OPTIMIZATION OF CLINICAL MANAGEMENT OF VIRAL INFECTIOUS DISEASES IN DRUG USERS

OPTIMIZACIÓN DEL MANEJO CLÍNICO DE ENFERMEDADES INFECCIOSAS VÍRICAS EN USUARIOS DE DROGAS

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DOCTORANDA/O

DIANA CORONA MATA

TÍTULO DE LA TESIS:

OPTIMIZATION OF CLINICAL MANAGEMENT OF VIRAL INFECTIOUS DISEASES IN DRUG USERS / OPTIMIZACIÓN DEL MANEJO CLÍNICO DE ENFERMEDADES INFECCIOSAS VÍRICAS EN USUARIOS DE DROGAS

INFORME RAZONADO DE LAS/LOS DIRECTORAS/ES DE LA TESIS
(se hará mención a la evolución y desarrollo de la tesis, así como a trabajos y publicaciones derivados de la misma)

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El presente proyecto de tesis doctoral está constituido por **tres publicaciones** realizadas en su totalidad en el grupo de investigación en Virología Clínica y Zoonosis del IMIBIC, sobre la optimización del manejo clínico de las infecciones virales más frecuentes en usuarios de drogas. Los resultados derivados de este proyecto de tesis doctoral han sido publicados en revistas internacionales indexadas en el Journal Citation Report. Estas publicaciones acumulan un factor de impacto de 21,2 puntos.

- **Corona-Mata D**, Rivero-Juárez A, Camacho Á, Ruiz-Torres L, Ruiz-Cáceres I, de la Fuente Darder B, Cáceres-Anillo D, de Guía Castro-Granados M, Lizaur-Barbudo M, Victoria Cabrera-Gisbert M, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A. Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers. Front Public Health. 2023; 11: 1092960. (FI 5,2 / Q1)

- **Corona-Mata D**, Rivero-Juárez A, Camacho Á, Ruiz-Torres L, Ruiz-Cáceres I, Pérez AB, de la Fuente Darder B, Cáceres-Anillo D, Castro-Granados MG, Lizaur-Barbudo M, Cabrera-Gisbert MV, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A. Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addiction Centres. Front Public Health. 2024; 11:1258095. (FI 5,2 / Q1)

- **Corona-Mata D**, Pérez-Valero I, Camacho A, Gutiérrez Liarte Á, Montero-Alonso M, Alemán MR, Ruiz-Seco P, Pérez González A, Riera M, Jarrin I, Rivero-Juárez A, Rivero A. Effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters. Int J Antimicrob Agents. 2024; 63 (1):107016. (FI 10,8 / Q1)

Todos estos trabajos han sido realizados por la doctoranda, con la supervisión de sus directores, y el apoyo técnico y científico de nuestro grupo de investigación. Durante el periodo doctoral, la doctoranda ha demostrado un gran interés y compromiso con nuestro grupo de investigación, convirtiéndose en parte fundamental del mismo. El compromiso y dedicación de la doctoranda, tanto en su tarea investigadora como asistencial, quedan reflejados en que ha sido beneficiaria de un contrato **Rio Hortega**. La obtención de este contrato ha sido un gran estímulo para la doctoranda a fin de afianzar su formación investigadora.

Por otro lado, ha cumplido todas las actividades formativas propuestas en el Programa de trabajo, destacando:

1. Presentación de comunicaciones en diferentes **Congresos Nacionales e Internacionales** de Enfermedades Infecciosas, como el European Conference on Clinical Microbiology and Infectious Diseases (ECCMID) y el Congreso Nacional de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica.

2. Formación reglada en **Estadística Básica aplicada en investigación biomédica y avanzada**, colaborando con el equipo de investigación AntiViral Research Center de la Universidad de California, San Diego.

3. Asistencia al **XI Congreso Científico de Investigadores en Formación** de la Universidad de Córdoba e IMIBIC.

4. Asistencia al **ciclo de seminarios** de investigación de IMIBIC.

5. Participación como docente en **jornadas de difusión** a la ciudadanía para la prevención del VIH y otras enfermedades de transmisión sexual.

6. Informe Favorable en calidad de **Tutor Clínico del Departamento de Ciencias Médicas y Quirúrgicas** de la Universidad deCórdoba, durante los cursos académicos 2021-2022 y 2022-2023, con un cómputo de 350 horas por curso académico, en la especialidad de Enfermedades Infecciosas.

7. Nombramiento como **Colaborador Honorario Ciencias de la Salud** del Departamento de Ciencias Médicas y Quirúrgicas de laUniversidad de Córdoba, durante los cursos académicos 2021-2022 y 2022-2023, teniendo programada su actividad docente para el curso académico 2023-2024 en los meses de abril y mayo (asignatura Enfermedades Infecciosas II).

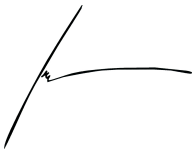
Por último, nos gustaría destacar que la doctoranda ha realizado una **estancia formativa** de tres meses (septiembre a diciembre de 2023) en la Universidad de San Diego - California (Estados Unidos), por la que solicitará la mención internacional del presente proyecto de tesis doctoral.

En resumen, consideramos que el presente proyecto de Tesis Doctoral reúne los méritos suficientes para optar al Grado de Doctor en Biomedicina por la Universidad de Córdoba.

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, a 9 de abril de 2024

Las/los directoras/es



Fdo.: Antonio Rivero Román

Nombre y Apellidos

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QUALITY INDICATORS OF THE PUBLICATIONS PRESENTED IN THE DOCTORAL THESIS PROJECT

Objetive	Title	Journal	Category	Position	Impact factor
To evaluate an intervention for the diagnosis and treatment of chronic hepatitis C in people with history or current drug use	Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centres	Frontiers in Public Health	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	25/180 (Q1/T1)	5.2
To evaluate the vaccination initiation rates against Hepatitis B in drug users and compare them with the vaccination rates obtained against SARS-Cov-2 in this same population and time period.	Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addictions Centres	Frontiers in Public Health	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH	25/180 (Q1/T1)	5.2
To assess the effectiveness and tolerability of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters.	Effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters	International Journal of Antimicrobial Agents	PHARMACOLOGY & PHARMACY	11/278 (Q1/D1/T1)	10.8

ACKOWLEGLEMENT

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GENERAL INDEX

SUMMARY

Controlling and eliminating infections such as those caused by the Hepatitis B virus, Hepatitis C virus, and Human Immunodeficiency Virus are priority objectives for the World Health Organization. Drug users constitute a particularly vulnerable population for acquiring these infections. The psycho-social problems stemming from drug consumption and stigma act as barriers that impede drug users' access to healthcare services and their engagement with them. This often leads to delayed diagnosis of these infections, treatment delays, and frequent interruptions and discontinuations of treatment. Consequently, there are two significant consequences: high morbidity and mortality rates from these infections among drug users and drug users serving as reservoirs for these infections. Therefore, addressing viral infections in drug users presents a challenge that involves improving the individual health of each patient and achieving infection control within this group to prevent its spread to the general population.

The burden of hepatitis C infection in people with a history of current drug use is a high risk of hepatic complications and transmission of infectious disease. This population is poorly linked to the health system, and it is difficult to achieve and support treatment because they have high rates of lost follow-up. We evaluate an intervention for the diagnosis and treatment of chronic hepatitis C and HIV in this population. Six hundred and eighty-three people attended the DAC and were asked to participate in health counseling and provide blood samples for testing HCV, HIV, and syphilis from April 2019 to June 2020. A total of 556 subjects were surveyed and tested. All of them were assigned to a patient navigation program to improve health education and link to the sanitary system. Of the 556 patients who agreed to participate in the study, 33 (5.9%) had active HCV infection. Twenty-eight patients (93.3%) completed treatment, and 26 achieved Sustained Viral Response (78.8%). Our study suggests that implementing strategies based on personalized intervention models can contribute to controlling HCV infection in DAC users.

