; "Possible interventions"[84]. The other steps are "Observation and collected data"; "Developed model"; "Examination for model"; "Linking model indicators and reality"; "Substitute specified scenarios"[84]. One of the needs this structured framework aims to quell is the challenges faced by the diverse content present and the inherent limitation from the challenges of epidemiological model selection and construction[84].

As models can be generically divided into 2 categories: data-driven models and mechanism-driven models[84]. With data-driven models being based on utilizing existing datasets to make predictions and mechanism-driven models being based on the transmission mechanism and its mathematical formulation through consideration of underling mechanisms principles both biological and social[84]. Therefore, it is understandable of what are the various conditions that are in play in deciding whether to apply one model or the other[84]. In the presence of vast quantities of available high-quality data, with a lack of proper understanding of the dynamics of disease transmission data driven models are recommended, and vice-versa for mechanism-driven ones[84]. However, it would be best to integrate both types of models, to have a better understanding of infectious disease situation[84]. And even between categories of models, ensemble or utilization of multiple models to then obtain a range of estimated values is preferred[83].

As for why the majority of publications are interested in analyzing the PWID subpopulation, when in consideration of the HCV/HIV coinfection dynamics. It is due to the dominance of the

doi:10.6342/NTU202501025

intravenous drug use transmission as well as the prevalence in the PWID population of HCV over the others[81]. In particular when compared to sexual transmission, which outside of HIV context, has been observed to be ineffective[81] and when comparing a global prevalence of HCV at 2-3%[81] whereas among PWID it is estimated in many countries to be above 50% and globally oscillating between 10-97%[81].

The simplest version of model for HCV transmission falls into the category of deterministic compartmental models, with 2 compartments: 1 for Susceptible (S) and another for chronically infected (I)[81]. With regards of the population being PWID, with the start of the usage of intravenous drugs, subjects are moved into the S compartment and move to the I compartment in the event they are infected, while also being able to leave any 2 of the compartments by ending the usage. The movement from compartments are mathematically described by either ordinary differential equations or by probabilistic mechanisms "stochastic"[81]. With determinant of choice being the current state of the disease in study[81]. For modelling the transmission of a disease for a small number of people or an initial outbreak, stochastic is the most appropriate[81].

The population of a deterministic compartmental model for HCV transmission among PWID, are to include features, which can also be implicit, but shall at least describe: 1) the duration of usage of intravenous drugs; 2) frequency of usage; 3) transmission risk[81]. An assumption that is made for the sake of simplicity in models, but that results in altering the reality of depicted events, is that the duration of usage is continuous with an average spanning 7 to 14 years, rather than depicting cessation periods, relapsing and cycling in and out of usage[81]. Another assumption follows the transmission risk associated with intravenous injection[81]. Dichotomous risk heterogeneity: high risk and low risk, to simplify the high heterogeneity that is given by the

doi:10.6342/NTU202501025

spectrum of risk values over the population when accounting for personal frequency of use and high-risk injection behaviors prone in networks of PWID[81] .

Two-compartments deterministic models can be further developed by adding an additional compartment, in consideration of the current, as discussed before, unobserved long-term immunity, the infected in I can once again be susceptible S post-treatment[81]. With treatment that is generally modelled with the assumption that its treatment rate are proportional to the subpopulation of interest, in this case PWID, rather than the total infected population[81]. Furthermore, the addition of allowing infected individuals to return to being susceptible adds complexity in determining the reinfection rate[81].

Previously built models such as the one proposed by Carvalho and Pinto in 2014 on coinfection of HIV and HCV included only sexual transmission as means of transmission for both viruses while arguing of the existence of growing IDU's in population and contribution[86]. However, such models being developed over 10 years from the date of writing, results outdated in multiple points. As previously observed in initial sections of this work, the upscaling of efficient treatment for HCV, increased attention and efforts in the healthcare world with regards of both diseases. The attention is shifted to transmission through IDU's and not vertical mother-child and sexual transmission, furthermore, lacking in aspect of re-infection.

Some of these aspects are corrected in newer models studying the coinfection of HCV and HIV with interest to the wide scaling of DAA access and its efficiency, such as the one proposed by Virlogeux et al. in 2017[87]. While however limiting itself to a short timeframe of 2012 and 2015, it gives view of initial perception of treatment rates, and the effects in transmission and epidemic

doi:10.6342/NTU202501025

dynamics held by eight risk groups, with MSM divided into high-risk and low-risk, PWID, as well as others[87].

Taking then into consideration Salazar-Vizcaya et al. 2016 model on HCV transmission in HIV infected MSM that are not PWID[88]. The population, and the model which are parameterized on a Swiss cohort, is compartmentalized by 2 risk groups according to whether they participate or not in high-risk behaviors associated with the transmission of HCV[88]. The groups are then further compartmentalized depending on status of care the individual is in: 1) HCV susceptible in care for HIV; 2) HCV susceptible not in care for HIV; 3) HCV infected in care for HIV ; 4) HCV infected not in care for HIV; 5) In care for HIV and in care for HCV[88]. Of particular interest is the development of a reinfection model, derivative and identical to the main model[88]. And of ulterior interest is the definition of high-risk behaviors for unsafe sex is regarded as "unprotected sex with occasional partners" and accounted for separately instead of included in the high-risk behaviors[88]. Given that not all who are categorized participating in unprotected sex with occasional partners performs acts of high-risk behaviors herein described as "condomless traumatic anal intercourse, fisting, use of recreational drugs, and group sex"[88] noted to be of interest in the transmission of HCV[88]. Therefore, in describing the HIV-infected MSM entering the out of care susceptible category and the fraction of individuals entering the compartment of high-risk group, the equation reflects 2 the terms[88]. With notice of a "high-risk/unsafe sex ratio"[88]. It is also noted how individuals can move from the group of without high-risk to high-risk on account of the "rate at which individuals start to have unsafe sex"[88], indicated as one of the "high-risk recruitment parameters"[88].

doi:10.6342/NTU202501025

Abiodun et al. 2022 mathematical model on HIV and HCV coinfection allows us to see the changes that have been taken into consideration, in an age where DAA are amply implemented[89]. As it is seen in statements of the model description for assumptions made, by not considering treatment failure for chronic HCV carriers, with regards to the already discussed highly effective new DAA combinations[89]. Another notable assumption is the one arguing for re-infection: "It is assumed that an individual could be re-infected with HCV even after successful treatment if expose or engage in high-risk behaviors such as injecting drugs, drinking alcohol, having multiple sex partners and sex between two men since the clearance & treatment does not confer permanent immunity."[89]. Lastly, of this model's assumptions, it is interesting the statement of assumption of spontaneous clearing for acutely infected individuals[89], and that those in treatment for HIV would not spread the virus[89], while coinfected PLHIV not in treatment for HIV would transmit HCV at a higher rate due to presumed higher viral load[89].

On quantifying risk behaviors

In precedent sections of this thesis, we have explored various works that have studied the risk factors that are associated with the target population of interest. However, while those factors that have been illustrated as percentages present the analyzed risk of the overall target population, they do not represent a way to identify those in the population who are at risk.

In 2017, Newsum et al. published the HCV-MOSAIC risk score in order to supplement the categorization of risk behaviors of PLHIV MSM[90]. Effectively granting a targeting testing system for the identification of MSM at an increased risk for HCV infection[90]. Albeit focusing on acute infection, given the cohort study chosen: MOSAIC, it has been validated through 3 other cohorts of PLHIV MSM[90]. Developed through self-administered questionnaires preceding HCV

doi:10.6342/NTU202501025

diagnosis and preceding enrollment in cohort[90]. With the HCV-MOSAIC risk score originated through simplification of the variables of the original MOSAIC questionnaire which was made by selecting for all statistically significant risk factors associated with AHCV in multivariable logistic regression model[90]. The results are aligned with what has been explicated multiple times in past sections referring to the high-risk behaviors. By referring to the beta values provided in the HCV-MOSAIC risk score, the highest valued variable is "Injecting drug use 12M", indicative for the self-reported IDU in the last 12 months[90]. With value of beta = 1.4, on par with "Ulcerative STI 12M", indicative of self-reported presence of sexually transmittable infections such as syphilis, genital herpes or lymphogranuloma venereum in the last 12 months[90].

Proposing a compartmental model addressed to the vision of personalized medicine.

To those partaking in mathematical models, it is most likely that they have been subject to the learning of Occam's razor[91,92]. "Entities should not be multiplied beyond necessity"[92] That is the rule of parsimony or simplicity, with which it is intended that the simpler is to be preferred to the more complex[91,92]. Therefore, it is preferred to have the minimal number of variables and parameters necessary to describe a system of interest, rather than an overabundance[93]. With interest being the redundancy of such many variables leads to overfitting the parameters leading to erroneous conclusions which may be farther from the truth than what is being hoped to achieve through the additional parameters, in an effort to not oversimplify the model[91,92,93].

doi:10.6342/NTU202501025

8. Proposed Model v01

It is with this preface to the section that I will proceed to describe a model built on the notions that have been gathered in this thesis, integrating them with the interest of furthering the concept of personalized medicine and a better understanding of the people living in this system.

This aim of this model is to better understand and portrait the dynamics occurring in transmission of HCV in the HIV population, therefore the HIV-HCV coinfected population, and the reinfection phenomena that is described to be on the rise and an obstacle to the 2030 eradication of HCV goals.

It is furthermore necessary to set some assumptions. Which are to reflect aspects extrapolated from the precedent literature review to reduce the complexity of the model and the computational power required and even more importantly reflect realistic data collection realities.

1) The targeted population is PLHIV, therefore it is presumed that these individuals are in contact with a healthcare provider or center, conferring possibilities of data collection.
2) Given the lack, at the moment of writing, of proper guidelines on treatment for AHCV and given the spontaneous clearing of infection possible even in PLHIV[94]. AHCV compartment pathways are that of progression to CHCV or recovery through spontaneous clearing.
3) Given that individuals that are treated do not gain immunity, individuals are once again susceptible to infection, for the sake of reducing complexity and aligning with reality, deaths in the compartment for Acute HCV infections from individuals having past HCV history, with regards of possible already present liver damage from past infection, should be taken into account as S2 deaths or in the Recovered compartment.

doi:10.6342/NTU202501025

4) Transmission in our groups of interests which are: MSM and PWID of PLHIV, are observed to have 2 main pathways of infection for HCV in developed and HI countries which are injection of drugs and sexual transmission among MSM as well as their combined effect, considering "chemsex". The transmission therefore follows a network-based structure rather than a homogeneous mixing, an assortative mixing, and should include a behavioral risk associated with these high-risk practices.

5) Age is continuous and takes its toll in mortality but also in behavior associated risks.

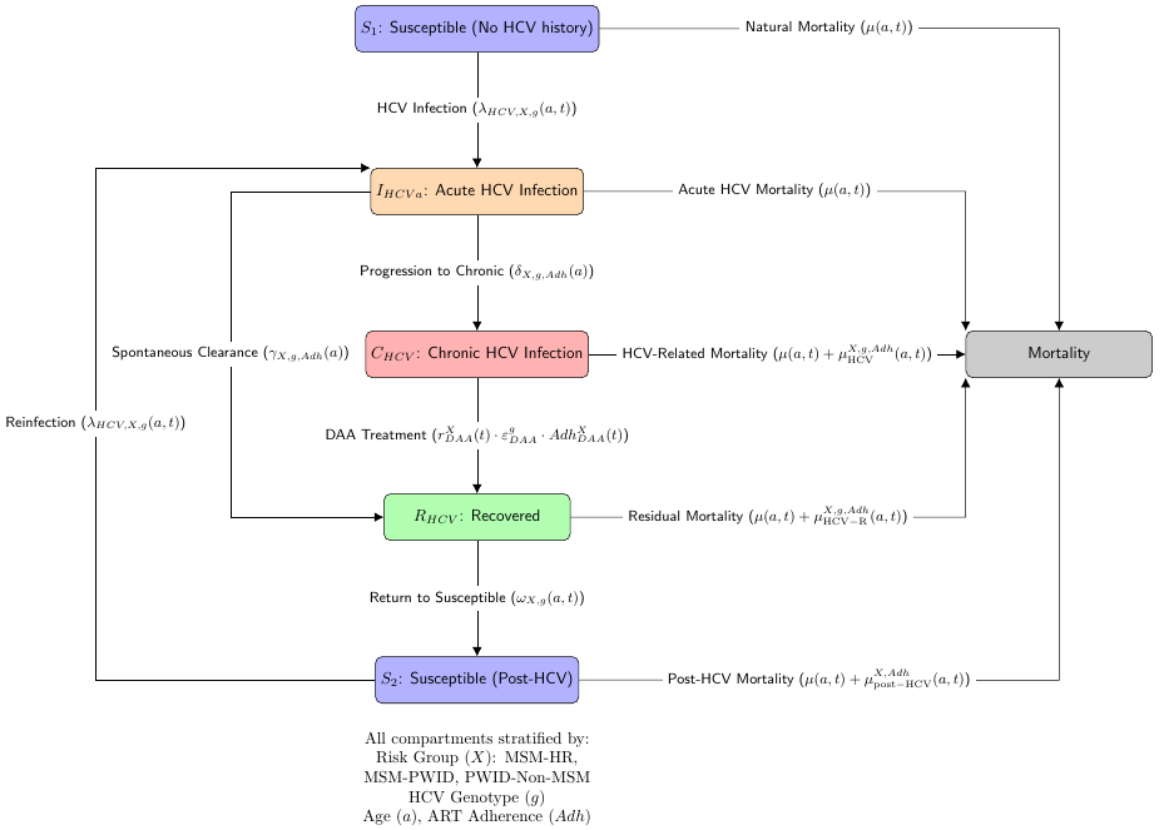


Figure 3, Proposed HIV/HCV Compartmental Model diagram flowchart, demonstrating the transition dynamics between compartments. MikTex 25.2 TeXworks version 0.6.10

The model is composed of 5 core compartments, describing the 5 main health states:

1) Susceptible without HCV history (S_1): Individuals not currently infected with HCV, with no prior HCV history.

doi:10.6342/NTU202501025

2) Susceptible with HCV history (S_2): Individuals not currently infected with HCV with HCV history.
3) Acute HCV Infection (I_{HCVa}): Individuals recently infected with HCV, before chronic state establishment.
4) Chronic HCV Infection (C_{HCV}): Long-term HCV Infection.
5) Recovered (R_{HCV}): Individuals who have cleared HCV.

   These compartments are then stratified by risk group (X), HCV genotype (g), age (a), and adherence to ART (Adh).

   And whereby risk group we intend: MSM_HR, MSM_PWID or PWID_non-MSM.

   Wanting to focus on categories which have been widely explored in the previous sections of this thesis and have been recognized as targets for the microelimination efforts in order to eradicate HCV.

Partial Derivative Equations (PDE), are utilized to explain the transition dynamics of the compartments:

The transmission dynamic is expressed through the force of infection:

$$\lambda_{HCV,i}^{g}(a,t) = \sum_{j \in \mathcal{N}_i} \beta_r^{X_j,g}(t) \cdot c_{ij}(a,a_j,t) \cdot \left(\frac{I_{HCVa,j}^{X_j,g}(a_j,t) + \rho \cdot C_{HCV,j}^{X_j,g}(a_j,t)}{N_j(t)} \right) + \beta_b^{g} \cdot B^{X}(a,t)$$

Incorporating:

1) Network based transmission $N_j(t)$: accounting for who connects with whom between all individuals: $S_1 + S_2 + I_{HCVa} + C_{HCV} + R_{HCV}$
2) Age stratification in contact patterns $c_{ij}(a,a_j,t)$
3) Infectiousness viral load differentiation ρ
4) Behavioral risk infection: $\beta_b^{g} B^{X}(a,t)$

doi:10.6342/NTU202501025

The intent of this equation is to explicate the existence of behavioral patterns and social connection which are prominent in our population of interest, and which are indicated as a main factor of transmission. Therefore, to express change over time, such as age and in response to interventions, of high-risk or risk indicated behavior:

$$B(a,t) = B_0(a) \cdot f(I(t), P(t), a)$$

Susceptible without HCV history (S_1):

$$\frac{\partial S_1^{X,Adh}(a,t)}{\partial t} + \frac{\partial S_1^{X,Adh}(a,t)}{\partial a} = -\sum_g \lambda_{HCV,i}^{g}(a,t) S_1^{X,Adh}(a,t) - \mu(a,t) S_1^{X,Adh}(a,t)$$

With intent of capturing:

1) The rate of change over time: $\frac{\partial S_1^{X,Adh}(a,t)}{\partial t}$
2) Age stratification: $\frac{\partial S_1^{X,Adh}(a,t)}{\partial a}$
3) New HCV infections across all genotypes: $\sum_g \lambda_{HCV,i}^{g}(a,t) S_1^{X,Adh}(a,t)$
4) Mortality: $\mu(a,t) S_1^{X,Adh}(a,t)$

Acute HCV Infection (I_{HCVa}):

$$\frac{\partial I_{HCVa}^{X,g,Adh}(a,t)}{\partial t} + \frac{\partial I_{HCVa}^{X,g,Adh}(a,t)}{\partial a} = \lambda_{HCV,i}^{g}(a,t) \cdot [S_1^{X,Adh}(a,t) + S_2^{X,Adh}(a,t)] - (\delta^{X,g,Adh}(a) + \gamma^{X,g,Adh}(a) + \mu(a,t)) \cdot I_{HCVa}^{X,g,Adh}(a,t)$$

With:

1) Inflow from both Susceptible compartments: $\lambda_{HCV,i}^{g}(a,t) \cdot [S_1^{X,Adh}(a,t) + S_2^{X,Adh}(a,t)]$
2) Progression to CHCV: $(\delta^{X,g,Adh}(a)$
3) Spontaneous clearance of HCV infection: $\gamma^{X,g,Adh}(a)$
4) Mortality: $\mu(a,t)) \cdot I_{HCVa}^{X,g,Adh}(a,t)$

Chronic HCV Infection (C_{HCV}):

$$\frac{\partial C_{HCV}^{X,g,Adh}(a,t)}{\partial t} + \frac{\partial C_{HCV}^{X,g,Adh}(a,t)}{\partial a} = \delta^{X,g,Adh}(a) \cdot I_{HCVa}^{X,g,Adh}(a,t) - r_{DAA}^{X}(t) \cdot \varepsilon_{DAA}^{g} \cdot Adh_{DAA}^{X}(t) \cdot C_{HCV}^{X,g,Adh}(a,t) - \mu(a,t) \cdot C_{HCV}^{X,g,Adh}(a,t) - \mu_{HCV}^{X,g,Adh}(a,t) \cdot C_{HCV}^{X,g,Adh}(a,t)$$

doi:10.6342/NTU202501025

Where:

$$\delta^{X,g,Adh}(a) = \delta^{X,g}_{base}(a) \cdot (1 - \varepsilon_{ART} \cdot Adh^{X}_{ART}(t))$$

And:

$$r^{X}_{DAA}(t) = r^{X}_{DAA,base} \cdot Adh^{X}_{DAA}(t)$$

With intent of avoiding a dichotomous categorization of the adherence levels, which can further change in time and can be influenced by background/behaviors. As well as the efficacy per genotype specific treatment, and treatment rate per risk group.