Persons with substance use disorder are at increased risk for hepatitis B virus (HBV) infection. Although most of them are attached to social health centers, the vaccination rate in this group is low. In this context, we designed a study to evaluate the prevalence of users of drug addiction centers (DAC) not immunized against hepatitis B and to compare the vaccination rate against hepatitis B with the rate of immunization against SARS-Cov-2 in two years of follow-up. A total of 325 subjects were surveyed and tested. At baseline, 65% (211/325) were candidates to initiate vaccination and were advisors to HBV vaccination. During the follow-up, 15/211 (7,2%) individuals received at least one dose of HBV vaccine. In the same period, 186/211 (88,2%) individuals received at least one dose against SARS-Cov-2. The comparison between vaccination rates reached statistically significant ($p < 0.001$). Our study manifests a low immunization rate against HBV in DAC users despite a high level of immunization for SARS-Cov-2 during the same period in the same population. Consequently, the lack of immunization against HVB in this population might be related to health policy issues more than to individuals linked to care and awareness.

Late presentation of HIV infection, defined by the presence of a CD4 + cell count < 200 cells/mm3 or AIDS-defining conditions (a widespread situation among drug users), remains a significant problem among people living with HIV. We assess the effectiveness and tolerability of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in late presenter treatment-naïve adult individuals from the CoRIS Cohort. The primary objective was the achievement of viral suppression (VS), defined as HIV RNA < 50 cop/mL. We evaluated 314 individuals. Individuals with AIDS-defining conditions initiating ART with BIC/FTC/TAF achieved higher rates of viral suppression at 24 weeks than other regimens. At 24 and 48 weeks after ART initiation, treatment discontinuations were lower with BIC/FTC/TAF than with other regimens. Our results suggest that BIC/FTC/TAF could be a preferred regimen as initial therapy in HIV late presenters because of its high effectiveness and good tolerability.

RESUMEN

El control y la eliminación de infecciones como las causadas por el virus de la Hepatitis B, el virus de la Hepatitis C y el Virus de Inmunodeficiencia Humana son objetivos prioritarios para la Organización Mundial de la Salud. Los usuarios de drogas constituyen una población particularmente vulnerable para adquirir estas infecciones. Los problemas psicosociales derivados del consumo de drogas y el estigma de padecerlas actúan como barreras que dificultan el acceso de esta población a los servicios de salud y su compromiso con ellos. Este hecho a menudo conduce al diagnóstico tardío, retraso en el tratamiento y frecuentes interrupciones y discontinuaciones del mismo. Como resultado, existen dos consecuencias significativas: altas tasas de morbilidad y mortalidad por estas infecciones entre los usuarios de drogas y que los usuarios de drogas sirven como reservorio para estas infecciones. Por lo tanto, abordar las infecciones virales en los usuarios de drogas presenta un desafío que implica mejorar la salud individual de cada paciente y lograr el control de la infección dentro de este grupo para prevenir su propagación a la población general.

La carga de la infección por hepatitis C en personas con antecedentes de consumo de drogas supone un alto riesgo de complicaciones hepáticas y transmisión de esta enfermedad infecciosa. Esta población está poco vinculada al sistema de salud y es difícil lograr y apoyar el tratamiento porque tienen altas tasas de pérdida de seguimiento. Evaluamos una intervención para el diagnóstico y tratamiento de la hepatitis C crónica y el VIH en esta población. Seiscientas ochenta y tres personas asistieron a los Centros de Drogas y Adicciones (CAD) y se les pidió que participaran en un estudio para el asesoramiento en salud y proporcionaran muestras de sangre para detección de VHC, VIH y sífilis de abril de 2019 a junio de 2020. Un total de 556 sujetos fueron encuestados y evaluados. Todos ellos fueron asignados a un programa de “navegación de pacientes” para mejorar la educación en salud y su vinculación al sistema sanitario. De los 556 pacientes que aceptaron participar en el estudio, 33 (5,9%) tenían infección activa por VHC. Veintiocho pacientes (93,3%) completaron el tratamiento y 26 alcanzaron Respuesta Viral Sostenida (78,8%). Nuestro estudio sugiere que implementar estrategias basadas en modelos de

intervención personalizados puede contribuir al control de la infección por VHC en usuarios de CAD.

Las personas con trastorno por consumo de sustancias tienen un mayor riesgo de infección por el virus de la hepatitis B (VHB). Aunque la mayoría de ellos están vinculados a centros de salud social, la tasa de vacunación en este grupo es baja. En este contexto, diseñamos un estudio para evaluar la prevalencia de usuarios de los CAD no inmunizados frente a la hepatitis B y comparar la tasa de vacunación contra la hepatitis B con la tasa de inmunización frente a SARS-CoV-2 durante dos años de seguimiento. Se encuestó y evaluó a un total de 325 sujetos. Al inicio, el 65% (211/325) eran candidatos para iniciar la vacunación y se les aconsejó vacunación frente a VHB en sus centros de destino. Durante el seguimiento, 15/211 (7,2%) individuos recibieron al menos una dosis de la vacuna frente a VHB. En el mismo período, 186/211 (88,2%) individuos recibieron al menos una dosis frente a SARS-CoV-2. La comparación entre las tasas de vacunación presentó diferencias estadísticamente significativas ($p < 0,001$). Nuestro estudio manifiesta una baja tasa de inmunización frente al VHB en los usuarios de CAD a pesar de un alto nivel de inmunización contra el SARS-CoV-2 durante el mismo período en la misma población. En consecuencia, la falta de inmunización contra el VHB en esta población podría estar relacionada con problemas de políticas de salud más que con factores de los individuos relacionados con el cuidado y la conciencia de salud.

La presentación tardía de la infección por VIH, definida por la presencia de un recuento de células CD4 + < 200 células/mm3 o condiciones definitorias de SIDA (una situación generalizada entre los usuarios de drogas), sigue siendo un problema importante entre las personas que viven con VIH. Evaluamos la eficacia y tolerabilidad de bictegravir/emtricitabina/tenofovir alafenamida (BIC/FTC/TAF) en el tratamiento de individuos adultos no tratados previamente y con presentación tardía de la cohorte española CoRIS. El objetivo principal fue lograr la supresión viral (SV), definida como ARN de VIH < 50 cop/mL. Evaluamos a 314 individuos. Los individuos con condiciones definitorias de SIDA que iniciaron tratamiento antirretroviral (TAR) con BIC/FTC/TAF lograron tasas

más altas de supresión viral a las 24 semanas que otros regímenes. A las 24 y 48 semanas después del inicio del TAR, las interrupciones del tratamiento fueron menores con BIC/FTC/TAF que con otros regímenes. Nuestros resultados sugieren que BIC/FTC/TAF podría ser un régimen preferido como terapia inicial en presentadores tardíos de VIH debido a su alta efectividad y buena tolerabilidad.