With the mortality is expressed as follows:

$$\boldsymbol{\mu^{X,g,Adh}_{HCV}(a,t) = \mu^{g}_{HCV,base}(a) \cdot k_{HIV}(a) \cdot k_{ART-liver}(Adh_{ART})}$$

Recovered (R_{HCV}):

$$\frac{\partial R^{X,g,\text{Adh}}_{\text{HCV}}(a,t,\tau)}{\partial t} + \frac{\partial R^{X,g,\text{Adh}}_{\text{HCV}}(a,t,\tau)}{\partial a} =$$

$$r^{X}_{\text{DAA}}(t) \cdot \varepsilon^{g}_{\text{DAA}} \cdot \text{Adh}^{X}_{\text{DAA}}(t) \cdot C^{X,g,\text{Adh}}_{\text{HCV}}(a,t)$$

$$+\gamma^{X,g,\text{Adh}}(a) \cdot I^{X,g,\text{Adh}}_{\text{HCVa}}(a,t)$$

$$-\omega^{X,g}(a,t) \cdot R^{X,g,\text{Adh}}_{\text{HCV}}(a,t,\tau)$$

$$-\mu(a,t) \cdot R^{X,g,\text{Adh}}_{\text{HCV}}(a,t,\tau)$$

$$-\mu^{X,g,\text{Adh}}_{\text{HCV-R}}(a,t,\tau) \cdot R^{X,g,\text{Adh}}_{\text{HCV}}(a,t,\tau)$$

Where $\boldsymbol{\mu^{X,g,Adh}_{HCV-R}(a,t)}$ indicates the residual mortality, representing additional health risk incurred post HCV clearance, in CHCV individuals, particularly increased risk of HCC development[95].

$$\mu_{\text{HCV-R}}(a,t,\tau) = \mu_{\text{HCV,base}}(a) \cdot k_{\text{residual}}(\tau,g) \cdot k_{\text{HIV}}(a) \cdot k_{\text{ART-liver}}(\text{Adh}_{\text{ART}})$$

Where:

$$k_{\text{residual}}(\tau,g) = k_{\min} + (k_{\max} - k_{\min}) \cdot (1 - e^{-r_g \cdot \tau})$$

And:

doi:10.6342/NTU202501025

$$k_{ART-liver}(Adh_{ART}) = 1 - \varepsilon_{ART-liver} \cdot Adh_{ART}^{X}(t)$$

With intention to capture as comprehensively as possible mortality due to liver damage, a time-dependent residual risk coefficient is introduced: $k_{\text{residual}}(\tau, g)$ whereby there is consideration for the cumulative time spent in infected states: τ. Furthermore, to closer mimic the pathology, minimal residual risk and maximum residual risks, to describe for short and long-term infections are accounted for by $k_{\min}\ and\ k_{\max}$. Other factors include how quickly risk accumulates based on the genotype with r_g. Then the base mortality of HCV stratified by age: $\mu_{\text{HCV,base}}(a)$ and for the coinfection effect of HIV that accelerates liver disease: $k_{HIV}(a)$; Lastly to capture the positive effects of ART on liver outcome:

$$k_{ART-liver}(Adh_{ART})$$

It is also necessary to note how given that there is not a immunity after treatment, the individual can return to the susceptible compartment, expressed as:

$$\omega^{X,g}(a,t)$$

Susceptible with HCV History (S_2)

$$\frac{\partial S_2^{X,Adh}(a,t)}{\partial t} + \frac{\partial S_2^{X,Adh}(a,t)}{\partial a} = -\sum_g \lambda_{HCV,i}^{g}(a,t) S_2^{X,Adh}(a,t) + \sum_g \omega^{X,g}(a,t) R_{HCV}^{X,g,Adh}(a,t) - \mu(a,t) S_2^{X,Adh}(a,t) - \mu_{post-HCV}^{X,Adh}(a,t) S_2^{X,Adh}(a,t)$$

With intent of capturing the individuals who have recovered from HCV and returned to the susceptible state:

1) The rate of change over time: $\frac{\partial S_2^{X,Adh}(a,t)}{\partial t}$
2) Stratification of age: $\frac{\partial S_2^{X,Adh}(a,t)}{\partial a}$
3) Infection from HCV: $\sum_g \lambda_{HCV,i}^{g}(a,t) S_2^{X,Adh}(a,t)$
4) Recovered patients who have finished treatment: $\sum_g \omega^{X,g}(a,t) R_{HCV}^{X,g,Adh}(a,t)$
5) Background mortality: $\mu(a,t) S_2^{X,Adh}(a,t)$
6) Increased risk of mortality in view of HCV history: $\mu_{post-HCV}^{X,Adh}(a,t) S_2^{X,Adh}(a,t)$

With the intent of portraying the dynamic of post HCV liver morbidity:

$$\mu_{post-HCV}^{X,Adh}(a,t) = \mu_{HCV,base}^{g}(a) \cdot k_{residual} \cdot k_{HIV}(a) \cdot k_{ART-liver}(Adh_{ART})$$

Where:

doi:10.6342/NTU202501025

1) Base mortality stratified by age $\mu^{g}_{HCV,base}(a)$
2) Coefficient for the residual risk post HCV clearance $k_{residual}$
3) Coefficient by which HIV coinfection accelerated HCV liver disease condition $k_{HIV}(a)$
4) Protective effect of ART on liver-related morbidity and mortality $k_{ART-liver}(Adh_{ART}) = 1 - \varepsilon_{ART-liver} \cdot Adh^{X}_{ART}(t)$

There are certain caveats to the model that has been here examined, that is of the data that is required to utilize it. One example of the problematics that might be encountered lies in the tracking adherence rates.

Furthermore, in studying the effects of HCV on the liver, we are bound by time constraints, as for example HCC would usually require a decade to manifest itself. With the widespread adoption of DAAs only occurring around 10 years ago, at the time of writing, the morbidity and subsequent mortality correlated with HCV infections shall only rise from now on.

9. Proposed Model v02 – A bridging the gap, using available data

Dataset: RECUR

The study has a study population HIV-positive individuals who have achieved SVR12 following HCV treatment through either DAA or IFN, with a follow-up period of 3 years to track for HCV reinfection.

The datasets provide us with certain baseline characteristics: 3 main subgroups are identified being MSM, PWID and MSM+PWID, with numbers of individuals pertaining to each subgroup being 200, 11 and 5 respectively. Furthermore, the reinfection event observed in each subgroup: MSM = 30, PWID = 1, MSM + PWID = 0), with the time from SVR12 to reinfection for individual patients as well as if and what genotype transition occurred in reinfection.

Methods

Using as reference for what data can be currently realistically obtained, in our case the RECUR study, another model namely v02 is hereby described, in order to render the transition between V01 to V03 easier to understand.

The model is intended to track HIV/HCV coinfected individuals and reinfection of HCV in HIV patients having HCV history, the genotype transition during reinfection, treatment success, and post successful treatment mortality, indicated as post-SVR mortality.

doi:10.6342/NTU202501025

Given the small cohort present in the RECUR study, Bayesian hierarchical model is utilized for parameter estimation.

The model consists of 4 compartments:

1) **Recovered ($RHCV$)**: Individuals who were successfully treated, either through DAA or IFN from HCV.
2) **Acute HCV Infection (I_{HCVa}):** Individuals reinfected with HCV.
3) **Chronic HCV ($CHCV_g$):** Individuals who have failed to spontaneously clear HCV, present persistent HCV infection and are divided by genotype.
4) **Residual Mortality ($\mu^{post-HCV}$):** For residual mortality, adjusted for fibrosis and behavioral risk factors.

Unlike v01, there is no tracking of naïve individuals, rather all individuals present HCV history, therefore compartments S1 and S2 are eliminated. The model is still stratified by the risk-groups of MSM, PWID, and MSM/PWID with varying reinfection rates where Bayesian hierarchical modeling is applied for parameter estimation given the small subgroup sizes. Dirichlet priors are utilized to ensure transition probabilities amount to 1 when during reinfection events HCV genotype change is observed. Beta-distributed probabilities accounting for uncertainty are utilized in rendering treatment success rates as stochastic, with variation per genotype and treatment type. Lastly, post-SVR mortality is set to vary depending on fibrosis and behavioral factors, with normal priors for modeling uncertainty in excess mortality risks.

Parameters

Before we describe the Ordinary Differential Equations governing the transition between compartments, fundamental parameters to this model, and assumptions that are taken to simplify the model are discussed:

1) Reinfection probability:

Describing the reinfection of individuals present in RHCV compartment

$$P_{\text{reinfection}}(t) = 1 - e^{-\lambda^{g}_{HCV,i}(t)t}$$

Where the force of infection:

$$\lambda^{g}_{HCV,i}(t) = \beta^{g}_{\text{sex}} \cdot \beta^{g}_{\text{drug}} \cdot C_0 \cdot e^{-\gamma t} \cdot p_{\text{HCV},g} \cdot R_{\text{ART}}(t)$$

Where:

doi:10.6342/NTU202501025

1) The force of infection $\lambda_{HCV,i}^{g}(t)$ declines over time with risk reduction conferred by adherence to ART treatment.
2) The HCV genotype's prevalence in the network of contacts is accounted for by: $p_{\mathrm{HCV},g}$, ensuring HCV genotype circulation patterns in MSM/PWID tracking.
3) To account for ART adherence and interventions that have been demonstrated to mitigate high-risk behaviors over time: Behavioral risk reduction due to ART: $R_{\mathrm{ART}}(t)$ and Contact rate decline over time: $C_0 e^{-\gamma t}$.
   Having $R_{\mathrm{ART}}(t) = e^{-\delta_{\mathrm{ART}} t}$
   Where δ_{ART} is the rate of behavior reduction over time after ART initiation
   Allowing for scaling down of force of infection as adherence to ART increases.
   Assuming a piecewise function for different time periods:
   $$C_i(t) = \begin{cases} C_0, & t < T_{\mathrm{ART}}\ (\text{before ART initiation}) \\ C_0 \cdot e^{-\gamma t}, & t \geq T_{\mathrm{ART}}\ (\text{post} - \text{ART}) \end{cases}$$
   Where γ is the parameter for ART-driven behavior change rate.
   T_{ART} indicates the time of ART introduction.
   C_0 indicates the parameter for baseline contact rate before ART introduction.
4) To capture subgroup-specific reinfection dynamics, such as IDU post treatment, chemsex or traumatic anal intercourse with casual male partners: $\beta_{\mathrm{sex}}^{g} \cdot \beta_{\mathrm{drug}}^{g}$, are risk multipliers parameters for MSM and PWID respectively.

2) Genotype Transition in reinfection:

To track the acquisition through reinfection of a different HCV genotype.

$$T_{g_1 \to g_2}^{*} \sim \mathrm{Dirichlet}(\alpha)$$

Where:

1) The probability of a reinfection with genotype g2 is given by: $T_{g_1 \to g_2}$.
2) The prior counts from given reinfections are given by: α.

3) Spontaneous Clearance probability:

To describe the phenomenon of spontaneous clearance in acute HCV infection.

$$P_{\mathrm{clearance}} = p_{\mathrm{clear}}^{HIV} \times G(g) \times B_{\mathrm{MSM}}^{I_{\mathrm{MSM}}} \times B_{\mathrm{PWID}}^{I_{\mathrm{PWID}}}$$

Where:

$$p_{\mathrm{clear}}^{HIV} = p_{\mathrm{clear}}^{HIV-} \times (1 - \theta)$$

Where:

doi:10.6342/NTU202501025

1) HIV coinfection is accounted for by p_{clear}^{HIV}
2) Spontaneous clearance variance depending on genotype: $G(g)$
   With values extrapolated from the RECUR study, we define it as:

$$G(g) = \begin{cases} 1.0, & g = 3 \text{ (higher clearance)} \\ 0.8, & g = 1 \text{ (lower clearance)} \\ 0.9, & g = 2,6 \text{ (moderate clearance)} \end{cases}$$

3) Interaction of behavioral risks, for individuals presenting overlapping risk factors is accounted for by $B_{\text{MSM}}^{I_{\text{MSM}}} \times B_{\text{PWID}}^{I_{\text{PWID}}}$, which individual behavioral risk modifiers values are extrapolated from the RECUR study.

4) Successful treatment in CHCV probability:

To track the treatment of CHCV individuals.

$$P_{\text{SVR}} = \varepsilon_{\text{DAA or IFN}}^{g}$$

$$\varepsilon_{\text{DAA or IFN}}^{g} \sim \text{Beta}(\alpha, \beta)$$

Where:

1) $\alpha = \text{SVR successes} + 1.$
2) $\beta = (\text{Total Treated} - \text{SVR successes}) + 1.$

5) Residual Mortality

To describe the residual mortality the individual faces after treatment of HCV.

$$\mu_{X,g}^{\text{post-HCV}}(a,t) = k_{\text{residual}} \cdot \mu_{\text{background}}(a,t)$$

Where:

For excess mortality, $k_{\text{residual}} = k_{\text{fibrosis}} \times k_{\text{behavior}}$ defines an interaction term, allowing for the overlapping of risks in individuals who might have an advanced state of fibrosis as well as being PWID, with assumption said behavior has negative effects on the survivability, and rather than being isolated additive effects synergistic.
Where: k_{fibrosis} represents excess mortality due to fibrosis stage (F0-F2 v F3-F4) and k_{behavior} represents excess mortality due to MSM/PWID behavior.

Second Proposed ODE System

doi:10.6342/NTU202501025

To describe the population dynamics of the compartmental model, an Ordinary Differential Equation system follows:

1) Movement from the Recovered Compartment

$$\frac{dRHCV}{dt} = -P_{\text{reinfection}}(t) \cdot RHCV + P_{\text{SVR}} \cdot CHCV$$

2) Movement from the Acute HCV Infection Compartment

$$\frac{dI_{HCVa}}{dt} = P_{\text{reinfection}}(t) \cdot RHCV - P_{\text{clearance}} \cdot I_{HCVa} - P_{\text{chronic}} \cdot I_{HCVa}$$

3) Movement from the Chronic HCV Infection Compartment

$$\frac{dCHCV}{dt} = P_{\text{chronic}} \cdot I_{HCVa} - P_{\text{SVR}} \cdot CHCV$$

4) Movement from the Death Compartment

$$\frac{dD}{dt} = \mu_{X,g}^{\text{post-HCV}} \cdot RHCV$$

Collapse of Processes/States into v02/v03

Process / State detail	**Required data**	**RECUR gives…**	**⇒ Collapse into v02/v03**
Age-structured flows	Full age-at-entry and age-specific incidence	Only median age (e.g. 33 y) for reinfected cases	Drop age; treat population as "all-ages"
S_1 vs S_2 (naïve vs prior HCV)	Counts of never-infected HIV^+ vs ever-cleared	All RECUR enrollees are post-SVR12	Single "Recovered" compartment (R)
Network contact matrix $c_{ij}(a, a')$	Who-injects-with-whom / sexual-network surveys	None	Fold into a single "force of infection" $\lambda(t)$
ART adherence strata	Per-patient adherence logs	None	Model as time-decay on $\lambda(t)$ after a fixed t_{ART}
Fibrosis & cirrhosis staging	F0–F4 fibrosis scores	Not reported	Single chronic state; residual mortality μ_C
Detailed genotype compartments	≥ 8 HCV genotypes	Baseline + reinfection genotypes (subtype calls)	Two macro-classes: "1" vs "others" (q_1, q_2)
Residual immunity dynamics $\omega_{(g)}$	Long-term immunoprotection assays	Not measured	Omit entirely

Table 4, Summary of simplifications apported by V02 from V03

10. On the applications of this model and Proposal of ModelV03

Distinguishing itself from ModelV01, V02 is designed with an approach that better reflects parsimony and is specifically built to work with RECUR's study reported data.

doi:10.6342/NTU202501025

This will be the principal model of this thesis. V03 will be thoroughly explained, beginning with the compartmentalization, ODE system, parameters and parameterization and ending with a R script pseudocode. With execution of the program and reporting of the results, sensitivity analysis is also performed. Sobol's indices, PRCC as well as local sensitivity analysis for simulations.

To demonstrate the robustness of V03, V03E and V03D are also produced. Where with V03 we find the core of this research project, V03E is provided as argument to the plasticity and generalizability of the model through a different dataset: EuroSIDA. V03D instead is an alternative model compartmentalization in argument of structure's robustness. Given that death is often not an output of interest in studies of Hepatitis C infections and reinfection spanning over a relative short amount of time, such as RECUR's follow up time of 3 years and EuroSIDA's follow up of 2 years. Further argument is then further reinforced by the sensitivity analysis results performed for V03.

Methods

As explained in the preface to this model introduction, when we utilize the RECUR study to parameterize, given the large disparity of individuals representing the subgroups as well as the reinfection events observed. While methods such as Bayesian Hierarchical models help to better represent the uncertainty, the model is bound to have limitation derived from the lack of quantity of data.

An example is that of mortality, while the study mentions liver-related morbidity and mortality of untreated HCV infections, it was not an outcome of interest and was not measured or analyzed. Therefore, assumptions are adopted, and the model is further simplified.

doi:10.6342/NTU202501025

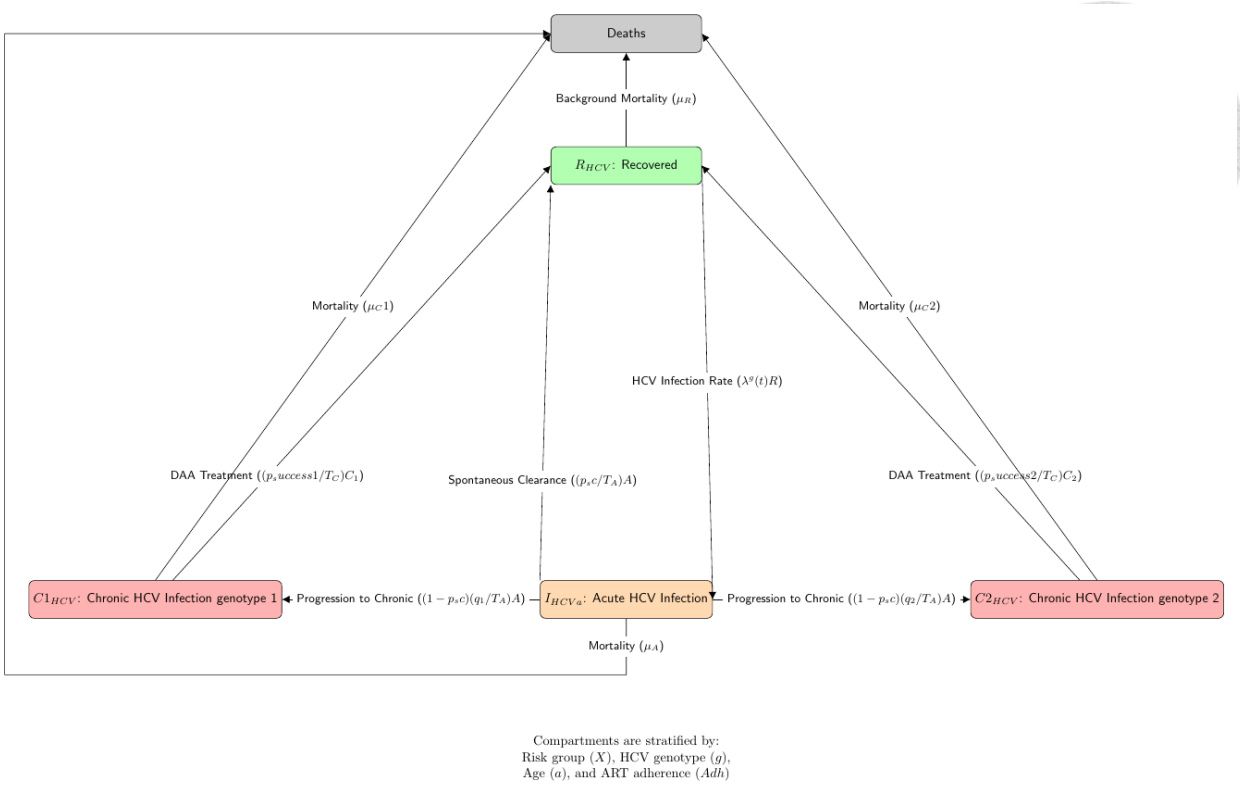


Figure 4, Flowchart Diagram of Compartmental Model v03

Third Proposed Compartments and ODE System

The **force of infection**, $\lambda(t)$, is defined as a piecewise function to account for behavioral change after ART initiation:

$$\lambda(t) = \begin{cases} \lambda_0, & \text{if } t < t_{ART} \\ \lambda_0\, e^{-r_{art}\,(t-t_{ART})}, & \text{if } t \geq t_{ART} \end{cases}$$

Where:

$$\lambda_0[g] = \lambda_{\text{base}} \times \beta[g]$$

Is the group-specific reinfection force in our hierarchical compartmental model.