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse events
AIDS	Acquired Immunoeficiency Syndrome
APRI	AST to Platelet Ratio Index
ART	Antiretroviral therapy
BIC/FTC/TAF	Bictegravir/Emtricitabine/tenofovir alafenamide
CEIC	Comité de Ética de la Investigación
CI	Confidence Interval
CoRIS	Cohort of the Spanish AIDS Research Network
DAA	Direct-acting antiviral
DAC	Drugs and Addiction Centres
DNA	Deoxyribonucleic acid
DRV/COBI/FTC/TAF	Darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DTG	Dolutegravir
DTG/ABC/3TC	Dolutegravir/Abacavir/Lamivudine
EDADES	Encuesta sobre Alcohol y Drogas de España
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ENA	Estrategia Nacional sobre Adicciones
ETR	End of Treatment Respone
FEDER	Fondo Europeo de Desarrollo Regional
FIB-4	Fibrosis-4 score
HBsAb	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B vIrus
HCV	Hepatitis C Virus
HDV	Hepatitis Delta Virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratios
INI	Integrase Inhibitors
IQR	Interquartile range
IR	Immunological recovery

ISCIII	Instituto de Salud Carlos III
ISR	Investigator Sponsored Research
ITT	Intention-to-treat
MSM	Men who have sex with men
MTR	Multitable regimens
NEP	Needle Exchange Program
OR	Odds ratio
OST	Opioid Substitute Therapy
OT	On treatment
PI	Protease Inhibitors
PLWH	People living with HIV
PWID	People who inject drugs
QD	"quaque die" or once a day
RNA	Ribonucleic acid
STR	Single Tablet Regimen
SVR	Sustained Viral Response
TLE	Transient Liver Elastography
UNAIDS	United Nations Programme on HIV/AIDS
VS	Viral suppression
WHO	World Health Organization

OBJECTIVES

1. To evaluate an intervention for the diagnosis and treatment of chronic hepatitis C in people with history or current drug use. Chapter 1
2. To evaluate the vaccination initiation rates against Hepatitis B in drug users and compare them with the vaccination rates obtained against SARS-Cov-2 in this same population and time period. Chapter 2
3. To assess the effectiveness and tolerability of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters. Chapter 3

INTRODUCTION

1. People who use drugs

1.1. Substance use disorders

Drug use, particularly injecting drug use, significantly heightens the risk of transmitting and acquiring blood-borne infections, such as HIV and hepatitis B and C viruses (HBV and HCV), as well as invasive bacterial infections. These infectious diseases impose a considerable burden of morbidity and mortality among drug users (1). Presently, as per the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) definition (2), risky consumption of psychoactive substances is characterized by consumption that leads to evident harm or adverse outcomes for the user, including dependence or any physical, psychological, or social issues, or entails a high likelihood or risk of experiencing such harm. Recreational drug use presents a societal issue impacting various facets of individuals, their surroundings, and society at large. It gives rise to disorders directly associated with substance use (expected drug effects) and other indirect disorders (intoxication, withdrawal, and substance-induced mental disorders like depressive or anxiety disorders). (3). Moreover, it correlates with health complications linked to the method of administration (cellulitis and phlebitis), an elevated infection risk (viruses transmitted parenterally), and a heightened incidence of tumors (e.g., lung or liver carcinoma). Individuals who use drugs face an augmented risk of intoxication and fatality. Furthermore, the emergence of new, more potent, addictive, and/or adulterated substances poses potential health hazards. (4). This complex web of factors makes people who use drugs a particularly vulnerable group.

1.2. Current situation of drug use in Spain

European reports on the status of drug consumption indicate that the use of illegal substances remains high despite the implementation of policies and legislation aimed at eradicating it. In Spain, we have data on drug use available periodically through the Survey on Alcohol and Drug Use (Encuesta sobre Alcohol y Drogas, EDADES), updated to 2022 (Table 1) (5). This report reveals a stable

trend in tobacco consumption, with alcohol being the most prevalent, and increasing use of hypnotics, cannabis, and new psychoactive substances. Conversely, there is a slight decrease in the consumption of heroin.

Prevalencia de consumo de sustancias psicoactivas alguna vez en la vida en la población de 15-64 años (%). España, 1995-2022.

	1995	1997	1999	2001	2003	2005	2007	2009	2011	2013	2015	2018	2020	2022
Tabaco	-	69,7	64,9	68,4	68,9	69,5	68,5	75,0	71,7	73,1	72,5	69,7	70,0	69,6
Alcohol	-	90,6	87,3	89,0	88,6	93,7	88,0	94,2	90,9	93,1	93,5	91,2	93,0	93,2
Hipnosedantes con o sin receta	-	-	-	-	-	8,7	15,4	13,4	19,5	22,2	18,7	20,8	22,5	23,5
Hipnosedantes sin receta	-	-	-	-	-	-	-	-	-	2,7	4,1	3,0	3,1	3,6
Analgésicos opioides con o sin receta	-	-	-	-	-	-	-	-	-	-	-	14,5	15,2	15,8
Analgésicos opioides sin receta	-	-	-	-	-	-	-	-	-	-	-	-	1,7	1,5
Cannabis	14,5	22,9	19,6	23,8	29,0	28,6	27,3	32,1	27,4	30,4	31,5	35,2	37,5	40,9
Éxtasis	2,0	2,5	2,4	4,0	4,6	4,4	4,3	4,9	3,6	4,3	3,6	3,6	5,0	5,1
Alucinógenos	2,1	2,9	1,9	2,8	3,0	3,4	3,8	3,7	2,9	3,8	3,8	4,5	5,5	5,4
Anfetaminas	2,3	2,7	2,2	2,9	3,2	3,4	3,8	3,7	3,3	3,8	3,6	4,0	4,3	4,6
Cocaína (polvo y/o base)	-	-	-	-	-	-	8,3	10,2	8,8	10,3	9,1	10,3	11,2	12,0
Cocaína en polvo	3,4	3,4	3,1	4,8	5,9	7,0	8,0	10,2	8,8	10,2	8,9	10,0	10,9	11,7
Cocaína base	0,3	0,4	0,4	0,5	0,5	0,6	1,8	0,9	0,9	1,0	0,8	1,3	1,4	1,7
Setas mágicas	-	-	-	-	-	-	-	-	2,4	1,9	2,0	2,4	3,5	3,3
Metanfetaminas	-	-	-	-	-	-	-	-	0,8	0,5	0,6	1,2	1,2	1,3
GHB	-	-	-	-	-	-	-	-	-	0,6	0,6	0,5	0,9	0,7
Heroína	0,8	0,6	0,5	0,6	0,9	0,7	0,8	0,6	0,6	0,7	0,6	0,6	0,7	0,6
Inhalables volátiles	0,7	0,8	0,6	0,8	1,0	0,8	1,1	0,6	0,8	0,6	0,5	0,6	0,8	0,9

FUENTE: OEDA Encuesta sobre Alcohol y Drogas en España (EDADES)

Table 1: Ever use of psychoactive substances in the population (%) in Spain (1995-2022)

To assess the health impact of substance consumption, we rely on indirect data such as admissions to treatment units provided by the 2022 Report on Alcohol, Tobacco, and Illegal Drugs in Spain (6). The profile of treatment admissions has undergone notable changes over time. While in the early 2000s, heroin was the substance generating the highest number of treatment demands, a decline in heroin-related demands began around 2004, coinciding with a significant increase in admissions for cocaine treatment. Cannabis has also seen a growing demand for detoxification therapy. In 2020, Spain recorded 38,544 admissions for abuse or dependence on psychoactive substances (excluding alcohol and tobacco). This number represents a 23% reduction in admissions compared to 2019, possibly due to mobility restrictions and the closure of some

addiction treatment centers during the SARS-CoV-2 pandemic. In the last assessed year, cocaine remains the drug causing the highest number of treatment admissions (45.4% of the total), followed by cannabis (27.5%) and opioids and their derivatives (22.1%).

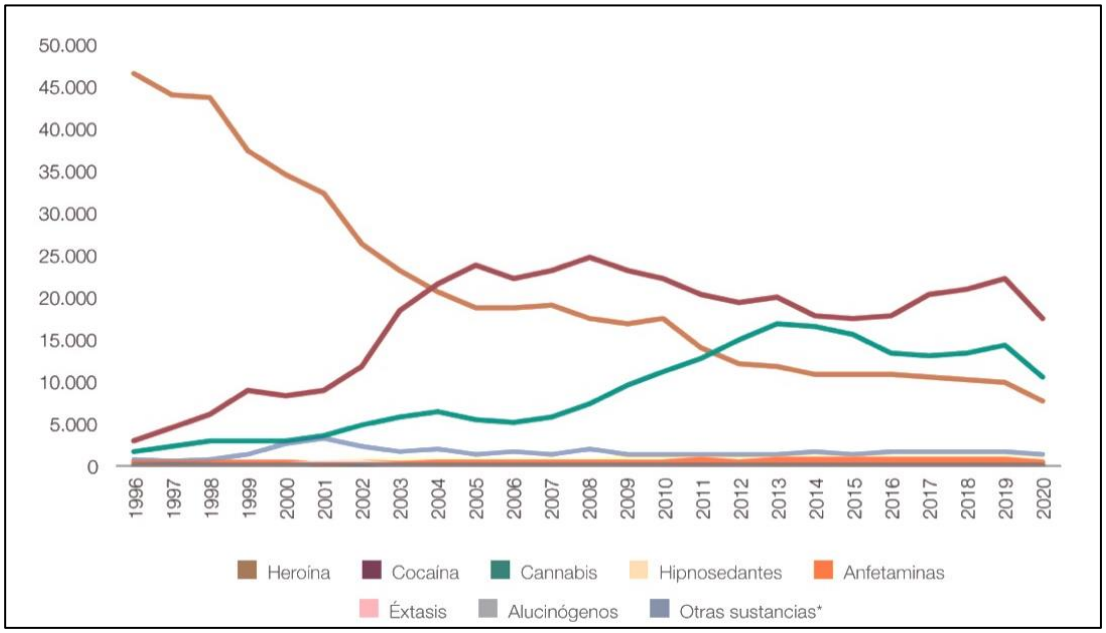

Figure 1: Number of admissions to treatment for illicit drugs. Spain, 1996-2020. Report 2022. Alcohol, tobacco and illegal drugs in Spain. Spanish Observatory on Drugs and Addictions. Spanish Ministry of Health.

These data reflect that, despite observing a decreasing trend in drug and alcohol consumption and abuse, there is still a significant number of consumers in our country. However, a significant limitation of these estimates is that they were conducted in 2020 and did not reflect the impact that the SARS-Cov2 pandemic may have had on this trend. In this regard, the pandemic has had a significant impact on units providing care to drug users, particularly affecting those users who require initial contact with this healthcare resource. Maintaining accessibility to the system and therapy adherence in this scenario has posed a significant challenge (7,8).

1.3. Healthcare for People who use drugs

The National Plan on Drugs and Addictions establishes the necessary measures and specific resources for the adequate healthcare of drug users. The action competencies of this plan are decentralized to the autonomous communities and cities. The decentralization of available resources results in significant differences in the care model depending on the region where the user receives treatment. Various social agents (public, private, and contracted) have established collaborative networks to address the lack of harmonization. These networks aim to provide healthcare and social assistance to people who use drugs from a comprehensive perspective while optimizing available resources more effectively (9). In this sense, the National Strategy on Addictions (Estrategia Nacional sobre Adicciones, ENA 2017-2024) has the following objectives: i) to guarantee comprehensive quality care by coordinating the addiction treatment network with the rest of the healthcare system, ii) to improve treatment and follow-up in healthcare services for individuals with chronic addictions and those of advanced age, iii) to integrate addiction management into community health plans, iv) to evaluate the impact and degree of implementation of the actions carried out, and finally, v) to promote comprehensive care by creating personalized itineraries based on the characteristics of each patient (10). Regarding specific objectives in healthcare, a fundamental pillar of the ENA 2017-2024 is the improvement and expansion of early diagnosis of transmissible infections (viral hepatitis, HIV) and ensuring access to treatment for people who use drugs (11).

Despite these efforts, several barriers are hindering the effectiveness of this strategy for assisting drug users in managing infectious diseases. Obstacles in preventive activities, screening, and treatment implementation greatly hinder infection control efforts. As a result, they pose a threat to the World Health Organization's (WHO) goals for eliminating viral hepatitis by 2030. This ambitious goal established by the WHO aims to reduce new infections by 90% and related deaths by 65%. To achieve these objectives, the WHO has developed a global strategy that includes: i) preventing mother-to-child transmission of hepatitis B, ii) increasing hepatitis B vaccine coverage, iii) improving access to

care and treatment for individuals infected with hepatitis B and C, iv) implementing programs for early detection and diagnosis of viral hepatitis, v) reducing economic and social barriers to access to care and prevention of viral hepatitis and vi) promoting liver health and raising public awareness about viral hepatitis (12). Similarly, United Nations Programme on HIV/AIDS, UNAIDS has set the ambitious "95-95-95" target for HIV. This target aims to ensure that in the coming years, 95% of people living with HIV are aware of their serostatus, 95% of those diagnosed with HIV receive continuous antiretroviral therapy, and 95% of those receiving antiretroviral therapy achieve viral suppression (13).

A population of particular importance in achieving these goals is drug users. Drug consumption increases the risk of contracting infections such as viral hepatitis and HIV, among others, especially using parenteral routes. Additionally, studies have demonstrated that untreated HIV and viral hepatitis reduce the quality of life and life expectancy of those infected, including people who inject drugs. (14). Therefore, it is necessary to approach the healthcare of this group with a comprehensive understanding of their reality, taking into account the intrinsic circumstances of this population and developing specific and personalized strategies to ensure better healthcare for them. Only in this way will we achieve the objectives set by the WHO and UNAIDS.

2. HBV, HCV and HIV Infection in people Who Use Drugs

Hepatitis B, hepatitis C, and HIV are top priorities for the WHO. Eliminating these diseases involves identifying vulnerable populations and implementing preventive, diagnostic, and treatment measures tailored to the needs and characteristics of each population and region. Therefore, the design of strategies should focus on providing care to the most affected individuals with the highest risk, aiming to prevent inequalities that hinder achieving the proposed goals for 2030 (15).

In our country, one of the critical populations to achieve this goal is people who use drugs. Due to their consumption habits, this population is more exposed to HCV, HBV, and HIV than the general population, thus facing a higher risk of advanced disease. Additionally, they tend to have lower adherence to healthcare, leading to late diagnosis of these infections and increased comorbidity. In Spain, the prevalence of infection among drug users in 2020 was 3.3% for HIV, 5.2% for HCV, and 0.4% for HBV (16). This prevalence is significantly higher than that of the general Spanish population, where the prevalence of HIV was 0.13%, 0.69% for HCV, and 0.05% for HBV (17).

2.1. Hepatitis B

Hepatitis B is a common cause of hepatitis, cirrhosis, and hepatocellular carcinoma. HBV is the most common cause of hepatocellular carcinoma worldwide, with attributable cases ranging from 50% in regions with low HBV endemicity to 70%-80% in highly endemic areas (18,19). Despite the efforts of health authorities to eliminate hepatitis B, the global infection prevalence remains high. Estimates suggest that 296 million people worldwide are currently living with hepatitis B (20). Approximately 8.4% (95% CI 4.7-13) of people who inject drugs are estimated to have active infection (defined by positive hepatitis B surface antigen, HBsAg), which translates to 1.2 million people worldwide (95% CI 0.7-1.9). In Spain, the prevalence of chronic hepatitis B among drug users was 0.5% in 2019 (21). The prevalence is higher in Asia and Eastern Europe (21).