Where:

1. λ_{base} is the baseline reinfection force common to all groups,
2. $\beta[g]$ is the behavioral risk multiplier for group g (e.g., MSM, PWID, MSM+PWID), with priors informed by behavioral data.

doi:10.6342/NTU202501025

1. **Recovered (R):**
   Individuals who are successfully treated (or who have spontaneously cleared an acute infection). They can lose individuals due to reinfection, but they also gain individuals from spontaneous clearance (from the acute phase) and from successful treatment of chronic infection.

$$\frac{dR}{dt} = -\lambda(t)\,R + \frac{p_{\text{success1}}}{T_C}\,C_1 + \frac{p_{\text{success2}}}{T_C}\,C_2 + \frac{p_{sc}}{T_A}\,A - \mu_R\,R$$

   Where:

   1) $\lambda(t)$: is the force of infection
   2) $\frac{p_{\text{success1}}}{T_C}\,C_1$ and $\frac{p_{\text{success2}}}{T_C}\,C_2$ represent the flow of the chronic compartments C1 and C2 back to R.
   3) T_C: is the average duration of the chronic state and T_A is the average duration of acute state
   4) p_{success} the treatment success probability
   5) $\frac{p_{sc}}{T_A}\,A$: represents the flow of individuals who spontaneously clear the acute HCV infection and return to R.
   6) μ_R: background mortality rate

2. **Acute Infection (A):**
   New reinfections move individuals from R into A. They exit A either by spontaneous clearance (with probability p_{sc}) or by progressing to chronic infection (with probability $1 - p_{sc}$). There is also an associated mortality.

$$\frac{dA}{dt} = \lambda(t)\,R - \frac{1}{T_A}\,A - \mu_A\,A$$

3. **Chronic Infection, Genotype 1 (C_1):**
   At the end of the acute phase, a fraction $(1 - p_{sc})$ of individuals progresses into chronic infection. A proportion q_1 of these are assigned to genotype 1. They can then be successfully treated (moving back to R) or experience mortality.

$$\frac{dC_1}{dt} = (1 - p_{sc})\,\frac{q_1}{T_A}\,A - \frac{p_{\text{success1}}}{T_C}\,C_1 - \mu_C\,C_1$$

4. **Chronic Infection, Genotype 2 (C_2):**
   Similarly, a fraction q_2 (with $q_1 + q_2 = 1$) of those progressing from the acute phase become chronic with genotype 2.

doi:10.6342/NTU202501025

$$\frac{dC_2}{dt} = (1 - p_{sc})\,\frac{q_2}{T_A}\,A - \frac{p_{\text{success2}}}{T_C}\,C_2 - \mu_C\,C_2$$

5. **Death (D):**
   This compartment accumulates deaths occurring in the other compartments.

$$\frac{dD}{dt} = \mu_R\,R + \mu_A\,A + \mu_C\,(C_1 + C_2)$$

Where deaths from the various compartments are summed, each having their respective mortality rate.

Dynamics of reinfection, acute HCV infection resolution to either spontaneous clearing or progression to CHCV, treatment success and mortality captured through this ODE system.

Of the assumptions and simplifications taken for this model, it is to be noted that Genotype transition has been simplified to either Genotype 1 or all other genotypes, indicated as Genotype 2.

Parameters and Parameterization

This section is meant to explain how each parameter was obtained or estimated.

- **Force of Infection:**
  - λ_{base} **(Baseline Force of Infection):** estimated from the RECUR study's observed reinfections using a gamma prior centered around 0.04 per year. With assumption that $\lambda_{\text{base}} \sim \text{Gamma}(2,50)$, giving a mean of 0.04 per year, aligning with reported incidence rates of ~4 per 100 PYFU.
  - $\boldsymbol{\beta[g]}$ **(Risk Multipliers for each group** $\boldsymbol{g}$**):** are estimated via Bayesian inference using hierarchical priors informed by behavioral data from the MOSAIC-HIV risck score study, in combination with the RECUR study.
    - **For MSM (group 1):** Lognormal prior centered at **1.0** (baseline risk).
    - **For PWID (group 2):** Lognormal prior centered at **1.3** (higher risk due to injection drug use).
    - **or MSM+PWID (group 3):** Lognormal prior centered at **1.6**, reflecting potential synergistic risk effects.
    - The priors are set as:$\beta[1] \sim \text{Lognormal}(\log(1.0),0.1)\beta[2] \sim \text{Lognormal}(\log(1.3),0.5)\beta[3] \sim \text{Lognormal}(\log(1.6),0.7)$
    - Therefore, through these priors, we allow the model to estimate each risk group's force of infection while incorporating prior knowledge.

doi:10.6342/NTU202501025

- $\lambda_0[g]$ **(Subgroup-Specific Force of Infection):**
  - Inferred indirectly through Bayesian inference
  - Through computation of estimated parameters: $\lambda_0[g] = \lambda_{\text{base}} \times \beta[g]$

- **Acute Infection**
  - p_{sc} **(Spontaneous Clearance Probability in Acute Phase)**
    - Estimated from prior literature: with clearance rate between 20-30% in HIV+ MSM
    - Therefore, assumption is made with $p_{sc} \sim \text{Beta}(2,6)$ (mean ~25%).
  - T_A **(Duration of Acute Phase in Years):**
    - Estimated from prior literature: acute infection duration as 4–6 months.
    - Therefore, assumption is made with $T_A \sim \text{Normal}(0.5,0.1)$ (mean = 0.5 years)
- **Chronic Infection**
  - $q[1], q[2]$ **(Genotype Transition Probabilities):**
    - Estimated from HCV genotyper distribution in HIV+MSM in RECUR and MOSAIC-HIV
    - Defined as a Dirichlet prior, ensuring that:
      - $q[1] + q[2] = 1$
      - $q \sim \text{Dirichlet}(1,1)$, permitting flexibility
  - $p_{\text{success1}}, p_{\text{success2}}$ **(Treatment Success Probabilities):**
    - ***Estimated from prior literature*: *RECUR and published DAA efficacy***
      - With 95-98% success rate
      - Therefore, we assume that: $p_{\text{success1}}, p_{\text{success2}} \sim \text{Beta}(95,5)$.
  - T_C **(Duration in Chronic Phase Before Treatment):**
    - ***Estimated from prior lierature*: *treatment data in RECUR study***
      - With mean of 1 year
      - Modeled as: $T_C \sim \text{Normal}(1,0.2)$,
- **Mortality**
  - μ_R **(Mortality Rate in Recovered Compartment):**
    - ***Estimated from prior literature*: *RECUR general mortality rates***
    - Mean ~2% per year:$\mu_R \sim \text{Normal}(0.02,0.01)$
  - μ_A **(Mortality Rate in Acute HCV):**
    - Estimated from acute HCV mortality
    - Mean ~2% per year:$\mu_A \sim \text{Normal}(0.02,0.01)$
  - μ_C **(Mortality Rate in Chronic HCV):**
    - Estimated from long-term HCV-related mortality data
    - Mean ~3% per year:$\mu_C \sim \text{Normal}(0.03,0.01)$
- **Behavioral Change**

doi:10.6342/NTU202501025

- r_{art} **(Rate of Behavior Change After ART):**
  - $\boldsymbol{Estimated\ from\ prior\ literature\ assumption}$
  - Estimated as 5% per year, reflecting studies showing risk reduction over time: $r_{art} \sim \text{Normal}(0.05, 0.02)$
- t_{ART} **(Time of ART-Driven Behavior Change Onset):**
  - Estimated from prior literature: RECUR and MOSAIC studies on behavior change post AR
  - Mean = 2 years: $t_{ART} \sim \text{Normal}(2, 0.5)$

- **Binomial Likelihood Aggregated Data**
  - $N[g]$ **(Baseline Population Per Group):**
    - $\boldsymbol{Estimated\ from\ prior\ literature}$: $\boldsymbol{RECUR}$
    - MSM = 200, PWID = 11, MSM+PWID = 5.
  - $Y[g]$ **(Observed Reinfections Per Group):**
    - Estimated from prior literature: RECUR
    - MSM = 30, PWID = 1, MSM+PWID = 0.
  - T_{end} **(Follow-Up Duration):**
    - $\boldsymbol{From\ RECUR\ study\ follow-up\ time}$**: 3 years**

doi:10.6342/NTU202501025

Model v03 Parameters and Data Comparison

Parameter	Role in v03	RECUR provides...	Estimable?	Action & Justification
λ_0	Baseline annual reinfection hazard	Total reinfections = 31 among $N_{\text{MSM}} + N_{\text{PWID}} + N_{\text{MSM+PWID}} = 216$ over 3 yr (Supplementary Table)	Yes	Fit a Poisson/Binomial hazard: $31 \approx \text{Binomial}(216, 1 - e^{-3\lambda_0\bar{\beta}})$. This pins down $\lambda_0\bar{\beta}$.
β_g (g=MSM, PWID, MSM+PWID)	Group-specific risk multipliers	Reinf./N: MSM 30/200; PWID 1/11; MSM+PWID 0/5 (Supplementary Table)	Yes, but with wide CI	Estimate relative hazards β_g via a hierarchical Binomial model. Small n in PWID subgroups → large posterior uncertainty, but identifiable.
r_{ART}	Rate at which reinfection hazard decays post-ART	No data on individual ART adherence timing	No	Fix from literature (e.g. behavioral-risk reduction ~5%/yr after ART) or drop the decay and treat λ constant.
t_{ART}	Calendar time of ART's risk-reduction onset	No per-patient ART-start dates; only SVR dates	No	Fix to year DAA became widely available in Taiwan (e.g. 2015 or 2017) or omit: fit constant λ.
p_{sc}	Acute spontaneous clearance probability	RECUR records reinfections only—no "acute only" clears	No	Fix to meta-analysis value ($\approx 25\%$) (Supplementary Table).
T_A	Duration of acute phase	No serial HCV-RNA sampling to pin down phase length	No	Fix to literature (≈ 0.5 yr). Collapse $I_a \to C$ flows into exit rate $1/T_A$.
q_1, q_2	Reinfection genotype split (1 vs "other")	Each reinfected patient's pre-/post-GT (31 cases) (Supplementary Table)	Yes	Count transitions (e.g. $1 \to 2$ occurred x times); estimate via Dirichlet posterior on those 31 events.
p_{SVR_1}, p_{SVR_2}	SVR probability on retreatment (chronic C_1/C_2)	RECUR does not report retreatment outcomes	No	Drop second-line retreatment from model (only model first reinfection).
T_C	Time from chronic reinfection to retreatment	No data on "time to retreatment"	No	Omit or fix to plausible value (e.g. 0.33 yr = 4 mo). In v03 we allow $C \to R$ via p_{SVR} without explicit wait.
μ_R, μ_A, μ_C	Mortality in R, A, and C	Follow-up too short (no recorded deaths)	No	Collapse into single "death bucket" or set all $\mu = 0$ over 3 yr (negligible bias).
ω	Rate $R \to S_2$ (loss of post-SVR immunity)	No measure of waning immunity	No	Omit—reinfection goes straight $R \to A$ via λ, no S_2 in v03.

Table 5, Model V03 Parameters and parameterization

doi:10.6342/NTU202501025

Practical Implementation: R script Pseudocode

Here follows the R script, in pseudocode format, for the above-mentioned ModelV03

1. **Load Required Libraries**
    - (Optionally) Install packages (commented out):
        - ggplot2, rstan, deSolve
    - **Load libraries:**
        - Load the library for solving ODEs.
        - Load the library for Bayesian inference using Stan.
        - Load the library for plotting.
2. **Define the ODE Model Function (hcv_model)**
    - **Function Signature:** hcv_model(time, state, parameters)
    - **Inside the function:**
        - Convert the input state and parameters into individual variables.
        - **Computing the Force of Infection (lambda):**
            - ♣ If the current time is less than the ART initiation time (t_ART):
                - Set lambda equal to the baseline force of infection (lambda0).
            - ♣ Else (time ≥ t_ART):
                - Set lambda equal to lambda0 multiplied by an exponential decay factor (using the behavior change rate r_art and time since ART began).
        - **Compute the Derivatives for Each Compartment:**
            - ♣ **Recovered (R):**
                - Decrease due to reinfection: subtract lambda * R.
                - Increase due to successful treatment from two chronic compartments: add (p_success1/T_C) * C1 and (p_success2/T_C) * C2.

doi:10.6342/NTU202501025

- Increase from spontaneous clearance from the acute compartment: add `(p_sc/T_A) * A`.
- Decrease due to mortality in the recovered compartment: subtract `mu_R * R`.

♣ **Acute (A):**

- Increase due to new reinfections: add `lambda * R`.
- Decrease due to progression out of acute phase: subtract `(1/T_A) * A`.
- Decrease due to acute mortality: subtract `mu_A * A`.

♣ **Chronic (C1 and C2):**

- For each chronic compartment:
- A fraction `(1 - p_sc)` of the acute cases progress to chronic state.
- They are divided into genotype groups by multiplying by either `q1` or `q2` and dividing by `T_A`.
- They then decrease due to treatment success and mortality.
- **C1:** Subtract `(p_success1/T_C) * C1` and `mu_C * C1`.
- **C2:** Subtract `(p_success2/T_C) * C2` and `mu_C * C2`.

♣ **Death (D):**

- Accumulate deaths from all compartments:
- Add `mu_R * R`, `mu_A * A`, and `mu_C * (C1 + C2)`.

- **Return:** A list containing the derivatives `[dR, dA, dC1, dC2, dD]`.

3. **Define Aggregated RECUR Data**
   - Set the number of risk groups: `G = 3`
   - Create a vector for the baseline counts per group: `N_vec = [200, 11, 5]`
   - Create a vector for the observed reinfection counts: `Y_vec = [30, 1, 0]`

doi:10.6342/NTU202501025

- Set the follow-up period (in years): `T_end = 3.0`

4. **Define Common Model Parameters and Initial Conditions**
   - Create a list (or vector) named `common_params` containing:
     - `r_art = 0.05` # Behavior change rate due to ART (per year)
     - `t_ART = 2` # Time when ART effect begins (years)
     - `p_sc = 0.25` # Spontaneous clearance probability in the acute phase
     - `T_A = 0.5` # Duration of the acute phase (years)
     - `q1 = 0.49` # Genotype transition probability for genotype 1
     - `q2 = 0.51` # Genotype transition probability for genotype 2 (q1 + q2 = 1)
     - `p_success1 = 0.95` # Treatment success probability for chronic genotype 1
     - `p_success2 = 0.95` # Treatment success probability for chronic genotype 2
     - `T_C = 1` # Duration in chronic phase before treatment (years)
     - `mu_R = 0.02` # Mortality rate in the recovered compartment
     - `mu_A = 0.02` # Mortality rate in the acute compartment
     - `mu_C = 0.03` # Mortality rate in the chronic compartments
5. **Define the Stan Model Code (as a Multiline String)**
   - **Stan Code Structure:**
     - **Functions Block:**
       - ♣ Define an ODE function (`hcv_ode`) that:
         - Unpacks the state variables: R, A, C1, C2, D.
         - Unpacks the model parameters from a vector `theta` (including `lambda0`, `r_art`, `t_ART`, etc.).
         - Computes `lambda` using the same piecewise condition as in the R function.
         - Computes the derivatives (`dR`, `dA`, `dC1`, `dC2`, `dD`) as in the R function.
         - Returns the vector of derivatives.

doi:10.6342/NTU202501025

- **Data Block:**
  - ♣ Declare:
    - The number of risk groups G.
    - Integer arrays N (baseline counts) and Y (observed reinfections) for each group.
    - The follow-up time T_end.
- **Parameters Block:**
  - ♣ Declare parameters to be estimated:
    - A baseline force lambda_base.
    - A vector beta of risk multipliers (one per group).
    - Common parameters: r_art, t_ART, p_sc, T_A, a simplex q (for genotype probabilities), p_success1, p_success2, T_C, mu_R, mu_A, and mu_C.
- **Transformed Parameters Block:**
  - ♣ For each risk group (loop over g from 1 to G):
    - Compute group-specific lambda0 as lambda_base * beta[g].
    - Store all 13 parameters for that group in a row of a matrix theta (each element corresponds to a parameter used in the ODE function).
- **Model Block:**
  - ♣ **Specify Priors:**
    - Set a Gamma prior on lambda_base (mean ~0.04).
    - Set lognormal priors for each group's risk multiplier beta (with different centers and uncertainties based on external behavioral data).
    - Set normal, beta, and Dirichlet priors on the other common parameters (with values informed by literature or study data).

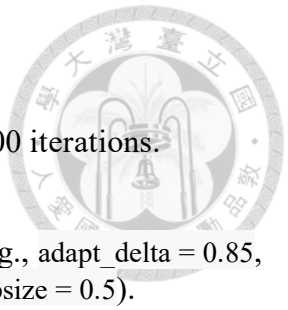
doi:10.6342/NTU202501025

- ♣ **Likelihood:**
  - For each group:
  - Define an initial state vector `y_init` with all individuals in the recovered compartment (first element equals `N[g]`) and zeros elsewhere.
  - Use an ODE solver (`integrate_ode_rk45`) to simulate the model from time `0` to `T_end` using the group-specific parameter vector `theta[g]`.
  - Compute the cumulative probability of reinfection `p_reinf` as `1 - (predicted_R / N[g])`.
  - Model the observed number of reinfections `Y[g]` as a binomial outcome with size `N[g]` and probability `p_reinf`.

- **Generated Quantities Block:**
  - ♣ For each group, re-calculate the cumulative reinfection probability (denoted as `p_reinf_pred`) using the same ODE integration.

6. **Compile the Stan Model**
   - Use the Stan function (e.g., `stan_model()`) to compile the Stan code stored in the string.
7. **Prepare Data for Bayesian Fitting**
   - Create a list (or dictionary) named `stan_data` that includes:
     - The number of groups `G`.
     - The baseline counts `N` (from `N_vec`).
     - The observed reinfections `Y` (from `Y_vec`).
     - The follow-up duration `T_end`.
8. **Run Bayesian Sampling Using rstan**
   - Call the `sampling()` function on the compiled Stan model with:
     - The prepared `stan_data`.
     - Sampling settings such as:

doi:10.6342/NTU202501025



- ♣ 2000 iterations.
- ♣ 4 chains.
- ♣ A warmup period of 500 iterations.
- ♣ Thinning factor of 1.
- ♣ Control parameters (e.g., adapt_delta = 0.85, max_treedepth = 10, stepsize = 0.5).

- Store the fitted model output in a variable (e.g., fit).

9. **Print Summary of Key Parameters**

   - Print the summary of the fitted model, displaying key parameters including:
     - lambda_base, beta, the computed group-specific lambda0, r_art, t_ART, p_sc, T_A, q, p_success1, p_success2, T_C, mu_R, mu_A, mu_C, and the predicted cumulative reinfection probabilities p_reinf_pred.

10. **Posterior Predictive Checks**

    - **Extract Posterior Samples:**
      - Extract the posterior samples from the fitted Stan model.
      - Specifically, extract the samples for p_reinf_pred, which has dimensions (iterations x number of groups).
    - **Compute Summary Statistics for Each Group:**
      - For each risk group:
        - ♣ Compute the mean predicted reinfection probability.
        - ♣ Compute the 2.5% (lower) and 97.5% (upper) quantiles (forming a 95% credible interval).
      - Compute the observed reinfection proportions by dividing Y_vec by N_vec.

END SCRIPT

doi:10.6342/NTU202501025

Alternative Dataset: EuroSIDA study[96], Model V03E

EuroSIDA study being a prospective observational cohort study following PLHIV[96]. With patients coming from over from 39 countries across Europe as well as Isreal and Argentina and with 118 collaborating clinics[96]. The database has data of over 24000 individuals with annual collection of among other characterizing information: hepatitis C treatment alongside dates of start and stop, serology, virology as well as fibrosis of liver[96].

Utilizing Amele et al. (2021) "HCV reinfection after HCV therapy among HIV/HCV-coinfected individuals in Europe" study where individuals were recruited from the EuroSIDA cohort with particular interest to individuals presenting the characteristic of being already once successfully treated from HCV. Which is defined as having achieved SVR, after treatment from either IFN-based or DAA-based drugs. And with having at least one HCV-RNA positive results in the next 24 months, which is the follow-up duration. The total number of participants fitting these criteria out of the, at the time of writing 23 005 PLHIV, 1022[96].