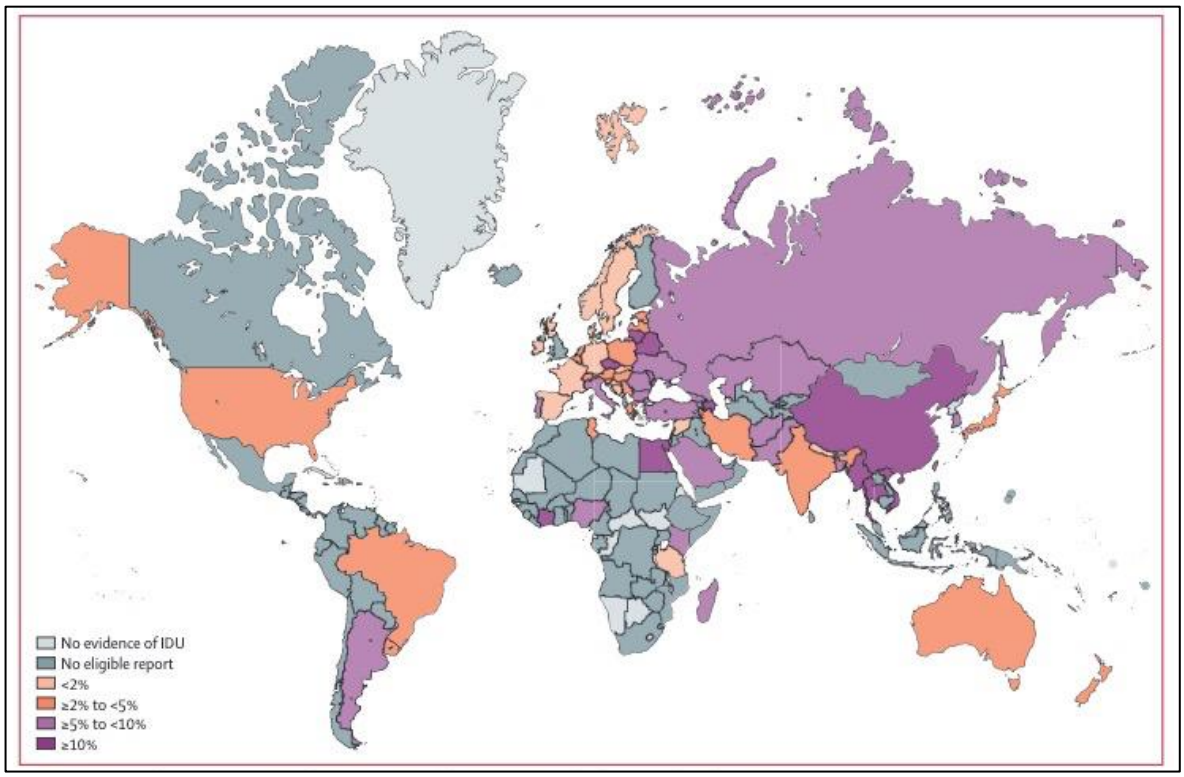

Figure 2: Estimated prevalence of HBsAg in injecting drug users by country. Degenhardt L et al. 2017

Currently, we do not have an antiviral treatment that achieves the cure of hepatitis B infection. Although nucleoside analog drugs like Tenofovir or Entecavir are highly effective at suppressing viral replication of HBV, they do not eliminate the circular DNA of the virus (cccDNA) that persists in the nucleus of infected hepatocytes. Therefore, when treatment is interrupted, the infection reactivates. Additionally, the HBV genome integrates into the host genome and could promote oncogenesis and the development of hepatocellular carcinoma (22). The treatment's current objective is to suppress viral replication in this situation sustainably. Treatment prevents or delays the progression from hepatic fibrosis to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death.

However, we have a highly effective vaccine for hepatitis B virus. Currently, an inactivated vaccine composed of the main surface protein of the virus (HBsAg) is available, produced in genetically modified yeast (Saccharomyces cerevisiae) cultures by incorporating plasmids with the viral gene encoding this protein (23). The Hepatitis B vaccine was marketed in the

1970s, and the WHO recommends its universal administration and includes it in the childhood vaccination schedule. Estimates indicate that at least three doses of the vaccine have been received by 84% of the global population(24), demonstrating a high level of global immunization (25). In Spain, according to the results of the Second National Seroprevalence Study, the level of protection against HBV is high, thanks to its universal and free administration in the pediatric population since 1996. The populations with the highest vaccine coverage are those who received the last vaccine dose before one year and those who received vaccination during adolescence (12-13 years) (Figure 3).

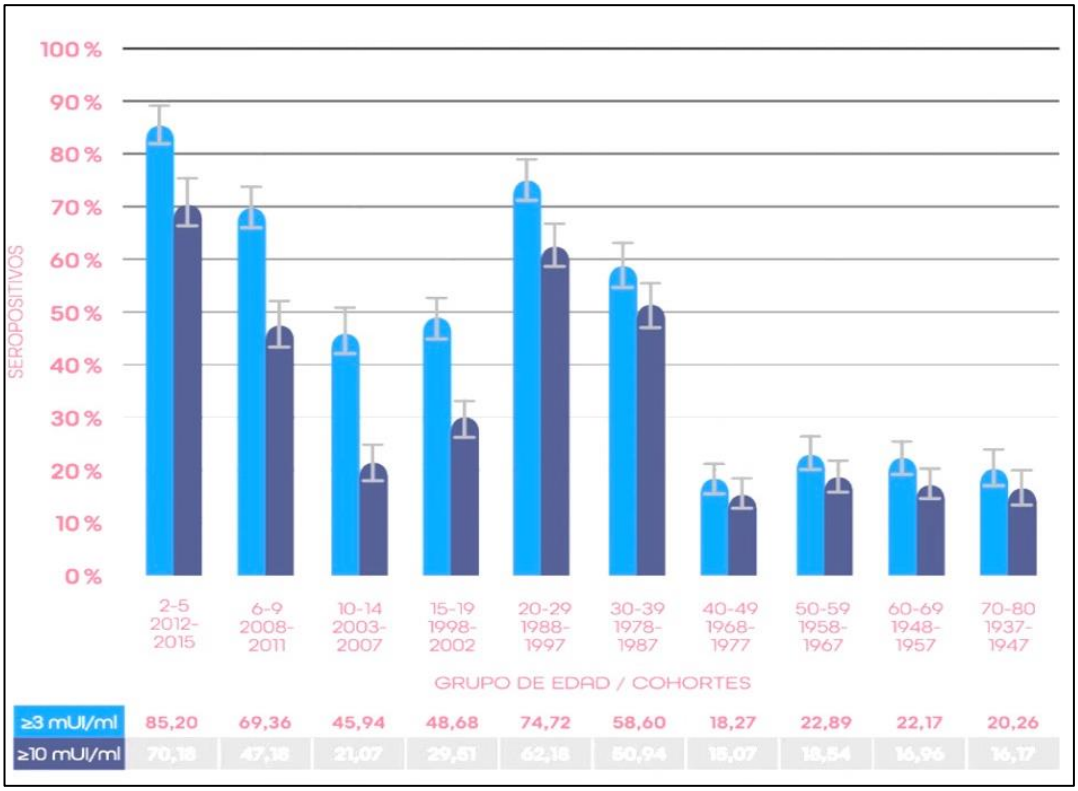

Figure 3: Seroprevalence of HBsAb in the general population in Spain by age group. Second National Seroprevalence Study. 2022

Post-marketing studies have demonstrated that a three-dose regimen induces protective concentrations of anti-HBs in over 90% of healthy adults under 40 years old, although immunogenicity decreases inversely with age (25). The decline in immunity in populations over 40 years old is noteworthy, as individuals in this age group, if they have not belonged to risk groups, have been excluded from possible vaccination rescues.

According to the report on Alcohol, Tobacco, and Drugs, only 35% of parenteral drug users are aware of their serological status for HBV (6). Estimating the number of unvaccinated drug users against hepatitis B among those over 40 years old and those without immunity, which would require vaccination rescue among those under 40 years old, is difficult. Vaccination rates against hepatitis B in drug users are low (26). This low vaccination rate has been assessed in individuals attending addiction centers, especially in younger populations or those with longer vaccination schedules (6-month regimens) (27). Various strategies have been attempted to achieve vaccination in this group, including accelerated vaccination during admission to detoxification centers (28), prisions (29,30) and syringe exchange programs (27) (31–33), which have not achieved sufficient vaccination rate to ensure proper vaccine coverage in this population. Ensuring drug users' adherence to the healthcare system and achieving high vaccination rates in drug users are essential avenues for eliminating HBV.