Of interest is that the study reports no significant odds of reinfection differentiation in between PWID v MSM[96]. For this reason, we reparametrize our model with data from this study.

Therefore, here is presented a calibration of ModelV03 as ModelV03E utilizing EuroSIDA data.

```
// Set up EuroSIDA aggregated data

SET G = 3  // Number of risk groups

SET N_vec = [272, 531, 219]  // Number of individuals per group

SET Y_vec = [20, 39, 16]  // Observed reinfections per group

SET T_end = 2  // Follow-up time in years
```

Given that ModelV03E is just a reparameterization of ModelV03, and that a detailed explanation of the pseudocode is present in the original ModelV03, the modified ModelV03E, only the altered section is rendered explicit.

Again, 3 risk groups are defined based on transmission mode: Group 1 = MSM (272 individuals), Group 2= PWID (531 individuals) and Group 3 = Other (219 individuals), indicating possible overlap or other routes. With reinfections observed

doi:10.6342/NTU202501025

However, the dataset required to be manipulated in order to be used with aforementioned model, with extraction of individuals (N) in each risk group as well as computed/estimating the reinfection events (Y) observed in the follow up time set at 2 years(24 months) per EuroSIDA[96].

Having observed in Modelv03 higher reinfection in MSM against the other groups, the data in the EuroSIDA study has instead a more uniform rate across the subpopulation. Therefore, the model's posterior are expected to reflect a moderate baseline force of infection and modest group multipliers.

Alternative Compartmentalization, Model V03D (Deathless)

In lieu of what the sensitivity analysis will bring forward, that will be explained in the next chapter, a compartmental model of V03, without death is here described.

Given that the change to the equations is trivial, and that in terms of code, simply setting all parameters of death to 0 in the model's R script is sufficient to apport the changes. Herein V03D will be directly presented with its compartmental flowchart diagram.

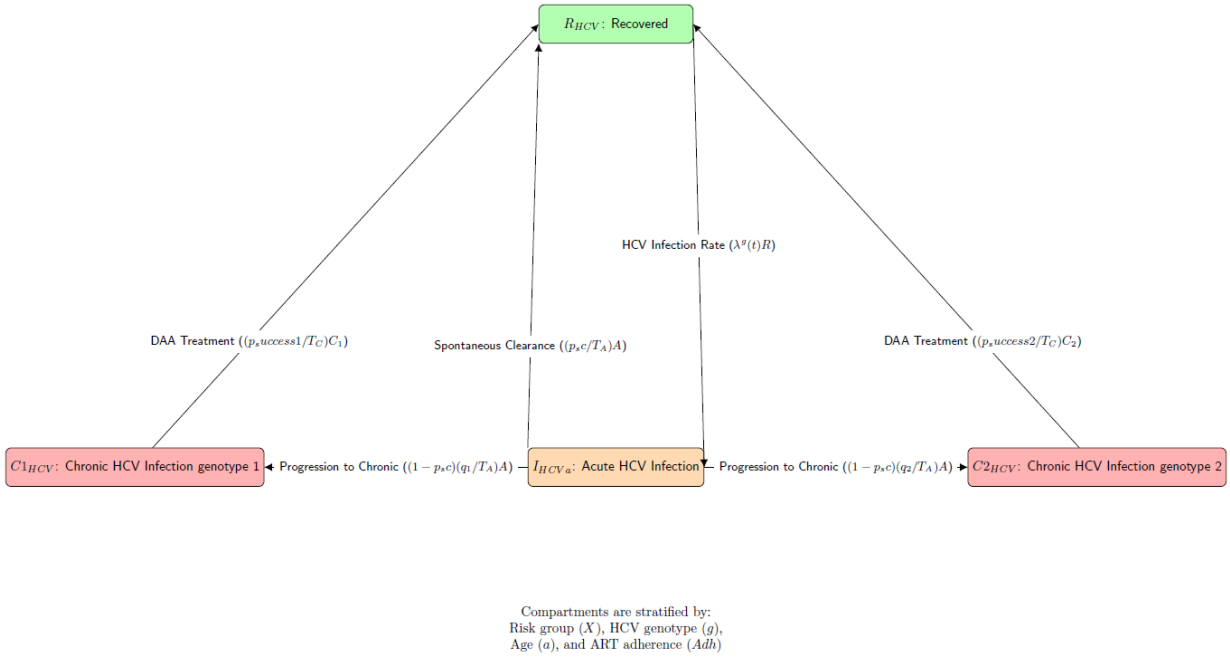


Figure 5, Flowchart Diagram of Alternative Compartmentalization

doi:10.6342/NTU202501025

11. Results:

V03 Results

1) Bayesian Parameter Estimation Results:

Table 3: Force of Infection Estimates

Group	λ_0 Mean	95% CI Lower	95% CI Upper
MSM	0.0536	0.0108	0.1121
PWID	0.0681	0.0103	0.1865
MSM+PWID	0.0805	0.0102	0.2568

Table 6: Bayesian Parameter Estimation with Convergence Diagnostics

Table n*, summarizes the force of infection estimates, with MSM+PWID having the highest value at 0.0805, with CI between 0.0102 and 0.2568. PWID follows with 0.0681 and CI between 0.0103 and 0.1865. MSM then with 0.0536 and CI between 0.0108 and 0.1121.

Table 1: Bayesian Parameter Estimates with Convergence Diagnostics and Disease Progression Parameters

Parameter	Role	Mean	SD	2.5%	50%	97.5%	n_{eff}	Rhat
λ_{base}	Baseline reinfection force	0.05	0.03	0.01	0.05	0.11	3617	1.00
β_1 (MSM)	Risk multiplier (MSM)	1.02	0.10	0.83	1.02	1.24	7205	1.00
β_2 (PWID)	Risk multiplier (PWID)	1.33	0.65	0.46	1.19	2.98	6496	1.00
β_3 (MSM+PWID)	Risk multiplier (MSM+PWID)	1.60	1.15	0.36	1.31	4.64	5545	1.00
r_{art}	ART behavior change rate	0.05	0.02	0.01	0.05	0.09	3118	1.00
t_{ART}	ART behavior change onset	2.00	0.50	1.03	2.00	2.98	5045	1.00
p_{sc}	Acute clearance probability	0.24	0.14	0.03	0.22	0.55	6736	1.00
T_A	Duration of acute phase	0.51	0.10	0.32	0.51	0.70	6804	1.00
q_1	Proportion to Genotype 1	0.50	0.29	0.03	0.50	0.98	7955	1.00
q_2	Proportion to Genotype 2	0.50	0.29	0.02	0.50	0.97	7955	1.00
$p_{success1}$	Treatment success (Gen.1)	0.95	0.02	0.90	0.95	0.98	6547	1.00
$p_{success2}$	Treatment success (Gen.2)	0.95	0.02	0.90	0.95	0.98	7269	1.00
T_C	Duration in chronic phase	1.01	0.19	0.64	1.01	1.39	5348	1.00
μ_R	Mortality in Recovered	0.03	0.01	0.01	0.03	0.04	2729	1.00
μ_A	Mortality in Acute	0.02	0.01	0.00	0.02	0.04	3834	1.00
μ_C	Mortality in Chronic	0.03	0.01	0.01	0.03	0.05	5855	1.00

Table n* summarizes the Bayesian parameters estimates as well as the convergence diagnostics. Given that Rhat>1.00 and high effective sample size, chain mixing chain mixing and convergence is deemed more than acceptable. The table also provides the posterior mean and CI for the model's parameters.

The baseline reinfection probability has mean value of 0.05 indicating a 5% baseline annual reinfection probability. A baseline value that is multiplied by a risk factor, namely risk multiplier

doi:10.6342/NTU202501025

of the groups of interest. With *MSM+PWID* holding the highest value at 1.60 mean, followed by 1.33 for *PWID* and 1.02 for *MSM*. r_art is found at 0.05 mean value, indicating the change rate of risk behavior at t_ART which is after 2 years in average. Q1 and Q2 are the proportions of genotypes, namely genotype 1 as Q1 and all other genotypes as Q2, and both have 0.50 as average value. The treatment success rate is high for both genotypes at 95%, namely p1 and p2. Duration of chronic phase, or time before treatment in chronic, is at median duration of 1 year and mortality parameters sit at 3% for recovered and chronic compartments and 2% for acute compartment.

doi:10.6342/NTU202501025

2) Sensitivity Analysis

a. Global Sensitivity Analysis: Sobol's Sensitivity Analysis

To ascertain the performance in terms of robustness of ModelV03, to further probe the effects of the variables on the outputs of our model, globalized sensitivity analysis is performed for the 3 groups of interest: *MSM*, *PWID* and *MSM+PWID*.

Sobol's Sensitivity Indices plots follow.

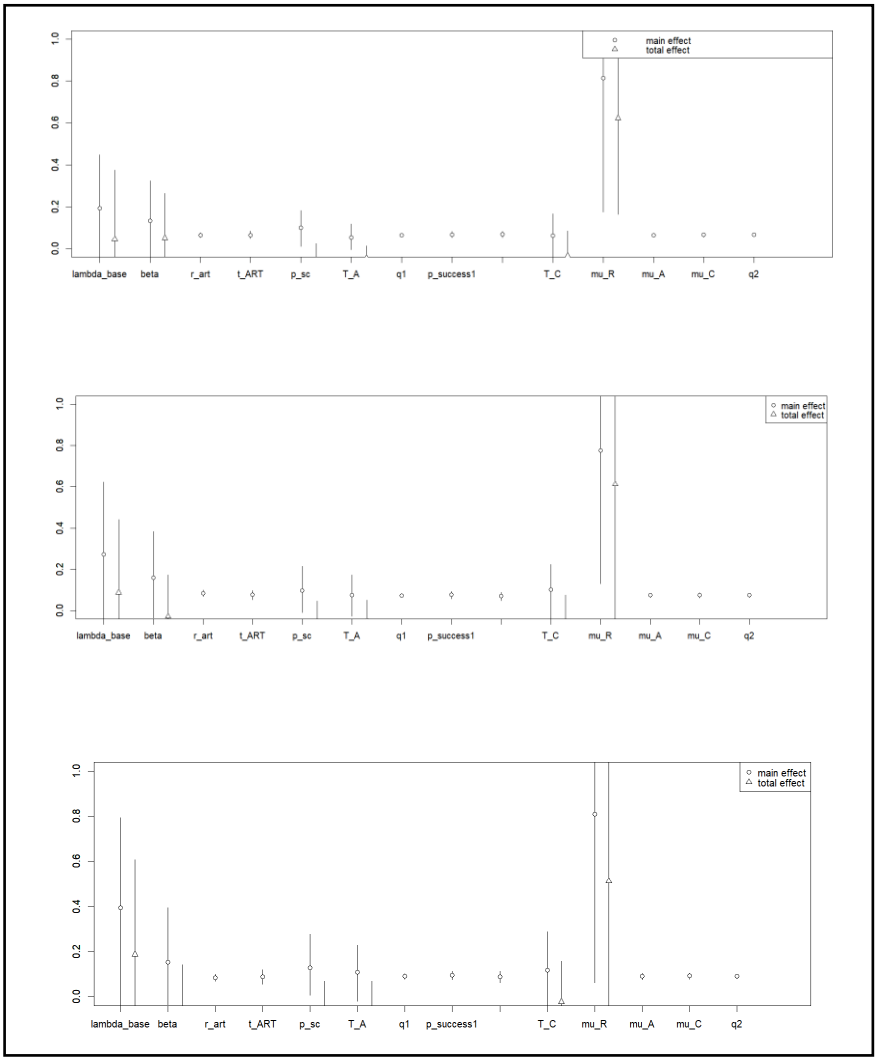


Figure 6, Sobol's Sensitivity Indices for MSM, PWID and MSM+PWID

Calculation that was operated through reparameterization analysis by treating the baseline force of infection and the risk multipliers as separate parameters: with *lambda = lambda_base x beta*. With beta assuming different values per group as described in the section treating ModelV03.

doi:10.6342/NTU202501025

In all groups, regardless of the small variation, the parameters which determine the most output variance: reinfection, is determined by mortality rate in the recovered compartment (*mu_R*): [0.830, 0.738, 0.773], ; baseline force of infection(*lambda_base*)= [0.213, 0.229, 0.371] , and the group's risk multiplier (beta) = [0.137, 0.135, 0.158].

b. Global Sensitivity Analysis: Partial Rank Correlation Coefficients Analysis

The findings from Sobol's are supported by PRCC, but also give insight in other parameters to be studied. Such as time in chronic phase before treatment (T_C), t_ART and r_ART (access to treatment procedures and subsequent change of behavior).

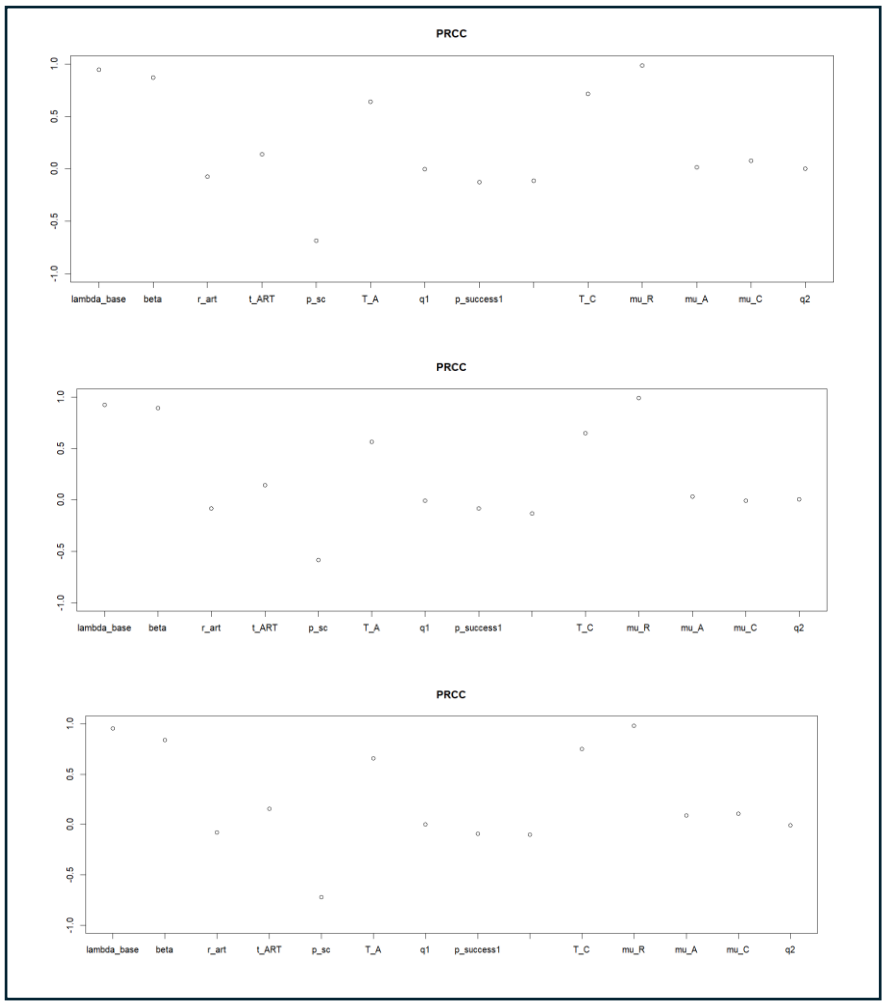


Figure 7, PRCC for MSM, PWID and MSM+PWID

doi:10.6342/NTU202501025

c) Local Sensitivity Analysis

To understand the effect of a parameter to the reinfection, local sensitivity analysis through the perturbation of the parameters value was performed to analyze possible scenarios.

Altering t_ART, with reduction to 1 year from 2 years as “Early ART”. T_C reduced from 1 year to 0.75 years and 0.5 years as “Faster Treatment”. As well as a combined effect of Early ART and Faster Treatment. Early ART + Faster Treatment 2 (T_C = 0.5 years), results in the greatest reduction of reinfection probability in all groups, 12% to 13.2% reduction compared to baseline. Followed closely by T_C = 0.5 years, 10.8% to 11.9%. A noticeable gap is then observed from T_C = 0.5 years and Early ART + Faster Treatment 1 (T_C = 0.75 years), 6.4% to 7.1%. Again, followed closely by T_C = 0.75 years, 5.1% to 5.6%. While Early ART, influences 1.5% to 1.6%.

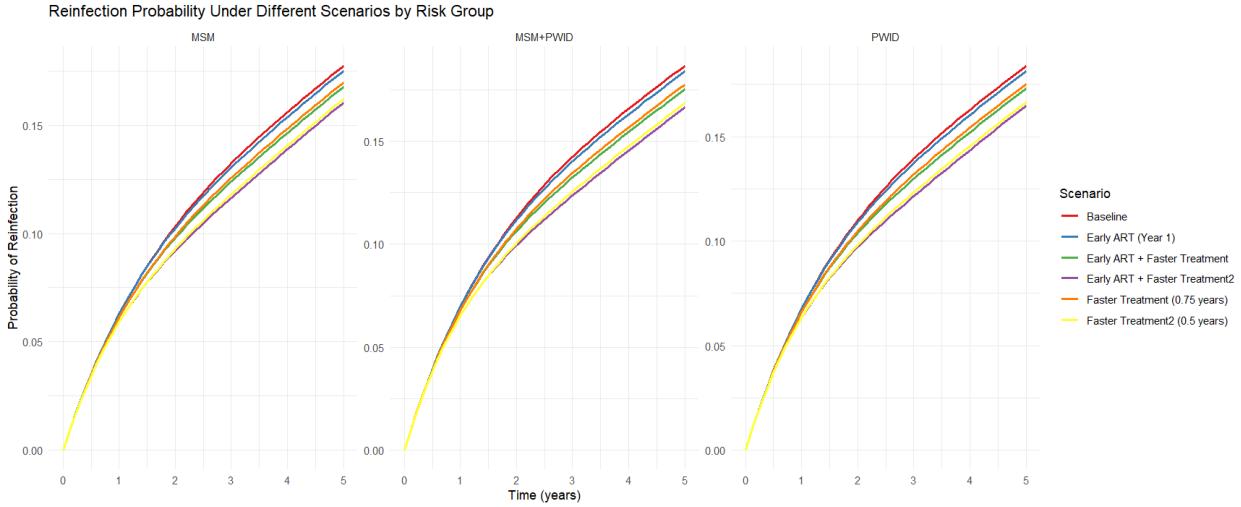


Figure 8, Local Sensitivity Analysis

doi:10.6342/NTU202501025

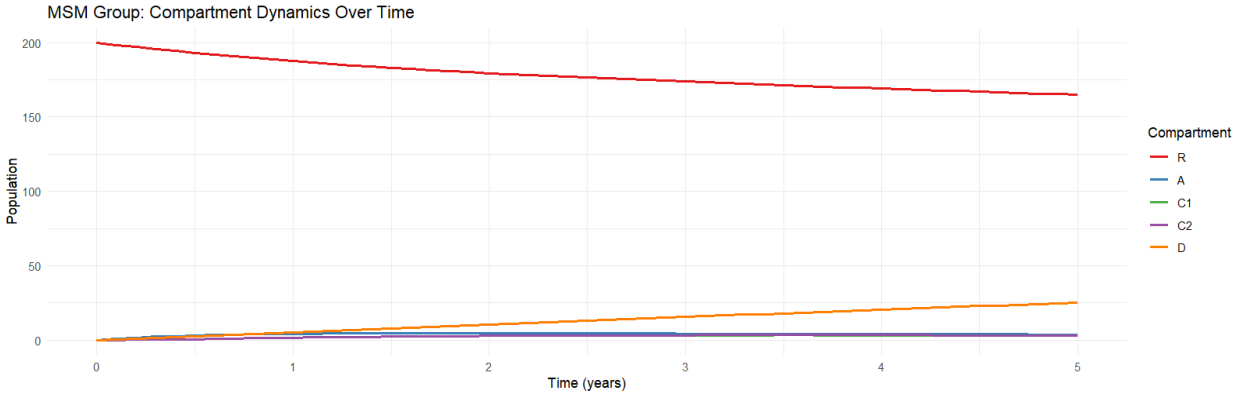
Three-year Reinfection Probability and Relative Reduction by Scenario and Group