Furthermore, hepatitis B vaccination is the only strategy for preventing hepatitis D. Hepatitis D is caused by the hepatitis delta virus (HDV). This RNA virus requires HBV for its assembly and spread(31). Individuals with HDV coinfection progress to advanced liver disease faster than those mono-infected with HBV. The global prevalence of anti-HDV antibodies in the HBV-infected population is estimated at 5-15%. Approximately 70% of new HDV transmissions in developed countries are associated with injectable drug use and high-risk sexual practices (32). In some countries, such as Italy, the prevalence of HDV infection has decreased by more than 50% between 1987 and 2019 due to universal vaccination of newborns against HBV and risk reduction strategies in injectable drug users. However, the immigration phenomenon from countries where HDV infection is prevalent and hepatitis B vaccination is low can raise this coinfection.(33). Therefore, HBV vaccination is the only available strategy that allows the elimination of two hepatotropic viruses, HBV and HDV.

2.2. Hepatitis C

Around 58 million people worldwide are living with hepatitis C, with an incidence of 1.5 million new infections each year (34). There are regions with a higher prevalence of infection, such as Western Europe, Latin America, the Caribbean, and North America (21) (Figure 5). The approach to eliminating hepatitis C has been segmented into subpopulations, prioritizing groups with a high incidence of infection or a high risk of developing comorbidity, a strategy known as micro-elimination (35). One of the groups with the highest incidence of hepatitis C in our setting, targeted by multiple micro-elimination strategies, is drug users, especially those who inject drugs. It is estimated that 38.8% (95% CI; 31.4-46.9) of parenteral drug users are living with hepatitis C, which equates to 5.8 million people worldwide (95% CI; 4.6-7) (21). In Spain, the prevalence of hepatitis C among drug users is 5.5%, being higher in those with a history of injecting drug use (36).

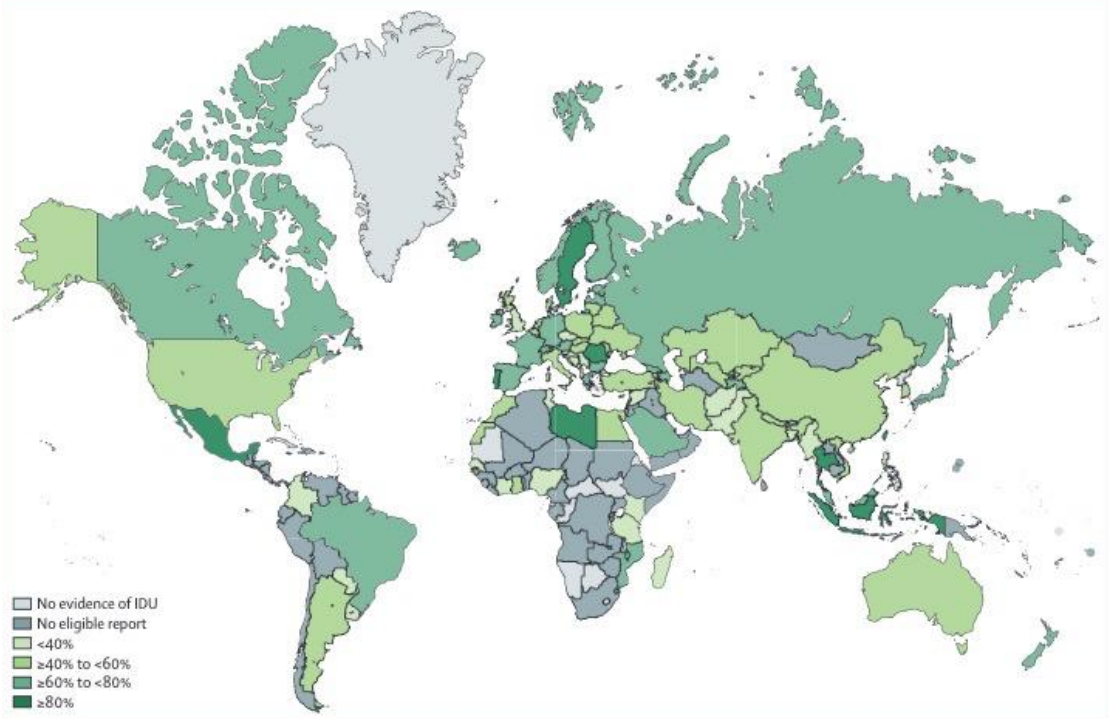

Figure 4: The estimated prevalence of anti-HCV in people who inject drugs by country. Degenhardt L et al. 2017

The prevalence of HCV infection has drastically declined since the implementation of Direct-Acting Antivirals (DAAs). Screening extension measures and treatment accessibility have been fundamental in the fight against HCV. These drugs achieve a functional cure of the infection, defined as a sustained virological response (SVR), after completing a treatment cycle of 8-12 weeks. Given their safety, simple dosing, and high efficacy (over 96%), DAAs constitute the ideal tool for eliminating HCV. Additionally, in cases of chronic hepatitis C with advanced liver disease, DAA treatment has been shown to reverse liver damage and improve fibrosis grade after achieving SVR, thus reducing the likelihood of hepatocellular carcinoma development. Therefore, DAA treatment represents a method of public health prevention and an improvement in individual patient comorbidity (37). Despite this, three challenges in the drug-using population need to be addressed to achieve HCV elimination in this population, given their low adherence to the healthcare system.

The first challenge in achieving the goal of HCV micro-elimination in drug users is to facilitate the diagnosis of the infection. In this regard, various strategies have been tested leveraging the engagement of drug users with addiction treatment centers, aiming to decentralize diagnosis to improve access for this population. Testing drug users at their reference addiction treatment centers offers the advantage of opportunistic screening in this high-prevalence population, thereby facilitating access to testing for this group, which sometimes, due to their socioeconomic status, may be hesitant to visit healthcare facilities. This strategy, known as Check-point or Point-of-care, provides immediate results, as antibodies can be detected within minutes using the provided testing medium and do not require specific healthcare training for administration (38,39). Its main drawback is that a positive antibody test for HCV does not indicate active infection, necessitating additional testing to confirm the presence of HCV RNA (40). Another limitation of Point-of-care is the difficulty in evaluating patients' degree of liver fibrosis. There are validated indirect markers to assess the degree of liver fibrosis, such as the APRI, FIB-4 score, or Transient Hepatic Elastography (THE) (41). Check-point and Point-of-

care strategies have sometimes bypassed this diagnostic process in favor of prioritizing screening and treatment, which can be significant in the patient's clinical management. Those patients with advanced fibrosis or cirrhosis could be undiagnosed, and despite achieving SVR, they may still have an increased risk of developing hepatocellular carcinoma, thus not allowing for an optimal patient follow-up strategy.

On the other hand, single-step diagnosis has successfully simplified the flowchart of hepatitis C diagnosis in laboratory and microbiology services. This strategy involves determining antibodies in the same sample and evaluating the presence of HCV RNA in case of a positive result. This strategy streamlines the diagnostic process and allows for faster treatment initiation (42). However, this strategy requires patient referral to the hospital for blood extraction, which can be challenging in this population.

The second challenge for microelimination among drug users is to ensure good adherence to the healthcare system, ensuring that once diagnosed, the patient initiates and completes the prescribed treatment. Various studies on treatment dispensation at the Point-of-Care provide all medication at the time of diagnosis, which may result in the patient not starting or not correctly adhering to treatment (43). The role of "Patient navigator" has been established to address this issue. This role aims to connect patients with the healthcare system by accompanying them to medical appointments and ensuring they receive continuous care and adhere to their treatment plans (44).

Finally, implementing treatment once the patient is diagnosed poses another significant challenge. For years, being an active substance user was a contraindication for antiviral treatment prescription (45). However, the effectiveness and safety demonstrated by DAA in drug users have rendered this recommendation obsolete, with no interactions between illegal drugs, opioids, and antivirals limiting or contraindicating therapy initiation (46–48). Some studies indicate that achieving effective treatment strategies in drug users is a critical element of the microelimination of HCV in this population (49).

Accordingly, the National Plan for HCV Elimination in Spain identified this population as a priority for initiating anti-HCV treatment (50).

Therefore, achieving HCV microelimination in this population requires a multidisciplinary approach covering various levels to overcome barriers to screening, treatment adherence, and comprehensive follow-up.

2.3. Human Immunodeficiency Virus (HIV)

Although currently the main transmission route of HIV is sexual, the prevalence of HIV infection among drug users is estimated at 18%, which amounts to 2.8 million people worldwide (21). However, in recent years, drug use associated with sex has been increasing. This practice, known as Chemsex, often involves the consumption of these substances via injection (slamming). This practice has translated into a significant increase in HIV infection cases associated with drug use in recent years (51,52).

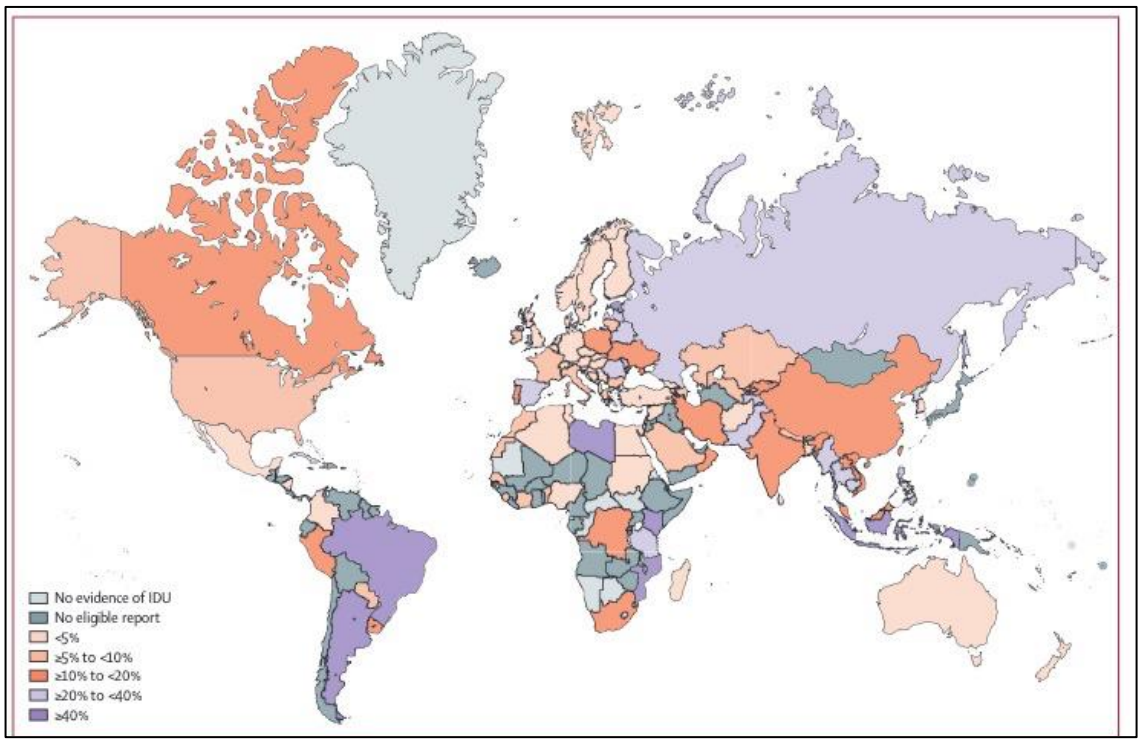

Figure 5: The estimated prevalence of people living with HIV among people who inject drugs by country. Degenhardt L et al. 2017

Just like with HCV, drug users with HIV have low engagement with the healthcare system, lower treatment adherence, and a higher likelihood of co-infections with other viruses, including HCV and HBV. Additionally, drug users are at higher risk of progressing to advanced infection status (CD4+ lymphocyte counts < 200 cells/mL or development of AIDS) without antiretroviral treatment and, therefore, experience complications of HIV infection during follow-up (53). Therefore, in addition to implementing preventive measures similar to those specified for HBV and HCV (needle exchange programs, opioid substitution therapy) and measures aimed at increasing diagnosis (facilitating access to the healthcare system, rapid tests, and screenings in drug addiction treatment centers), an essential aspect in this group is optimizing antiretroviral treatment (ART).

Actualized guidelines in HIV recommend initiating ART as soon as possible after diagnosis, regardless of symptoms or the degree of immunosuppression. Appropriately selecting the ART regimen is essential. The chosen regimen must meet various conditions: ease of administration, good tolerability, no requirement for prior genetic testing to ensure efficacy or safety (resistance testing, HLA-B*5701), minimal risk of pharmacological interactions, high likelihood of maintaining antiviral activity in the presence of high plasma viral loads and low CD4+ lymphocyte counts, and ability to suppress HBV replication in case of co-infection. In this scenario, the Antiretroviral Treatment Guidelines developed by GESIDA and the National Plan on HIV/AIDS, aligned with other international guidelines, recommend the therapeutic regimens specified in Table 2 (54).

3rd drug	ART	Comments
Guidelines applicable to the majority of patients that in randomized clinical trials have demonstrated efficacy not inferior or superior to other guidelines also currently considered as preferred and have additional advantages in terms of number of tablets, resistance barrier, tolerance, toxicity or low risk of drug interactions.		
Integrase Inhibitors	BIC/TAF/FTC	
	DTG/ABC/3TC	Abacavir is contraindicated in HLA-B*5701 positive patients. Do not use in patients with chronic hepatitis B.
	DTG + FTC/TAF*	
	DTG/3TC	Not recommended in patients with baseline CD4 < 200 cells /mm3. Do not use in patients with chronic hepatitis B Not recommended after failure of Pre-Exposure Prophylaxis without the result of the resistance study.

Table 2: Recommended preferred starting ART guidelines. GESIDA and the National Plan on HIV/AIDS, 2023

Among drug users, poor treatment adherence is common. People who use drugs pose a high risk of ART failure and the development of antiretroviral resistance. Protease Inhibitor (PI)-based ART regimens (Darunavir with ritonavir or cobicistat) have a high resistance barrier, which may be advantageous for drug users. However, their use carries a high risk of pharmacological interactions with various commonly used drugs (55). This is a significant drawback for their use in patients with active drug use. Integrase Inhibitors (INI) are highly effective drugs, well-tolerated, and have a better pharmacological interaction profile than protease inhibitors (54,56). Therefore, the use of INI-based regimens may be considered an excellent option for drug users.

The use of Single Tablet Regimen (STR) ART formulations administered once daily (QD) may be very suitable for drug users as they can facilitate treatment adherence, improve success rates, avoid covert monotherapy, and prevent the development of drug resistance. Additionally, various studies have observed that their use improves treatment adherence and increases patient satisfaction compared to multi-tablet regimens (MTR) (57–59). In this regard, INI-based STR-QD regimens are available for routine clinical practice.

Another notable aspect of ART selection is that drug users have a higher risk of co-infection with viral hepatitis. Special attention is needed to evaluate hepatitis B serological status, as active ART against it may be indicated (regimens containing Tenofovir). The prevalence of HIV/HBV co-infection in our country has remained stable at 3.5% over the last decade, although 40% of cases acknowledge parenteral drug use (60). Additionally, immunity to hepatitis B virus remains low in people living with HIV (61,62). Therefore, hepatitis B serological status is crucial in the evaluation of drug users before initiating ART, and if unavailable, it should be effective against possible HBV infection.