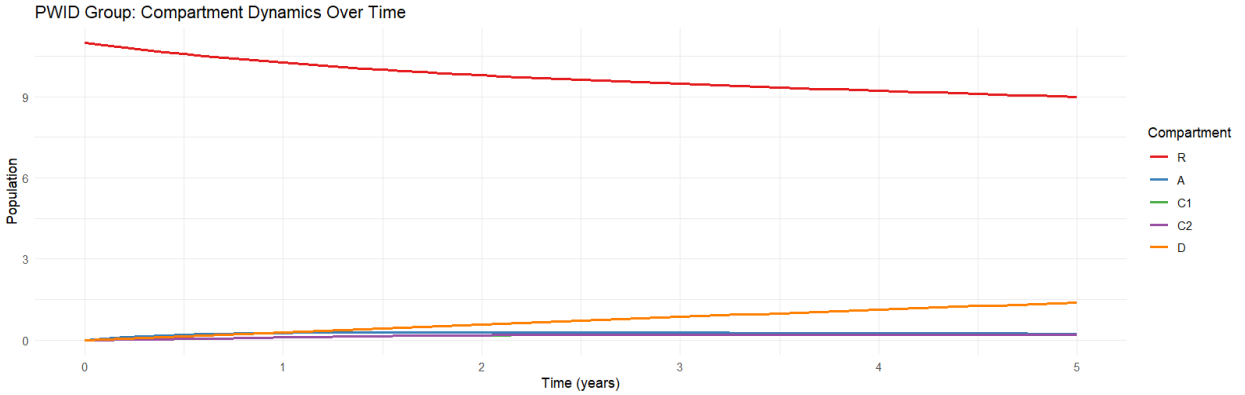
Group	Scenario	ReinfProb_3yr	Relative Reduction (%)
MSM	Baseline	0.132	0.0
MSM	Early ART (Year 1)	0.130	1.5
MSM	Faster Treatment (0.75 years)	0.126	5.1
MSM	Faster Treatment2 (0.5 years)	0.118	10.8
MSM	Early ART + Faster Treatment	0.124	6.4
MSM	Early ART + Faster Treatment2	0.116	12.0
PWID	Baseline	0.139	0.0
PWID	Early ART (Year 1)	0.137	1.6
PWID	Faster Treatment (0.75 years)	0.132	5.4
PWID	Faster Treatment2 (0.5 years)	0.123	11.6
PWID	Early ART + Faster Treatment	0.130	6.9
PWID	Early ART + Faster Treatment2	0.121	12.9
MSM+PWID	Baseline	0.142	0.0
MSM+PWID	Early ART (Year 1)	0.140	1.6
MSM+PWID	Faster Treatment (0.75 years)	0.134	5.6
MSM+PWID	Faster Treatment2 (0.5 years)	0.125	11.9
MSM+PWID	Early ART + Faster Treatment	0.132	7.1
MSM+PWID	Early ART + Faster Treatment2	0.124	13.2

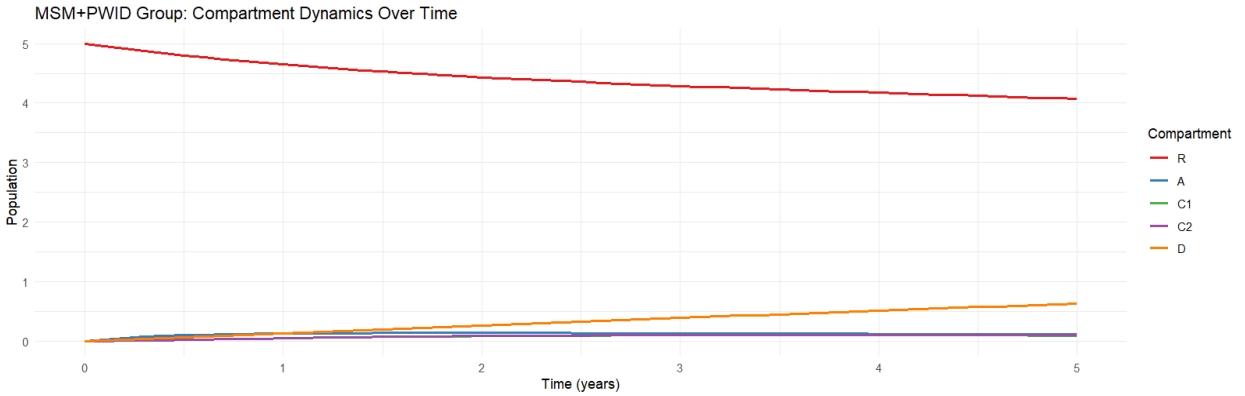
Table 7, Local Sensitivity Analysis

doi:10.6342/NTU202501025

3) Compartmental Dynamics







doi:10.6342/NTU202501025

Compartment Counts Over Time (Yearly Intervals) for MSM, PWID, and MSM+PWID

Time (yr)	Group	R	A	C_1	C_2	D
0.0	MSM	200.0000	0.0000	0.0000	0.0000	0.0000
1.0	MSM	187.5291	4.1327	1.5042	1.5253	5.3088
2.0	MSM	179.5167	4.4864	2.7414	2.7799	10.4756
3.0	MSM	173.7856	4.2754	3.1920	3.2369	15.5101
4.0	MSM	169.1259	3.9711	3.2220	3.2673	20.4136
5.0	MSM	164.9086	3.6841	3.0878	3.1313	25.1882
0.0	PWID	11.0000	0.0000	0.0000	0.0000	0.0000
1.0	PWID	10.2551	0.2612	0.0952	0.0965	0.2919
2.0	PWID	9.7927	0.2827	0.1731	0.1755	0.5759
3.0	PWID	9.4730	0.2691	0.2012	0.2040	0.8528
4.0	PWID	9.2192	0.2498	0.2028	0.2057	1.1224
5.0	PWID	8.9919	0.2318	0.1943	0.1970	1.3850
0.0	MSM+PWID	5.0000	0.0000	0.0000	0.0000	0.0000
1.0	MSM+PWID	4.6498	0.1254	0.0457	0.0464	0.1326
2.0	MSM+PWID	4.4354	0.1356	0.0831	0.0842	0.2617
3.0	MSM+PWID	4.2892	0.1289	0.0965	0.0978	0.3876
4.0	MSM+PWID	4.1744	0.1197	0.0972	0.0986	0.5101
5.0	MSM+PWID	4.0719	0.1111	0.0931	0.0944	0.6295

Table 8, Compartmental Dynamics

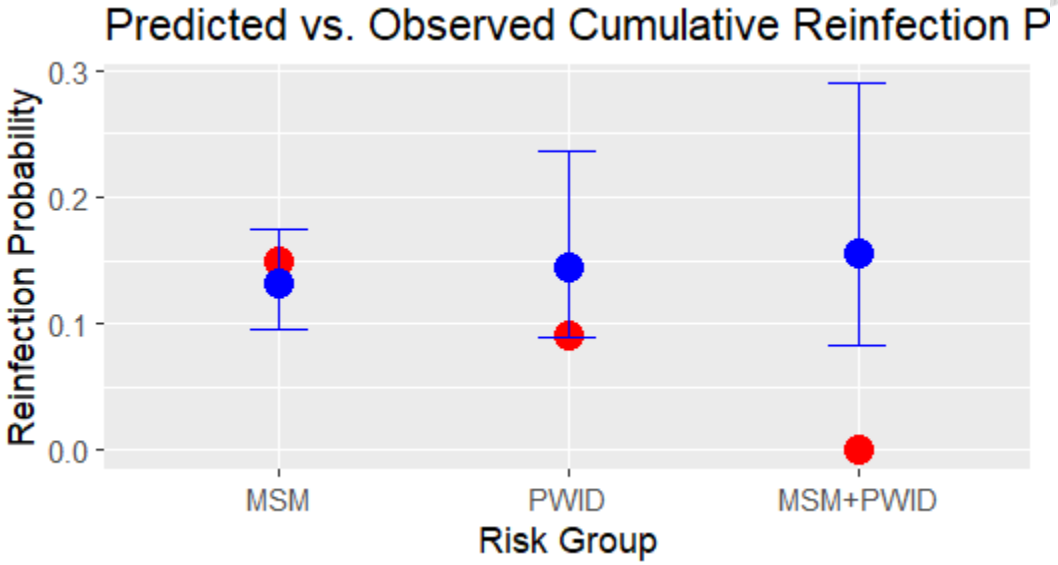
The plots and table, describing the compartmental dynamic over 5 years, report on a gradual depletion of the R compartment. *MSM*, the largest group, falls from 200 to 165 in 5 years. While compartment A rises in the first years it plateaus after the 3 years, while chronic compartments remain relatively small throughout. Mortality, cumulative, accumulates in a linear manner with 25 deaths by year 5. *PWID* and *MSM* compartments follow the same qualitative patterns but with ever increasing reduced scales.

doi:10.6342/NTU202501025

4) Reinfection Dynamics

V03 Predicted Reinfection Probability:

a) Predicted v Observed Cumulative Reinfection Probability



Posterior Predictive Checks: Predicted vs Observed Cumulative Reinfection Probabilities

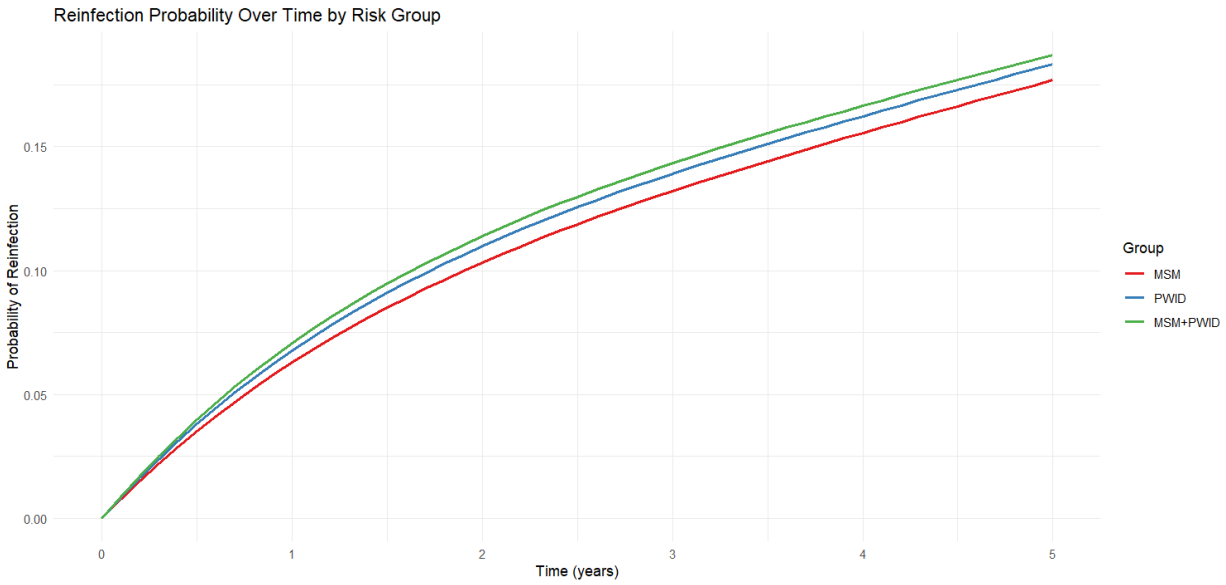
Group	p_{obs}	p_{mean}	2.5%	97.5%
MSM	0.15	0.1326	0.0957	0.1742
PWID	0.0909	0.1452	0.0895	0.2362
MSM+PWID	0.00	0.1550	0.0834	0.2904

The reinfection prediction by the model reports an increasing probability mean starting from *MSM* at 0.1326, *PWID* at 0.1452 and then *MSM+PWID* at 0.1550. Noticeable is the CI interval increasing among these groups, especially in *PWID* and *MSM+PWID*. With *MSM* having the smallest CI 0.0957 to 0.1742 and biggest held by MSM+PWID 0.0834 to 0.2904.

It is necessary to report how the model prediction matches *MSM* and *PWID* reinfection, while for *MSM+PWID* the observed number is 0.

doi:10.6342/NTU202501025

b) Reinfection Probability Time Series



Yearly Reinfection Probabilities by Group

Time (yr)	Group	Reinfection Probability
0.0	MSM	0.0000
1.0	MSM	0.0625
2.0	MSM	0.1027
3.0	MSM	0.1315
4.0	MSM	0.1548
5.0	MSM	0.1760
0.0	PWID	0.0000
1.0	PWID	0.0684
2.0	PWID	0.1108
3.0	PWID	0.1400
4.0	PWID	0.1631
5.0	PWID	0.1838
0.0	MSM+PWID	0.0000
1.0	MSM+PWID	0.0713
2.0	MSM+PWID	0.1147
3.0	MSM+PWID	0.1441
4.0	MSM+PWID	0.1671
5.0	MSM+PWID	0.1876

.

Dynamics of the reinfection over time are reported for all groups, where it is observed a similar quantitative pattern of slow grotwth over time and plateuing at about the 4th year.

doi:10.6342/NTU202501025

V03E Results:

1) Bayesian Parameter Estimation Results EuroSIDA dataset:

Force of Infection Estimates

Group	λ_0 Mean	95% CI Lower	95% CI Upper
MSM	0.0254	0.0042	0.0618
PWID	0.0296	0.0047	0.0666
Other	0.0323	0.0041	0.0807

Detailed Bayesian Parameter Estimates with Convergence Diagnostics and Disease Progression Parameters

Parameter	Role	Mean	SD	2.5%	50%	97.5%	n_{eff}	Rhat
λ_{base}	Baseline Reinfection Force	0.0253	0.0150	0.0042	0.0226	0.0606	3646.93	1.0006
β_1 (MSM)	Risk Multiplier (MSM)	1.0081	0.1002	0.8208	1.0049	1.2176	7375.85	1.0006
β_2 (PWID)	Risk Multiplier (PWID)	1.2706	0.5374	0.5182	1.1695	2.5588	6348.87	0.9997
β_3	Risk Multiplier (MSM+PWID)	1.4101	0.7763	0.4287	1.2391	3.3519	5672.78	1.0002
r_{art}	ART Behavior Change Rate	0.0501	0.0196	0.0122	0.0499	0.0891	5228.81	0.9996
t_{ART}	ART Behavior Onset (years)	1.9988	0.5052	1.0022	1.9987	2.9904	6002.72	0.9998
p_{sc}	Acute Clearance Prob.	0.2632	0.1457	0.0415	0.2463	0.5891	9848.56	0.9999
T_A	Duration of Acute Phase	0.4942	0.0999	0.3034	0.4945	0.6890	8061.68	0.9995
q_1	Prop. to Genotype 1	0.4934	0.2867	0.0251	0.4916	0.9734	8673.32	0.9995
q_2	Prop. to Genotype 2	0.5066	0.2867	0.0266	0.5084	0.9749	8673.32	0.9995
$p_{success1}$	Treatment Success (Gen1)	0.9501	0.0214	0.9012	0.9529	0.9838	8098.43	1.0001
$p_{success2}$	Treatment Success (Gen2)	0.9496	0.0217	0.9011	0.9522	0.9833	9376.68	0.9997
T_C	Duration in Chronic Phase	0.9885	0.2017	0.5942	0.9919	1.3854	6558.57	0.9998
μ_R	Mortality in Recovered	0.0236	0.0074	0.0081	0.0241	0.0367	3357.68	1.0002
μ_A	Mortality in Acute	0.0205	0.0096	0.0028	0.0202	0.0400	3370.41	1.0011
μ_C	Mortality in Chronic	0.0299	0.0101	0.0092	0.0300	0.0492	1998.35	1.0012

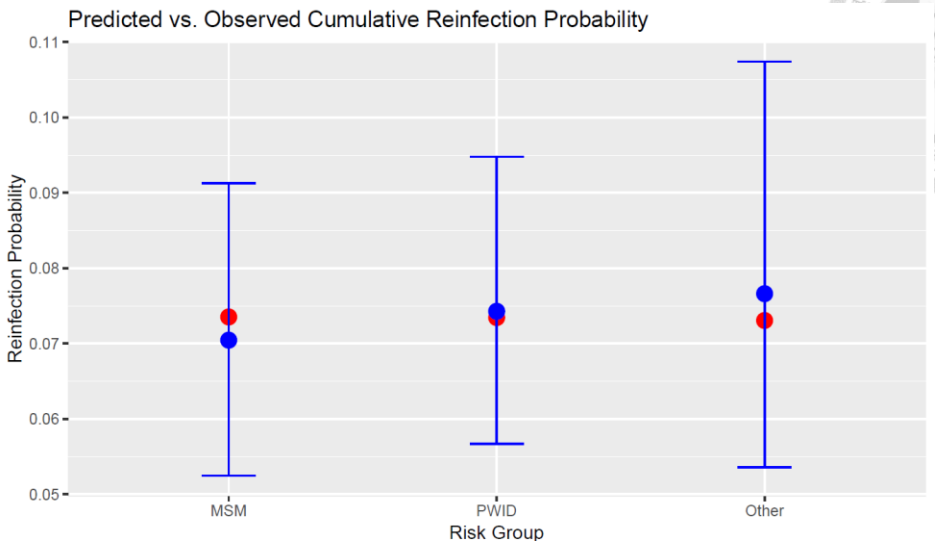
Force reinfection estimates, baseline reinfection force, was at 0.0253, with CI, at 0.0042 to 0.060. The estimated risk multiplier for each group: *MSM* mean 1.008 with CI at 0.8208 and 1.2176, *PWID* mean at 1.2706 with CI at 0.5374 and 2.5588, *MSM+PWID* (or *Other*) mean of 1.4101 with CI at 0.4287 and 3.3519.

Convergence diagnostics report all values close to 1, with the lowest value being 0.9995 for T_A, q1 and q2. The neff values it can be concluded that good chain convergence and mixing have occurred.

All other values align with V03 Bayesian parameters estimation results.

doi:10.6342/NTU202501025

2) V03E Predicted Reinfection Probability:



Posterior Predictive Checks for Reinfection Probability by Risk Group v Observed Cumulative Reinfection Probabilities

Group	p_{obs}	p_{mean}	p_{lower}	p_{upper}
MSM	0.07353	0.07045	0.05247	0.09125
PWID	0.07345	0.07428	0.05670	0.09478
Other	0.07306	0.07661	0.05361	0.10740

Reinfection predicted probabilities, report uniformity for all groups. With *MSM* predicted mean at 0.07045, *PWID* mean at 0.07428 and *Other* mean with 0.07661, while the observed values are 0.07353 for *MSM*, *PWID* at 0.07345 and *Other* at 0.07306. The CI values are all similar (0.05-0.09) with *Other* having the most uncertainty 0.05361 to 0.10740.

doi:10.6342/NTU202501025

V03D Results:

1) Bayesian Parameter Estimation V03D results:

Estimated Force of Infection by Group

Group	λ_{mean}	λ_{lower}	λ_{upper}
MSM	0.1137	0.0725	0.1690
PWID	0.1342	0.0449	0.3098
MSM+PWID	0.1434	0.0320	0.4079

Bayesian Parameter Estimates and Diagnostics

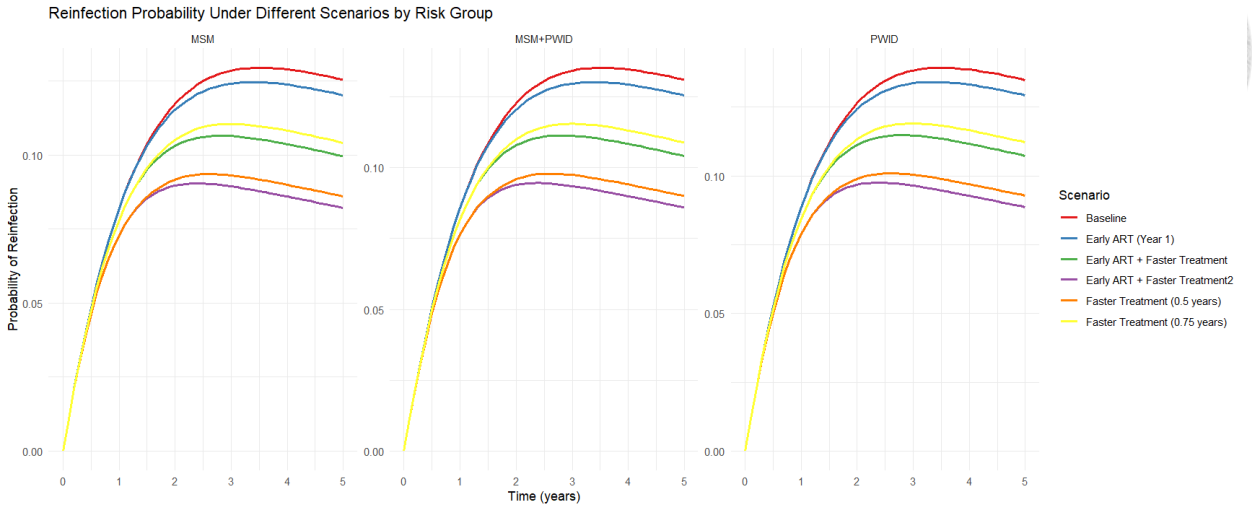
Parameter	Role	mean	se_mean	sd	2.5%	50%	97.5%	n_eff	Rhat
lambda_base	Baseline reinfection force	0.11	0.00	0.03	0.07	0.11	0.17	5779	1.00
beta[1]	Risk multiplier (MSM)	1.05	0.00	0.10	0.87	1.05	1.26	7589	1.00
beta[2]	Risk multiplier (PWID)	1.24	0.01	0.55	0.48	1.14	2.57	7488	1.00
beta[3]	Risk multiplier (MSM+PWID)	1.32	0.01	0.84	0.32	1.11	3.57	7102	1.00
r_art	ART behavior change rate	0.05	0.00	0.02	0.01	0.05	0.09	3826	1.00
t_ART	ART behavior change onset	2.03	0.01	0.49	1.06	2.03	3.00	5434	1.00
p_sc	Acute clearance probability	0.20	0.00	0.12	0.03	0.18	0.49	6771	1.00
T_A	Duration of acute phase	0.52	0.00	0.10	0.33	0.52	0.72	7091	1.00
q[1]	Proportion to Genotype 1	0.50	0.00	0.30	0.02	0.50	0.98	7674	1.00
q[2]	Proportion to Genotype 2	0.50	0.00	0.30	0.02	0.50	0.98	7674	1.00
p_success1	Treatment success (Gen.1)	0.95	0.00	0.02	0.90	0.95	0.98	7167	1.00
p_success2	Treatment success (Gen.2)	0.95	0.00	0.02	0.90	0.95	0.98	7730	1.00
T_C	Duration in chronic phase	1.06	0.00	0.19	0.68	1.06	1.44	6487	1.00

V03D results for Bayesian parameter estimation describe a similar situation as seen already in V03 and V03E.

Rhat and neff values demonstrate good chain mixing and convergence. Baseline reinfection force is of 0.11 mean value, with CI of 0.07 and 0.17, the group's risk multipliers have as mean value 1.05 and 0.87 to 1.26 CI for *MSM*, 1.24 average and 0.48 to 2.57 CI for *PWID*, 1.32 average and 0.32 to 3.57 CI for *MSM+PWID*.

doi:10.6342/NTU202501025

2) Local Sensitivity Analysis Simulation



Three-year Reinfection Probability and Relative Reduction by Scenario and Group

Group	Scenario	ReinfProb_3yr	Relative Reduction (%)
MSM	Baseline	0.128	0.0
MSM	Early ART (Year 1)	0.124	3.4
MSM	Faster Treatment (0.75 years)	0.110	14.0
MSM	Faster Treatment (0.5 years)	0.093	27.5
MSM	Early ART + Faster Treatment	0.106	17.2
MSM	Early ART + Faster Treatment2	0.089	30.4
PWID	Baseline	0.138	0.0
PWID	Early ART (Year 1)	0.134	3.4
PWID	Faster Treatment (0.75 years)	0.119	13.9
PWID	Faster Treatment (0.5 years)	0.100	27.4
PWID	Early ART + Faster Treatment	0.115	17.1
PWID	Early ART + Faster Treatment2	0.096	30.3
MSM+PWID	Baseline	0.134	0.0
MSM+PWID	Early ART (Year 1)	0.130	3.4
MSM+PWID	Faster Treatment (0.75 years)	0.115	14.0
MSM+PWID	Faster Treatment (0.5 years)	0.097	27.4
MSM+PWID	Early ART + Faster Treatment	0.111	17.1
MSM+PWID	Early ART + Faster Treatment2	0.093	30.3

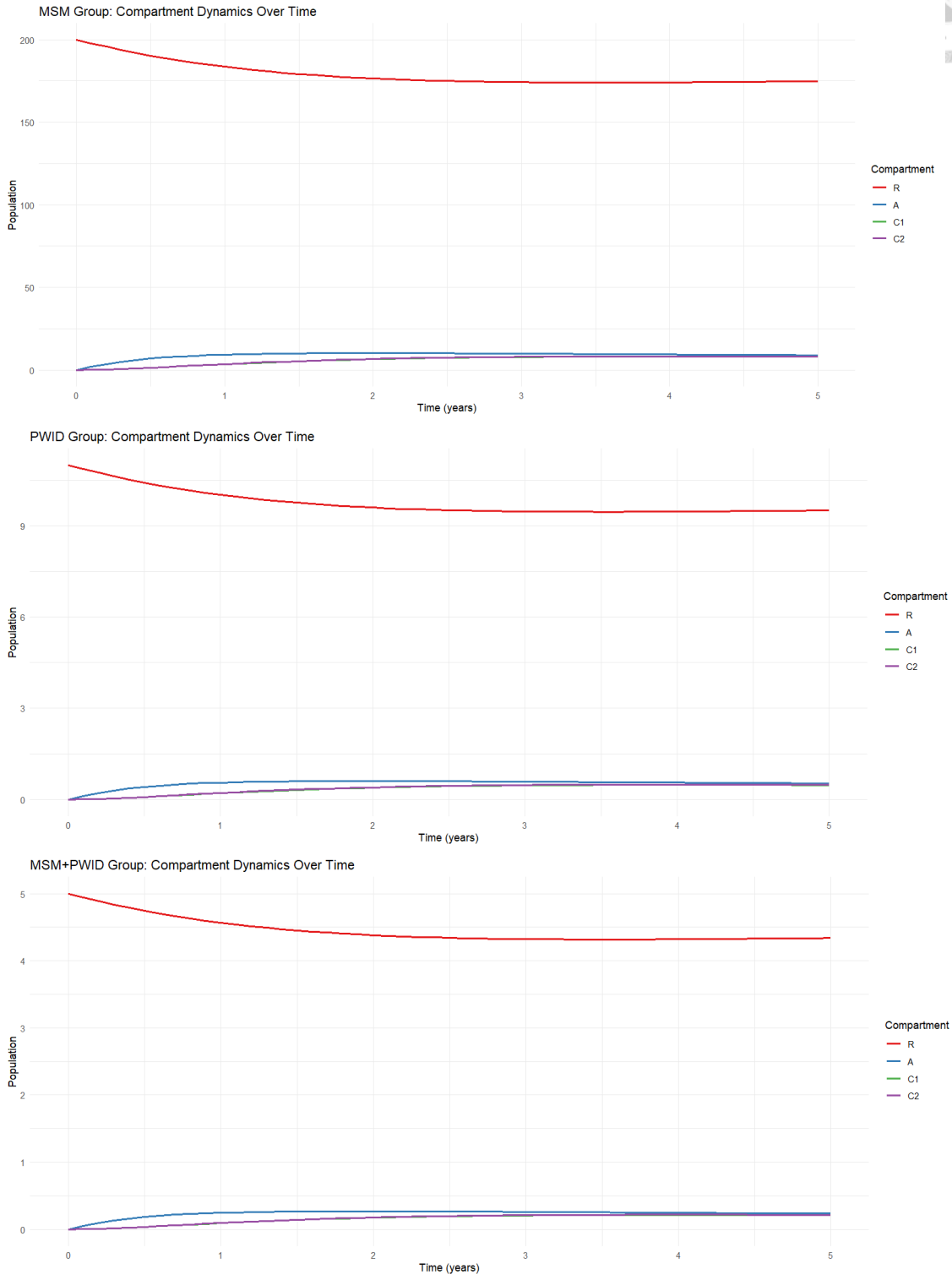
Perturbing the same parameters as it has been done in V03, to observe variation in reinfection for V03D.

The combined effect of Early ART and Faster Treatment. Early ART + Faster Treatment 2 (T_C = 0.5 years), results in the greatest reduction of reinfection probability in all groups, 30.4% to 30.3% reduction compared to baseline. Followed closely by T_C = 0.5 years, 27.5% to 27.4%. A noticeable gap is then observed from T_C = 0.5 years and Early ART + Faster Treatment 1 (T_C = 0.75 years), 17.2% to 17.1%. Again, followed closely by T_C = 0.75 years, 14.0% to 13.9%.

doi:10.6342/NTU202501025

While Early ART, influences 3.4%. Of interest is also the plateu effect observed throughout starting year 2.5.

3) Compartment Dynamics



doi:10.6342/NTU202501025

Compartment Counts at Yearly Intervals for MSM, PWID, and MSM + PWID

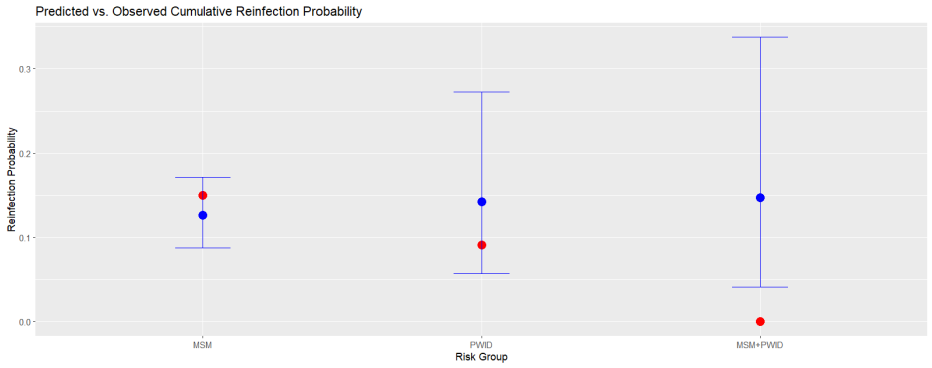
Time (yr)	Group	R	A	C_1	C_2
0.0	MSM	200.0000	0.000000	0.00000000	0.00000000
1.0	MSM	183.5972	9.314993	3.52770273	3.56009326
2.0	MSM	176.5111	10.200916	6.61347652	6.67450091
3.0	MSM	174.2302	9.891939	7.90235762	7.97554528
4.0	MSM	174.1290	9.408994	8.19297036	8.26904090
5.0	MSM	174.8011	8.973731	8.07505120	8.15014132
0.0	PWID	11.0000	0.000000	0.000000000	0.000000000
1.0	PWID	10.2551	0.261246	0.095209319	0.096545299
2.0	PWID	9.7927	0.282746	0.173077817	0.175509565
3.0	PWID	9.4730	0.269055	0.201157439	0.203986357
4.0	PWID	9.2192	0.249817	0.202834619	0.205688910
5.0	PWID	8.9919	0.231788	0.194311715	0.197047091
0.0	MSM+PWID	5.0000	0.000000	0.000000000	0.000000000
1.0	MSM+PWID	4.5662	0.246245	0.093367223	0.094224502
2.0	MSM+PWID	4.3802	0.268923	0.174639758	0.176251226
3.0	MSM+PWID	4.32097	0.260442	0.208329703	0.210259179
4.0	MSM+PWID	4.31876	0.247655	0.215792277	0.217795908
5.0	MSM+PWID	4.33657	0.236231	0.212610462	0.214587553

Compartmental Dynamics for V03D results demonstrate plateau starting year 3, across all groups and compartments indicating equilibrium achievement. With R compartment gradually decreasing until stabilizing. A's compartment has a slightly more rapid growth when compared to C1 and C2, peaking in value at year 2 and then plateauing. C1 and C2, which are undiscernible one another in the plotted graphs, but have marginally different values in the table, demonstrate same quantitative behavior. With slow growth until year 3 at which point plateau incours.

doi:10.6342/NTU202501025

4) Reinfection Dynamics

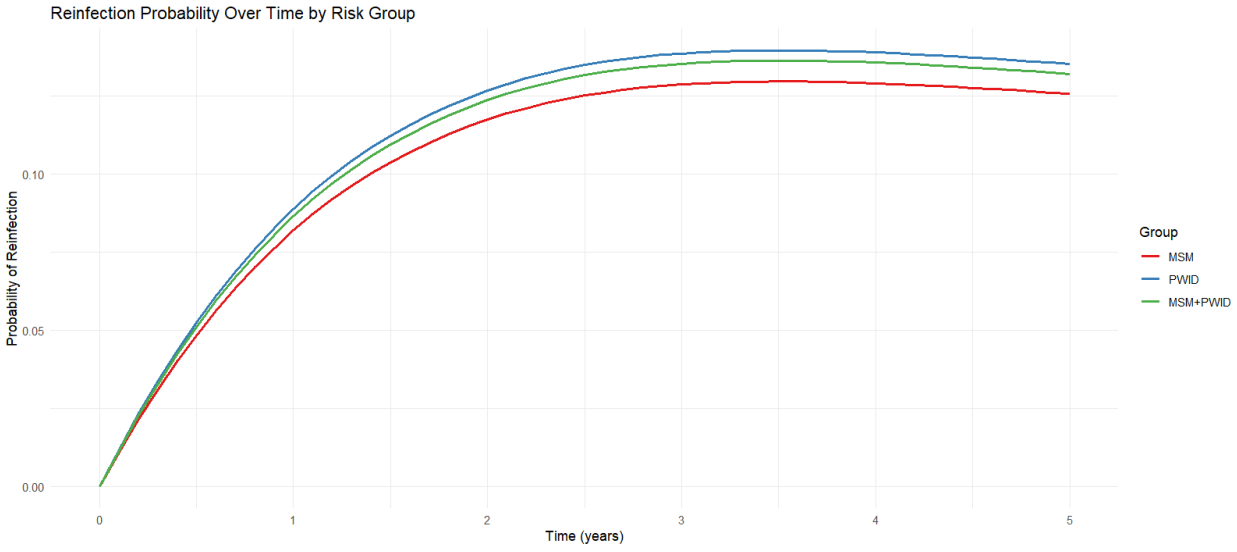
V03D Predicted Reinfection Probability:



Posterior Predictive Checks for Reinfection Probability by Risk Group

Group	p_{obs}	p_{mean}	p_{lower}	p_{upper}
MSM	0.15000	0.12619	0.08740	0.17116
PWID	0.09091	0.14209	0.05682	0.27249
MSM+PWID	0.00000	0.14680	0.04099	0.33767

The predicted reinfection probability results in the mean value of 0.12619 with CI of 0.08740 for MSM, 0.14209 with CI of 0.05682 for PWID and 0.14680 with CI of 0.04099 and 0.33767 for MSM+PWID. The same conditions as V03 predictive check apply, that is that the lack of substantial representation for all groups interferes with a valid posterior predictive check comparison against observed reinfections.



doi:10.6342/NTU202501025

Yearly Reinfection Probabilities by Group

Time (yr)	Group	Reinfection Probability
0.0	MSM	0.0000
1.0	MSM	0.08195
2.0	MSM	0.11732
3.0	MSM	0.12861
4.0	MSM	0.12902
5.0	MSM	0.12558
0.0	PWID	0.0000
1.0	PWID	0.08876
2.0	PWID	0.12665
3.0	PWID	0.13855
4.0	PWID	0.13886
5.0	PWID	0.13513
0.0	MSM+PWID	0.0000
1.0	MSM+PWID	0.08650
2.0	MSM+PWID	0.12356
3.0	MSM+PWID	0.13526
4.0	MSM+PWID	0.13560
5.0	MSM+PWID	0.13197

The time series analysis of the predicted reinfection dynamic among groups demonstrates that all follow the same quantitative dynamic of reaching peak value at year 4, after which plateau is reached. With MSM group highest value reached being 0.12902 at year 4 which then at year 5 becomes 0.12558. PWID highest is 0.13886 which in the following year becomes 0.13513 and for MSM+PWID the highest value is 0.13560 that then becomes 0.13197.

12. Discussion, Limitations and Conclusion

Analyzing the results obtained with V03 starting from the Bayesian parameter estimations and force of reinfection. Baseline reinfection force per year aligns with expected incidence of 4 per 100 PYFU, as described in the RECUR study. Risk multiplier for MSM, has estimates close to 1, which fits our expectation of utilizing this subgroup as the baseline. PWID Risk multiplier as well as that of MSM+PWID are higher but present wide uncertainty. In similar manner to the risk multipliers: MSM force of infection has value equal to that of the baseline, with MSM+PWID having the higher value reflecting the compounding risk followed by PWID. Which also present the highest intervals of uncertainty caused by the small sample size of the RECUR study particularly for these subgroups. V03D model results present similr conditions, and it can be reasoned that the cause is the same as V03, small sample size. V03E on the other hand, while presenting high uncertainty intervals, has the mean of the predicted reinfection closesly matching those of the observed reinfections of the EuroSIDA dataset for all the groups. Furthermore, EuroSIDA's dataset and V03E allow for observation of a uniform reinfection rate rather than pronounced differences among groups.

The global sensitivity analysis results influence positively the argument that focused group interventions do noticeably influence the reinfection rate. Adding fuel to the ever-growing

doi:10.6342/NTU202501025

consensus of more precise data being required on account of the patient's behavior and how to address it. Local sensitivity results instead demonstrate just how important the reduction of time before treatment of chronic state has in impact leading to an overall diminished cumulative reinfection. The time before ART treatment, as an indicator of behavior changes due to ART treatment, as well as the time in chronic state before treatment demonstrate how a delay in establishing contact with healthcare resources, screening and treatment, aliments a non-negligible reinfection probability, and through the results it is clear that a reduction of even 25%, 3 months, bringing the average time between treatments to 9 months instead of 10, sensibly reduces the reinfection probability. It should not be neglected that the model utilized could substantially be improved upon, especially in the aspects of network between patients, change of behavior and addition of stochasticity, which will have a noticeable effect on the results.

In V03 and V03D, given the lack of a death compartment in V03D, plateau effect as well as equilibrium are noticeable in the compartment dynamics, local sensitivity analysis as well as the reinfection over-time study. Given the absence of an outflow in V03D, equilibrium is reached, with halting of growth and decays for all compartments. The consequence is that the results obtained more closely resemble that observed in V03E, which data better represented all groups of interest. That is that reinfection probability is reported as quite homogeneous among all groups of interest rather than heterogeneous, or with groups presenting a better likelihood of achieving reinfection. Regardless this provides argument to the robustness in the primary model outcomes irrespective of the mortality parameter. The model central prediction of reinfection rates, depends mainly on reinfection dynamics rather than mortality and therefore the results produced remain consistent. A potential explanation to the negligible difference can be found also in the present relatively short time-line, where reinfection dynamics overshadows long-term mortality. Consequently, we have indication that mortality parameters while they are theoretically influential, do not alter short-term reinfection prediction.

To begin our closing arguments, this thesis investigated HCV reinfection dynamics in the HCV/HIV coinfected population with a focus on high-risk subgroups in Taiwan, through mathematical modeling and empirical data from the RECUR study by Liu et al., 2022.

The extensive literature review preceding the modeling section of this thesis is believed to be needed for proper interpretation of results obtained.

In this investigation the incidence of HCV reinfection among the Coinfected with HIV individuals remains consistent with what was observed in the record cohort and aligns with what has been reported in International Studies of similar populations. Approximately 4 to 6 per 100 PYFU in people living with HIV. The modeling confirms a baseline annual reinfection hazard of about 4% in the post treatment cohort following the line that has been established through a-priori knowledge one important finding of this investigation is that no risk group demonstrated a significantly higher reinfection rate then others that were within the scope of our cohort this being said the model

doi:10.6342/NTU202501025

treated the men who have sex with men and MSM as the reference group having a risk multiplier of around 1.0 and estimate higher for multipliers of people who inject drugs and the combined risk of people who inject drugs and MSM it is to be noted that the differences that came arose with wide uncertainty intervals and did not diverge drastically from baseline furthermore when reparameterizing the model with with a larger dataset: EuroSIDA the reinfection probability observed were essentially uniform: approximately 7% across all risk groups considered in the cohort. This reinforces that the reinfection risk is distributed and not just limited to singular risk group. These findings demonstrate no significant difference in reinfection odds between detected MSM and PWID suggesting that once an HCV patient is cured if such patient has any ongoing risk behaviors, they shall remain vulnerable to infection at a non-negligible rate therefore underscoring the need for vigilant follow-up and prevention across all subgroups of risk. In our main data set the cumulative reinfection incidence in HIV positive patients was recorded at 14.4% over 3 years, defined as higher than in HCV more infected patients said at 0.9% over 3 years of course in the same clinical settings the data aligns with the notion that HIV positive individuals who are engaging in high-risk behaviors represent a core risk population for the reinfection phenomena. It is important to address the limitations of this study: that 92.6% of the HCV/HIV coinfected patients in the RECUR cohort were defined as MSM with almost all reinfections: 30 out of 31 attributable to high-risk sexual exposure and only a single case attributed to injection drug use. Therefore, we can or could say that the lack of detectable difference in their infection rate between the various at-risk groups in our analysis may be the result of bias from the limited sample of non-MSM cases. Regardless, this pattern highlights the need for localization. A local epidemiology pattern where sexual transmission among MSM drives HCV spread in the HIV positive community as this is the case in Taiwan, whereas according to literature, PWID are the main driver in Western countries. To summarize the results of this investigation through modeling are that post-SVR reinfection is an ever-present risk at a moderate incidence level, which cannot be ignored if the Eradication goals want to be accomplished, in the coinfected populations and that these are consistent with global observations. Furthermore, supporting the fact that no single behavioral subgroup of those at risk can be ignored in the prevention to reinfection efforts.

Of these behaviors further studying needs to be conducted. To begin with the greater reinfection rates observed in the DAA-era as described in the temporal trend reported in the RECUR study from 2005 to 2021. Several factors which may be converging could be the drivers as explained in previous sections. Expansion of treatment to high-risk individuals could be a factor describing an increase in reinfectable hosts. Given that more individuals with persistent risk behaviors were able to access the treatment, get cured and then return to susceptibility. Risk compensation and treatment optimism could be another driver. With the wide scale availability in recent years of the treatment and it's highly effectiveness with reduced side effects and tolerability may have reduced the perceived sense of severity for HCV. With potential to leading riskier behavior post SVR achievement, given a belief of risky practices carrying less consequences, inadvertently boosting transmission. Furthermore, a two-speed between integrating preventive services and treatment

doi:10.6342/NTU202501025

access could allow nor negligence in behaviors and return in susceptibility pool. Lastly, similar to the first point raised, statistical bias may be in act given the increased monitoring, an increase in monitoring might lead to a increase in observed reinfection rates.

Comprehensiveness should then be regarded as paramount. The post-DAA landscape requires a paradigm shift from curing to maintenance. With HCV reinfection to be managed in the same urgency as initial infection. With further support included by integration of behavioral interventions and counseling during the aftercare of treatment.

This is of extreme importance in consideration of the 2030 elimination targets. The stable reinfection rates in the high-risk networks threatens a sustained transmission. Reinfection could account for a growing proportion of HCV cases in the DAA era, with warnings from mathematical models observing a cyclical challenge in counteracting the elimination efforts. It falls therefore to necessity to not only keep reducing infections through high treatment uptake but also to reduce the reinfection opportunities.

Limitation of the study

Throughout the result section, mentions of limitations are scattered, this section is dedicated to providing clarity through recollection.

Constraints are faced with the sample size and generability. The RECUR cohort modelled, was relatively small, with big differences in terms of numbers in the groups of interest. E.g. PWID = n 11, MSM+PWID = n 5 and MSM = n 200. The imbalance limited the detection of differences between risk groups yielding wide credible intervals for the parameters of importances such as the risk multipliers. The uncertainty in the obtained estimates is evident in PWID-related risk, while a higher reinfection hazard for PWID and even higher for dual-risk individuals is suggested by the model, there is strong uncertainty over the magnitude due to “sparse data” problem. A Bayesian Hierarchical approach was therefore adopted to try to reduce the constraints imposed by sparse data and disparity among group sizes. The results obtained for subgroup comparison are therefore to be viewed as exploratory.

Other limitation lies with the data on risk behavior and ascertainment. Given that self-reported behavior is inherently imperfect, with biases in underrepresented stigmatized activities and corollary of misclassification of reinfection routes. Mitigation of this was attempted through the MSM+PWID group, but there remains potential of unmeasured confounders, such as sexual transmission in occasional chemsex, with bring challenge in attributing with certainty Similarly other limitations that are inherit to the dataset are transferred to this investigation by corollary, such as follow-up and loss to follow-up. With COVID having a possible effect disrupting in the last years of the studies. As consequence it might be acceptable that the reinfection incidence reported should be seen as a conservative estimate. Another constraint is found by longevity of

doi:10.6342/NTU202501025

study, in interest of risk behavior patterns over time, for limit in recurrent reinfection beyond the first.

Assumptions that have been taken during the modelling process to simplify the reality are to be considered as could influence results. A constant force of infection withing each group, with exponential decay after a notional time of ART initiation for behavioral change was assumed. However, these are dynamic, with existence of individuals who may reduce risk after HCV infection but there might also be "superspreader" individuals who contribute disproportionately. The compartmental model could not capture such heterogeneity at individual level or a temporal fluctuation of risk. This could have an effect in oversimplifying the transmission process. In cases where short-term spikers in reinfection due to high-risk network contact during an outbreak would be smoothed out. Mortality and removal from risk-pool are also assumptions, in particular due to reliance to external estimates for an all-cause mortality in the recovered compartment cohort, since mortality wasn't a researched outcome in the main study of interest. Given the results obtained from the global sensitivity analysis, in how mortality is one of the highest influences in our model output variability, more so that other infection parameters, should the assumption be erroneous it appreciatively influences the predicted reinfection hazard. There in fact could be an overestimation of the removals due to death or other causes. Most other clinical parameters have been held constant, e.g. spontaneous clearing rate or treating success probability, based on literature. Lastly there was no capturing whether a certain subgroup had lower retreatment success or slower re-engagement in care.

Finally, this study is observational and not interventional. While identification of associations is possible, not causation can be proved or quantified by how much each factor contributes to the reinfection risk. Due to the dataset not being suited for multivariate risk factor analysis. As both in RECUR and EuroSIDA, no significant baseline predictors were found. Unmeasured confounders might be found at a network level or at healthcare engagement that could not be accounted for.

Despise these limitations, the findings of this work find coherence with the established literature and successful validation against external dataset: EuroSIDA, lending credibility to the conclusions.

Future Directions

The investigation provides several roads that can be taken for future improvements and research prospectives, with some being mentioned admist the sections, here they are gathered in a coherent manner.

Enhanced data gathering efforts are paramount. Given that these align with the set goals of HCV eradication, with the required screening rates and uptakes, systematic following of patients at an international collaborative scale on a longer time scale could capture a more akin to nature reality,

doi:10.6342/NTU202501025

with multiple reinfection events and detailed behavioral data. Providing the opportunity for multivariate risk modeling and identifying factors most strongly predicting reinfection.

With an increase in data and data quality would follow the improvements and refinements of mathematical models in order to incorporate heterogeneity and behavioral dynamics. A feedback loop of data in short. With access to descriptive individual data, simulation of individual interactions in high-risk behavior networks of MSM, PWID or overlapping become possible with agent-based models or network models. This doesn't discard the current Bayesian compartmental proposed model which could be upscaled to incorporate city-level or network-level stochastic effects if data on social/sexual networks is provided. Furthermore, with increased data, the prior distributions can be updated with empirically derived rates and probability, increase prediction accuracy.

Policy wise, the recommendations that can be provided would align with the current framework for HCV's elimination all the while addressing reinfection. Unrestricted treatment, with universal HCV treatment policies with encouragement to re-engage in care. Moreover, a reinfection metric should be implemented, or at least a success metric based on those remaining in a non-infected state as treatment alone given lack of immunity does not reflect reinfection occurrences. The integration of services can play a huge role, with embedded services in HIV and STI clinics as well as any other points described or indicated as a contact for most-affected populations. Returning on the unified combat approach suggested but the WHO, but extended to the linkage to, continued and simplified care.

Finally, and to conclude, HCV elimination would depend on the maintaining of the momentum of treatment scale-up as well as simultaneously deploying aggressive measures to prevent reinfections.

This study would serve its use as steppingstone, with quantification of the reinfection challenge and how it is a true obstacle to the elimination efforts with added importance in the context of HCV-HIV coinfection. With requirements of moving beyond the paradigm of DAA-era, to that of a continuum of care, one of holistic sustained prevention.

doi:10.6342/NTU202501025

Bibliography

[1] World Health Organization: WHO. (2020, March 11). *Hepatitis*. https://www.who.int/health-topics/hepatitis.

[2] *Hepatitis C - symptoms and causes*. (n.d.). https://www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/hepatitis-c

[3] *Hepatitis*. (2025, February 28). Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/hepatitis

[4] *Hepatitis*. (n.d.). Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/hepatitis

[5] World Health Organization: WHO. (2025, February 12). *Hepatitis A*. https://www.who.int/news-room/fact-sheets/detail/hepatitis-a

[6] World Health Organization: WHO. (2023, July 20). *Hepatitis E*. https://www.who.int/news-room/fact-sheets/detail/hepatitis-e

[7] World Health Organization: WHO. (2023, July 20). *Hepatitis D*. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d

[8] World Health Organization: WHO & World Health Organization: WHO. (2024, April 9). *Hepatitis B*. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

[9] World Health Organization: WHO & World Health Organization: WHO. (2024, April 9). Hepatitis C. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

[10] Laugi, H. (2021). Discovery of Hepatitis C virus: 2020 Nobel Prize in Medicine. *Euroasian Journal of Hepato-Gastroenterology*, *10*(2), 105–108. https://doi.org/10.5005/jp-journals-10018-1326

[11] *Hepatitis C | CDC Yellow Book 2024*. (n.d.). https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/hepatitis-c

[12] Ball, J. K., Tarr, A. W., & McKeating, J. A. (2014). The past, present and future of neutralizing antibodies for hepatitis C virus. *Antiviral Research*, *105*, 100–111. https://doi.org/10.1016/j.antiviral.2014.02.013

[13] Oancea, C. N., Butaru, A. E., Streba, C. T., Pirici, D., Rogoveanu, I., Diculescu, M. M., & Gheonea, D. I. (2021). Global hepatitis C elimination: history, evolution, revolutionary changes and barriers to overcome. *Romanian Journal of Morphology and Embryology*, *61*(3), 643–653. https://doi.org/10.47162/rjme.61.3.02

[14] Hoofnagle, J. H., Mullen, K. D., Jones, D. B., Rustgi, V., Di Bisceglie, A., Peters, M., Waggoner, J. G., Park, Y., & Jones, E. A. (1986). Treatment of Chronic Non-A, Non-B Hepatitis with Recombinant Human Alpha Interferon. *New England Journal of Medicine*, *315*(25), 1575–1578. https://doi.org/10.1056/nejm198612183152503

[15] Alberti, A., Chemello, L., Noventa, F., Cavalletto, L., & De Salvo, G. (1997). Therapy of hepatitis C: Re-treatment with alpha interferon. *Hepatology*, *26*(Supplement 3), 137S-142S. https://doi.org/10.1002/hep.510260724

doi:10.6342/NTU202501025

[16] Nawaz, A., Manzoor, A., Ahmed, S., Ahmed, N., Abbas, W., Mir, M. A., Bilal, M., Sheikh, A., Ahmad, S., Jeelani, I., & Nakagawa, T. (2024). Therapeutic approaches for chronic hepatitis C: a concise review. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1334160

[17] *Pegylated interferons*. (2001). PubMed. https://pubmed.ncbi.nlm.nih.gov/12120178/

[18] Fabrizi, F., Dixit, V., Messa, P., & Martin, P. (2010). Pegylated interferon monotherapy of chronic hepatitis C in dialysis patients: Meta-analysis of clinical trials. *Journal of Medical Virology*, *82*(5), 768–775. https://doi.org/10.1002/jmv.21542

[19] *Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review*. (2013, June 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/23619254/

[20] Geddawy, A., Ibrahim, Y. F., Elbahie, N. M., & Ibrahim, M. A. (2017). Direct acting anti-hepatitis C virus drugs: Clinical pharmacology and future direction. *Journal of Translational Internal Medicine*, *5*(1), 8–17. https://doi.org/10.1515/jtim-2017-0007

[21] *Monitoring patients who are starting HCV treatment, are on treatment, or have completed therapy | HCV Guidance*. (n.d.). https://www.hcvguidelines.org/evaluate/monitoring

[22]National Institute of Diabetes and Digestive and Kidney Diseases. (2022, January 26). *Boceprevir*. LiverTox - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK548247/

[23] *Glecaprevir/pibrentasvir ultra-short treatment to cure HCV infection: case report and literature review*. (2020, December 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/33257639/

[24] *EPCLUSA | European Medicines Agency (EMA)*. (n.d.). European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR/epclusa

[25] Pawlotsky, J., Negro, F., Aghemo, A., Berenguer, M., Dalgard, O., Dusheiko, G., Marra, F., Puoti, M., & Wedemeyer, H. (2020). EASL recommendations on treatment of hepatitis C: Final update of the series☆. *Journal of Hepatology*, *73*(5), 1170–1218. https://doi.org/10.1016/j.jhep.2020.08.018

[26] Omata, M., Kanda, T., Wei, L., Yu, M., Chuang, W., Ibrahim, A., Lesmana, C. R. A., Sollano, J., Kumar, M., Jindal, A., Sharma, B. C., Hamid, S. S., Dokmeci, A. K., Mamun-Al-Mahtab, N., McCaughan, G. W., Wasim, J., Crawford, D. H. G., Kao, J., Yokosuka, O., . . . Sarin, S. K. (2016). APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatology International*, *10*(5), 702–726. https://doi.org/10.1007/s12072-016-9717-6

[27] Esteban, R., Domínguez-Hernández, R., Cantero, H., & Casado, M. Á. (2024). Evaluation of the clinical and economic value of sofosbuvir/velpatasvir (SOF/VEL) in patients with chronic hepatitis C in Spain during the last 5 years. *Gastroenterología Y Hepatología*, *47*(10), 502199. https://doi.org/10.1016/j.gastrohep.2024.502199

[28] Mangia, A., Milligan, S., Khalili, M., Fagiuoli, S., Shafran, S. D., Carrat, F., Ouzan, D., Papatheodoridis, G., Ramji, A., Borgia, S. M., Wedemeyer, H., Losappio, R., Pérez-Hernandez, F., Wick, N., Brown, R. S., Lampertico, P., Doucette, K., Ntalla, I., Ramroth, H., . . . Turnes, J. (2020). Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: Analysis of 5552 patients from 12 cohorts. *Liver International*, *40*(8), 1841–1852. https://doi.org/10.1111/liv.14537

doi:10.6342/NTU202501025

[29] *The value of sofosbuvir/velpatasvir (SOF/VEL) as a pangenotypic and panfibrotic HCV treatment in implementing a test-and-treat strategy in prisons: real-world care management from 6 countries*. (n.d.). https://www.natap.org/2020/AASLD/AASLD_14.htm

[30] Zignego, A. L., Monti, M., & Gragnani, L. (2018). Sofosbuvir/Velpatasvir for the treatment of Hepatitis C Virus infection. *PubMed*, *89*(3), 321–331. https://doi.org/10.23750/abm.v89i3.7718

[31] Mangia, A., Cenderello, G., Copetti, M., Verucchi, G., Piazzolla, V., Lorusso, C., Santoro, R., Squillante, M. M., Orlandini, A., Minisini, R., & Ciancio, A. (2019). SVR12 Higher than 97% in GT3 Cirrhotic Patients with Evidence of Portal Hypertension Treated with SOF/VEL without Ribavirin: A Nation-Wide Cohort Study. *Cells*, *8*(4), 313. https://doi.org/10.3390/cells8040313

[32] Office of the Commissioner. (2017, August 3). *FDA approves Mavyret for Hepatitis C*. U.S. Food And Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-mavyret-hepatitis-c

[33] Liu, C., Liu, C., Hung, C., Hsieh, S., Su, T., Sun, H., Tseng, T., Chen, P., Chen, D., & Kao, J. (2019). Glecaprevir/pibrentasvir for patients with chronic hepatitis C virus infection: Real-world effectiveness and safety in Taiwan. *Liver International*, *40*(4), 758–768. https://doi.org/10.1111/liv.14295

[34] Liu, C., Yang, S., Peng, C., Lin, W., Liu, C., Su, T., Tseng, T., Chen, P., Chen, D., & Kao, J. (2020). Glecaprevir/pibrentasvir for patients with chronic hepatitis C virus infection and severe renal impairment. *Journal of Viral Hepatitis*, *27*(6), 568–575. https://doi.org/10.1111/jvh.13265

[35] Liu, C., Peng, C., Liu, C., Chen, C., Lo, C., Tseng, K., Su, P., Kao, W., Tsai, M., Tung, H., Cheng, H., Lee, F., Huang, C., Huang, K., Shih, Y., Yang, S., Wu, J., Lai, H., Fang, Y., . . . Kao, J. (2023).
[36] Sofosbuvir/velpatasvir/voxilaprevir for patients with chronic hepatitis C virus infection previously treated with NS5A direct-acting antivirals: a real-world multicenter cohort in Taiwan. *Hepatology International*, *17*(2), 291–302. https://doi.org/10.1007/s12072-022-10475-9
[37] Martinello, M., Solomon, S. S., Terrault, N. A., & Dore, G. J. (2023). Hepatitis C. *The Lancet*, *402*(10407), 1085–1096. https://doi.org/10.1016/s0140-6736(23)01320-x

[38] Borgia, S. M., Hedskog, C., Parhy, B., Hyland, R. H., Stamm, L. M., Brainard, D. M., Subramanian, M. G., McHutchison, J. G., Mo, H., Svarovskaia, E., & Shafran, S. D. (2018). Identification of a novel hepatitis C virus genotype from Punjab, India: Expanding classification of hepatitis C virus into 8 genotypes. *The Journal of Infectious Diseases*, *218*(11), 1722–1729. https://doi.org/10.1093/infdis/jiy401

[39] Sarrazin, C. (2021). Treatment failure with DAA therapy: Importance of resistance. *Journal of Hepatology*, *74*(6), 1472–1482. https://doi.org/10.1016/j.jhep.2021.03.004

[40]*Transforming our World: The 2030 Agenda for Sustainable Development | Department of Economic and Social Affairs*. (n.d.). https://sdgs.un.org/publications/transforming-our-world-2030-agenda-sustainable-development-17981

[41] Hiv/Aids. (2016, May 3). *Global health sector strategy on HIV: 2016-2021*. https://www.who.int/publications/i/item/WHO-HIV-2016.05

[42] Gamkrelidze, I., Pawlotsky, J., Lazarus, J. V., Feld, J. J., Zeuzem, S., Bao, Y., Santos, A. G. P. D., Gonzalez, Y. S., & Razavi, H. (2021). Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. *Liver International*, *41*(3), 456–463. https://doi.org/10.1111/liv.14779

[43] Programmes, G. H. H. a. S. (2012, July 19). *Prevention and Control of Viral hepatitis Infection: Framework for Global Action*. https://www.who.int/publications/i/item/prevention-and-control-of-viral-hepatitis-infection-framework-for-global-action

doi:10.6342/NTU202501025

[44] *Global health sector strategies*. (2025, March 25). https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies

[45] Programmes, G. H. H. a. S. (2024, April 9). *Global hepatitis report 2024: action for access in low- and middle-income countries*. https://www.who.int/publications/i/item/9789240091672

[46] Gamkrelidze, I., Pawlotsky, J., Lazarus, J. V., Feld, J. J., Zeuzem, S., Bao, Y., Santos, A. G. P. D., Gonzalez, Y. S., & Razavi, H. (2021). Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. *Liver International*, *41*(3), 456–463. https://doi.org/10.1111/liv.14779

[47] Solomon, S. S., Wagner-Cardoso, S., Smeaton, L., Sowah, L. A., Wimbish, C., Robbins, G., Brates, I., Scello, C., Son, A., Avihingsanon, A., Linas, B., Anthony, D., Nunes, E. P., Kliemann, D. A., Supparatpinyo, K., Kityo, C., Tebas, P., Bennet, J. A., Santana-Bagur, J., . . . Sulkowski, M. (2022). A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *the Lancet. Gastroenterology & Hepatology*, *7*(4), 307–317. https://doi.org/10.1016/s2468-1253(21)00397-6

[48] Yu, M., Tai, C., Mo, L., Kuo, H., Huang, C., Tseng, K., Lo, C., Bair, M., Wang, S., Huang, J., Yeh, M., Chen, C., Tsai, M., Huang, C., Lee, P., Yang, T., Huang, Y., Chong, L., Chen, C., . . . Peng, C. (2024). An algorithm for simplified hepatitis C virus treatment with non-specialist care based on nation-wide data from Taiwan. *Hepatology International*, *18*(2), 461–475. https://doi.org/10.1007/s12072-023-10609-7

[49] Pan, C. Q., & Park, J. S. (2024). Revamping hepatitis C global eradication efforts: towards simplified and enhanced screening, prevention, and treatment. *Translational Gastroenterology and Hepatology*, *9*, 30. https://doi.org/10.21037/tgh-23-104

[50] Klein, M. B. (2022). Simplifying HCV treatment: a pathway to elimination and model for delivering health care to vulnerable populations. *the Lancet. Gastroenterology & Hepatology*, *7*(4), 277–279. https://doi.org/10.1016/s2468-1253(21)00467-2

[51] Dore, G. J., Feld, J. J., Thompson, A., Martinello, M., Muir, A. J., Agarwal, K., Müllhaupt, B., Wedemeyer, H., Lacombe, K., Matthews, G. V., Schultz, M., Klein, M., Hezode, C., Mercade, G. E., Kho, D., Petoumenos, K., Marks, P., Tatsch, F., Santos, A. G. P. D., & Gane, E. (2019). Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial. *Journal of Hepatology*, *72*(3), 431–440. https://doi.org/10.1016/j.jhep.2019.10.010

[52] Oru, E., Trickey, A., Shirali, R., Kanters, S., & Easterbrook, P. (2021). Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health*, *9*(4), e431–e445. https://doi.org/10.1016/s2214-109x(20)30505-2

[53] Jordan, A. E., Cleland, C. M., Schackman, B. R., Wyka, K., Perlman, D. C., & Nash, D. (2019). Hepatitis C virus (HCV) care continuum outcomes and HCV community viral loads among patients in an opioid treatment program. *The Journal of Infectious Diseases*, *222*(Supplement_5), S335–S345. https://doi.org/10.1093/infdis/jiz686

[54] *A systematic literature review of interventions to increase linkage to care and adherence to treatment for hepatitis B and C, HIV and tuberculosis among people who inject drugs*. (2022, November 22). European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/publications-data/systematic-literature-review-interventions-increase-linkage-care-and-adherence

[55] Lazarus, J. V., Wiktor, S., Colombo, M., & Thursz, M. (2017). Micro-elimination – A path to global elimination of hepatitis C. *Journal of Hepatology*, *67*(4), 665–666. https://doi.org/10.1016/j.jhep.2017.06.033

doi:10.6342/NTU202501025

[56] Lazarus, J. V., Picchio, C. A., Byrne, C. J., Crespo, J., Colombo, M., Cooke, G. S., Dore, G. J., Grebely, J., Ward, J. W., & Dillon, J. F. (2022). A Global Systematic Review of Hepatitis C Elimination Efforts through Micro-Elimination. *Seminars in Liver Disease*, *42*(02), 159–172. https://doi.org/10.1055/a-1777-6112

[57] Alkhawaldeh, I. M., Moawad, M. H. E. D., & Al-Jafari, M. (2024). The impact of Hepatitis C Microelimination Strategies in HCV/HIC co-infected Individuals: A current state of art. *JAP Academy Journal*, *2*(2). https://doi.org/10.58877/japaj.v2i2.133

[58] Falade-Nwulia, O., Sulkowski, M. S., Merkow, A., Latkin, C., & Mehta, S. H. (2018). Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *Journal of Viral Hepatitis*, *25*(3), 220–227. https://doi.org/10.1111/jvh.12859

[59] Wyles, D. L., Kang, M., Matining, R. M., Murphy, R. L., & Peters, M. G. (2021). Continued Low Rates of Hepatitis C Virus (HCV) Recurrence in HCV/HIV- and HCV-Infected Participants Who Achieved Sustained Virologic Response After Direct-Acting Antiviral Treatment: Final Results From the AIDS Clinical Trials Group A5320 Viral Hepatitis C Infection Long-term Cohort Study (V-HICS). *Open Forum Infectious Diseases*, *8*(12). https://doi.org/10.1093/ofid/ofab511

[60] Carson, J. M., Hajarizadeh, B., Hanson, J., O'Beirne, J., Iser, D., Read, P., Balcomb, A., Davies, J., Doyle, J. S., Yee, J., Martinello, M., Marks, P., Dore, G. J., & Matthews, G. V. (2021). Effectiveness of treatment for hepatitis C virus reinfection following direct acting antiviral therapy in the REACH-C cohort. *International Journal of Drug Policy*, *96*, 103422. https://doi.org/10.1016/j.drugpo.2021.103422

[61]Sacks-Davis, R., Van Santen, D. K., Boyd, A., Young, J., Stewart, A., Doyle, J. S., Rauch, A., Mugglin, C., Klein, M., Van Der Valk, M., Smit, C., Jarrin, I., Berenguer, J., Lacombe, K., Requena, M., Wittkop, L., Leleux, O., Bonnet, F., Salmon, D., . . . Vincensini, J. (2024). Changes in incidence of hepatitis C virus reinfection and access to direct-acting antiviral therapies in people with HIV from six countries, 2010–19: an analysis of data from a consortium of prospective cohort studies. *The Lancet HIV*, *11*(2), e106–e116. https://doi.org/10.1016/s2352-3018(23)00267-9

[62] Martinello, M., Carson, J. M., Van Der Valk, M., Rockstroh, J. K., Ingiliz, P., Hellard, M., Nelson, M., Lutz, T., Bhagani, S., Kim, A. Y., Hull, M., Cordes, C., Moon, J., Feld, J. J., Gane, E., Rauch, A., Bruneau, J., Tu, E., Applegate, T., . . . Matthews, G. V. (2023). Reinfection incidence and risk among people treated for recent hepatitis C virus infection. *AIDS*. https://doi.org/10.1097/qad.0000000000003651

[63] Falade-Nwulia, O., Sulkowski, M. S., Merkow, A., Latkin, C., & Mehta, S. H. (2018). Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *Journal of Viral Hepatitis*, *25*(3), 220–227. https://doi.org/10.1111/jvh.12859

[64] Deeks, S. G., Overbaugh, J., Phillips, A., & Buchbinder, S. (2015). HIV infection. *Nature Reviews Disease Primers*, *1*(1). https://doi.org/10.1038/nrdp.2015.35

[65] Palacio-Vieira, J., Reyes-Urueña, J.M., Imaz, A. *et al.* Strategies to reengage patients lost to follow up in HIV care in high income countries, a scoping review. *BMC Public Health* **21**, 1596 (2021). https://doi.org/10.1186/s12889-021-11613-y

[66] Hiv.Gov. (2025, February 19). *HIV.gov Archives: National HIV/AIDS Strategies and Reports*. HIV.gov. https://www.hiv.gov/nhas-archives

[67] "Fast-Track Targets 90-90-90 95-95-95 ZERO - UNAIDS." https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf.

doi:10.6342/NTU202501025

[68] *USAID's leadership to sustain and Accelerate the HIV response | Global Health | U.S. Agency for International Development*. (n.d.). U.S. Agency For International Development. https://web.archive.org/web/20250201195958/https://www.usaid.gov/global-health/health-areas/hiv-and-aids/hiv-sustainability

[69] Sepúlveda-Crespo, D., Volpi, C., Amigot-Sánchez, R., Yélamos, M. B., Díez, C., Gómez, J., Hontañón, V., Berenguer, J., González-García, J., Martín-Escolano, R., Resino, S., & Martínez, I. (2024). Sustained Long-Term Decline in Anti-HCV Neutralizing Antibodies in HIV/HCV-Coinfected Patients Five Years after HCV Therapy: A Retrospective Study. *Pharmaceuticals*, *17*(9), 1152. https://doi.org/10.3390/ph17091152

[70] Zarębska-Michaluk, D., Rzymski, P., Kanecki, K., Tyszko, P., Lewtak, K., Goryński, P., Genowska, A., Parczewski, M., & Flisiak, R. (2024). Hospitalizations and deaths among people coinfected with HIV and HCV. *Scientific Reports*, *14*(1). https://doi.org/10.1038/s41598-024-80289-2

[71] Sikavi, C., Chen, P. H., Lee, A. D., Saab, E. G., Choi, G., & Saab, S. (2017). Hepatitis C and human immunodeficiency virus coinfection in the era of direct-acting antiviral agents: No longer a difficult-to-treat population. *Hepatology*, *67*(3), 847–857. https://doi.org/10.1002/hep.29642

[72] Bartlett, S. R., Verich, A., Carson, J., Hosseini-Hooshyar, S., Read, P., Baker, D., Post, J. J., Finlayson, R., Bloch, M., Doyle, J. S., Shaw, D., Hellard, M., Martinez, M., Marks, P., Dore, G. J., Matthews, G. V., Applegate, T., & Martinello, M. (2022). Patterns and correlates of hepatitis C virus phylogenetic clustering among people living with HIV in Australia in the direct-acting antiviral era: A molecular epidemiology study among participants in the CEASE cohort. *Health Science Reports*, *5*(5). https://doi.org/10.1002/hsr2.719

[73] Kronfli, N., Bhatnagar, S. R., Hull, M. W., Moodie, E. E., Cox, J., Walmsley, S., Gill, J., Cooper, C., Martel-Laferrière, V., Pick, N., & Klein, M. B. (2019). Trends in cause-specific mortality in HIV–hepatitis C coinfection following hepatitis C treatment scale-up. AIDS, 33(6), 1013–1022. https://doi.org/10.1097/qad.0000000000002156

[74] Chalouni, M., Pol, S., Sogni, P., Fontaine, H., Lacombe, K., Marc-Lacombe, J., Esterle, L., Dorival, C., Bourlière, M., Bani-Sadr, F., De Ledinghen, V., Zucman, D., Larrey, D., Salmon, D., Carrat, F., Wittkop, L., Salmon, D., Wittkop, L., Sogni, P., . . . Lebrasseur-Longuet, D. (2020). Increased mortality in HIV/HCV-coinfected compared to HCV-monoinfected patients in the DAA era due to non-liver-related death. Journal of Hepatology, 74(1), 37–47. https://doi.org/10.1016/j.jhep.2020.08.008

[75] MacGregor, L., Martin, N. K., Mukandavire, C., Hickson, F., Weatherburn, P., Hickman, M., & Vickerman, P. (2017). Behavioural, not biological, factors drive the HCV epidemic among HIV-positive MSM: HCV and HIV modelling analysis including HCV treatment-as-prevention impact. International Journal of Epidemiology, 46(5), 1582–1592. https://doi.org/10.1093/ije/dyx075

[76] Chen-Hua Liu, Hsin-Yun Sun, Cheng-Yuan Peng, Szu-Min Hsieh, Sheng-Shun Yang, Wei-Yu Kao, Yu-Lueng Shih, Chih-Lin Lin, Chun-Jen Liu, Wang-Hui Sheng, Yi-Chun Lo, Wen-Chun Liu, Jo-Hsuan Wu, Tung-Hung Su, Tai-Chung Tseng, Pei-Jer Chen, Chien-Ching Hung, Jia-Horng Kao, Hepatitis C Virus Reinfection in People With HIV in Taiwan After Achieving Sustained Virologic Response With Antiviral Treatment: The RECUR Study, *Open Forum Infectious Diseases*, Volume 9, Issue 8, August 2022, ofac348, https://doi.org/10.1093/ofid/ofac348

[77] Russo, P., Pani, L., Staniscia, T., Romano, F., & Marzioni, M. (2020). Impact of reimbursement limits on patient access to direct-acting antivirals in Italy: analysis of data from national registries. *DOAJ (DOAJ: Directory of Open Access Journals)*, *24*(10), 5758–5768. https://doi.org/10.26355/eurrev_202005_21368

[78] Snell, G., Marshall, A. D., Van Gennip, J., Bonn, M., Butler-McPhee, J., Cooper, C. L., Kronfli, N., Williams, S., Bruneau, J., Feld, J. J., Janjua, N. Z., Klein, M., Cunningham, N., Grebely, J., & Bartlett, S. R. (2023). Public reimbursement policies in Canada for direct-acting antiviral treatment of hepatitis C virus infection: A descriptive study. *Canadian Liver Journal*, *6*(2), 190–200. https://doi.org/10.3138/canlivj-2022-0040

doi:10.6342/NTU202501025

[79] Salazar-Vizcaya, L., Kouyos, R. D., Fehr, J., Braun, D., Estill, J., Bernasconi, E., Delaloye, J., Stöckle, M., Schmid, P., Rougemont, M., Wandeler, G., Günthard, H. F., Keiser, O., & Rauch, A. (2017). On the potential of a short-term intensive intervention to interrupt HCV transmission in HIV-positive men who have sex with men: A mathematical modelling study. *Journal of Viral Hepatitis*, *25*(1), 10–18. https://doi.org/10.1111/jvh.12752

[80] Amele, S., Sandri, A. K., Rodger, A., Vandekerckhove, L., Benfield, T., Milinkovic, A., Duvivier, C., Stellbrink, H., Sambatakou, H., Chkhartishvili, N., Caldeira, L., Laguno, M., Domingo, P., Wandeler, G., Gisinger, M., Kuzovatova, E., Dragovic, G., Knysz, B., Matulionyte, R., . . . Peters, L. (2021). HCV reinfection after HCV therapy among HIV/HCV-coinfected individuals in Europe. *HIV Medicine*, *23*(6), 684–692. https://doi.org/10.1111/hiv.13212

[81] Scott, N., Hellard, M., & McBryde, E. S. (2016). Modeling hepatitis C virus transmission among people who inject drugs: Assumptions, limitations and future challenges. *Virulence*, *7*(2), 201–208.
[82] Nixon, K., Jindal, S., Parker, F., Marshall, M., Reich, N. G., Ghobadi, K., Lee, E. C., Truelove, S., & Gardner, L. (2022). Real-time COVID-19 forecasting: challenges and opportunities of model performance and translation. *The Lancet Digital Health*, *4*(10), e699–e701. https://doi.org/10.1016/s2589-7500(22)00167-4

[83] Shepherd, M. (2020, May 23). People's misunderstandings of coronavirus predictions are eerily similar to those about weather forecasts. *Forbes*. https://www.forbes.com/sites/marshallshepherd/2020/05/22/misunderstanding-of-coronavirus-predictions-is-eerily-similar-to-weather-forecasting/

[84] Rui, J., Li, K., Wei, H., Guo, X., Zhao, Z., Wang, Y., Song, W., Abudunaibi, B., & Chen, T. (2024). MODELS: a six-step framework for developing an infectious disease model. *Infectious Diseases of Poverty*, *13*(1). https://doi.org/10.1186/s40249-024-01195-3

[85] Pollett, S., Johansson, M. A., Reich, N. G., Brett-Major, D., Del Valle, S. Y., Venkatramanan, S., Lowe, R., Porco, T., Berry, I. M., Deshpande, A., Kraemer, M. U. G., Blazes, D. L., Pan-Ngum, W., Vespigiani, A., Mate, S. E., Silal, S. P., Kandula, S., Sippy, R., Quandelacy, T. M., . . . Rivers, C. (2021). Recommended reporting items for epidemic forecasting and prediction research: The EPIFORGE 2020 guidelines. *PLoS Medicine*, *18*(10), e1003793. https://doi.org/10.1371/journal.pmed.1003793

[86] Carvalho, A. R., & Pinto, C. M. (2014). A coinfection model for HIV and HCV. *Biosystems*, *124*, 46–60. https://doi.org/10.1016/j.biosystems.2014.08.004

[87] Virlogeux, V., Zoulim, F., Pugliese, P., Poizot-Martin, I., Valantin, M., Cuzin, L., Reynes, J., Billaud, E., Huleux, T., Bani-Sadr, F., Rey, D., Frésard, A., Jacomet, C., Duvivier, C., Cheret, A., Hustache-Mathieu, L., Hoen, B., Cabié, A., & Cotte, L. (2017). Modeling HIV-HCV coinfection epidemiology in the direct-acting antiviral era: the road to elimination. *BMC Medicine*, *15*(1). https://doi.org/10.1186/s12916-017-0979-1

[88] Salazar-Vizcaya, L., Kouyos, R. D., Zahnd, C., Wandeler, G., Battegay, M., Darling, K. E. A., Bernasconi, E., Calmy, A., Vernazza, P., Furrer, H., Egger, M., Keiser, O., & Rauch, A. (2016). Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. *Hepatology*, *64*(6), 1856–1869. https://doi.org/10.1002/hep.28769

[89] Abiodun, O. E., Adebimpe, O., Ndako, J. A., Oludoun, O., Aladeitan, B., & Adeniyi, M. (2022). Mathematical modeling of HIV-HCV co-infection model: Impact of parameters on reproduction number. *F1000Research*, *11*, 1153. https://doi.org/10.12688/f1000research.124555.2

[90] Newsum, A. M., Stolte, I. G., Van Der Meer, J. T., Schinkel, J., Van Der Valk, M., Vanhommerig, J. W., Buvé, A., Danta, M., Hogewoning, A., & Prins, M. (2017). Development and validation of the HCV-MOSAIC risk score to assist testing for acute hepatitis C virus (HCV) infection in HIV-infected men who have sex with men (MSM). *Eurosurveillance*, *22*(21). https://doi.org/10.2807/1560-7917.es.2017.22.21.30540

doi:10.6342/NTU202501025

[91] Feldman, J. (2016). The simplicity principle in perception and cognition. *Wiley Interdisciplinary Reviews Cognitive Science*, *7*(5), 330–340. https://doi.org/10.1002/wcs.1406

[92] McFadden, J. (2023). Razor sharp: The role of Occam's razor in science. *Annals of the New York Academy of Sciences*, *1530*(1), 8–17. https://doi.org/10.1111/nyas.15086

[93] Antal, B. B., Chesebro, A. G., Strey, H. H., Mujica-Parodi, L. R., & Weistuch, C. (2024). Achieving Occam's razor: Deep learning for optimal model reduction. *PLoS Computational Biology*, *20*(7), e1012283. https://doi.org/10.1371/journal.pcbi.1012283

[94] Liu, C., & Kao, J. (2023). Acute hepatitis C virus infection: clinical update and remaining challenges. *Clinical and Molecular Hepatology*, *29*(3), 623–642. https://doi.org/10.3350/cmh.2022.0349

[95] Ogawa, E., Kawano, A., Kohjima, M., Koyanagi, T., Dohmen, K., Ooho, A., Satoh, T., Takahashi, K., Furusyo, N., Kajiwara, E., Azuma, K., Ichiki, Y., Sugimoto, R., Amagase, H., Senju, T., Tanaka, M., Nakamuta, M., Nomura, H., & Hayashi, J. (2025). Long-Term liver morbidity and mortality after hepatitis C virus elimination by Direct-Acting antivirals. *Journal of Gastroenterology and Hepatology*. https://doi.org/10.1111/jgh.16892

[96] *CHIP – Centre of Excellence for Health, Immunity and Infections*. (n.d.). https://chip.dk/Research/Studies/EuroSIDA

doi:10.6342/NTU202501025