Lastly, over 40% of new HIV diagnoses related to injecting drug use in Europe were late diagnoses. In this regard, a recent meta-analysis including international cohort studies observed that parenteral drug users had a higher frequency of late diagnosis than sexually acquired infections (MSM) (OR 1.51 95% CI 0.96-2.06) (63). Late diagnosis of HIV infection implies a higher risk of mortality or developing HIV-associated morbidities and a poorer response to antiretroviral treatment, and everything points to drug users being more likely to be diagnosed late with HIV, with advanced immunosuppression or AIDS. Late diagnosis must be considered in the choice of ART regimen. Evaluating the effectiveness of ART in late presenters is essential for the proper management of drug users living with HIV.

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RESULTS

Chapter 1

Corona-Mata D, Rivero-Juárez A, Camacho Á, Ruiz-Torres L, Ruiz-Cáceres I, de la Fuente Darder B, Cáceres-Anillo D, de Guía Castro-Granados M, Lizaur-Barbudo M, Victoria Cabrera-Gisbert M, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A. Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers. Front Public Health. 2023 Feb 2;11:1092960. doi: 10.3389/fpubh.2023.1092960. PMID: 36817894; PMCID: PMC9932806.
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Chapter 3

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CHAPTER 1

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Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers

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Background and aims: The burden hepatitis C infection in people with history or current drug use suppose a high risk of hepatic complications and transmission infectious disease. This population is poor linked to heath system and is difficult to achieve them and support treatment because they have high rates of lost follow-up. Our aim was to evaluate an intervention for the diagnosis and treatment of chronic hepatitis C and HIV in this population.

Methods: Six-hundred and eighty-three people attended in Drugs and Addictions Centers (DAC) were asked to participate in health counseling and provide blood sample for test HCV, HIV, and syphilis from April 2019 to June 2020. Totally 556 subjects were surveyed and tested. All of them were assigned to a patient navigation program to improve health education and linking to the sanitary system. Hepatitis C infection patients were evaluated in an ampliated medical consult to evaluate hepatic stage with transient liver elastography and initiated Direct Acting Antivirals to achieve Sustained Viral Response.

Results: Of the 556 patients who agreed to participate in the study, 33 (5.9%) had active HCV infection. Of the 33 patients infected with HCV, three were lost to follow-up once the diagnosis of HCV infection was made. Twenty-eight patients (93.3%) completed treatment and 26 achieved Sustained Viral Response (78.8%). Of the 30 patients, seven (23.3%) had advanced fibrosis, and of these, four (16.6%) had liver cirrhosis. One of the cirrhotic patients had hepatic space-occupying lesions at the baseline evaluation and was diagnosed with hepatocarcinoma.

Conclusions: Our study suggests that the implementation of strategies based on personalized intervention models can contribute to the control of HCV infection in DAC users.

KEYWORDS

hepatitis C, elimination, microelimination, drugs users, addiction centers, cirrhosis

Introduction

The high cure rates (>95%), the excellent tolerability profile of direct-acting antivirals (DAAs) and their universal use have drastically improved the prognosis of patients with chronic hepatitis C virus (HCV) infection (1). This scenario has allowed global programs to be launched with the objective of eliminating HCV by 2030 (2). One of the strategic objectives of these programs is to drastically reduce the rates of HCV infection in the most vulnerable populations, that is, those with greater risk of infection or disease progression (e.g., HIV infection, advanced liver disease, hemophiliacs, children, PWID). These strategies are known as microelimination strategies (3). Various actions have been carried out with the objective of achieving the microelimination of hepatitis C in some of these vulnerable populations, such as people living with HIV (PLWH) (4), individuals admitted to prisons (5) or people who are currently injected or have a history of injecting drugs (PWID) (6). Strategies aimed at individuals coinfected with HIV/HCV have been very effective because most of these patients are under active health control and monitoring (7). Strategies aimed at the microelimination of HCV in high-risk populations incarcerated in prisons have also shown high efficacy for reasons of accessibility and sanitary control during their admission to prison (8). However, microelimination strategies in PWID have been less effective, mainly due to the great difficulty of capturing and maintaining this population in the health system (9). The low efficacy of the strategies aimed at the microelimination of HCV in PWID has important consequences in the control of the infection. First, the difficulty in diagnosing and treating HCV infection increases the individual risk of liver disease progression (10). In addition, any untreated HCV-infected PWID is a reservoir of the virus that can cause the transmission and dissemination of the infection in its environment (11). Therefore, identifying new strategies to identify and treat HCV infection in PWID is a priority objective for the control of HCV infection.

Drug and addiction centers (DAC) treat patients with drug or toxic substance dependence and provide an excellent opportunity to access PWID patients. Different strategies focused on this opportunity have been designed and tested, including point-of-care strategies that include rapid antibody tests against HCV with subsequent referral to reference centers or test-and-treat strategies that include the dispensing of treatment in the centers (12–16). However, these strategies have not had the proposed efficacy and suffer from aspects as important as the comprehensive assessment of these patients (including the degree of liver fibrosis and the screening of advanced liver disease) and health education in risk prevention and diagnosis of comorbidities, among others. In this scenario, we designed a study to evaluate a strategy of supervised care of patients for screening, comprehensive evaluation (including screening for advanced liver disease) and treatment of HCV infection in users of DACs.

Materials and methods

Design and study population

This was a longitudinal prospective experimental study designed to evaluate an intervention for the diagnosis and treatment of chronic hepatitis C and HIV in a population of 12 DACs of the province of Córdoba (Andalusia, southern Spain) without direct access to HCV screening. These centers target all patients with drug or toxic substance dependence of Córdoba, city composed by 319.515, inhabitants. The study began in April 2019, and patient recruitment ended in July 2020. Patients treated in the DACs who met the following inclusion criteria were included: (i) over 18 years of age; (ii) in follow-up for one of their cessation programs. Patients under active follow-up by the Health System due to HIV infection or HCV infection were excluded.

Intervention

The intervention strategy consisted of five steps.

Step 1: Patient navigator, education and multidisciplinary team

Candidate patients were identified in DACs by specialists in drugs and addictions. The information about them (including history of drug addiction) was transmitted by them to the Disease Service, where the study coordinator assigned a patient navigator responsible for the recruitment and monitoring of patients and provided risk assessment, health education, treatment adherence counseling, and medication coordination. To carry out this task, two patient navigators were hired (a nurse and a nursing assistant) with full dedication to the project. The patient navigators contacted each of the assigned patients to agree on a face-to-face appointment. This contact was repeated with at least three additional contact attempts for those patients who did not respond to the initial contact until the appointment was made. Patients who did not attend the scheduled appointment were repeatedly contacted until they attended.

A multidisciplinary and coordinated care plan was supervised by the study coordinator and designed for individuals involved in the strategy: addiction physicians, infectious disease specialists, hepatologists, social workers, pharmacists, nurses and patient navigators.

Step 2: Assessment and screening in a single act visit

The patients were treated in a specific consultation for a single act in which counseling for health promotion was performed, anthropometric data (weight, height) were obtained, blood pressure was measured, and blood analysis was performed for haemogram determination. Biochemistry, liver profile and serology of HCV, HIV and *Treponema pallidum.*

Step 3: Communication of results

All patients were informed by telephone of the results of the examinations performed. The information was also transmitted to the health personnel of the DACs. A new appointment was reconciled in a single medical consultation for patients diagnosed with HCV infection, according to the procedure expressed in point 1.

TABLE 1 Descriptive analysis of the study population.

Variable	Global	Participants accept screening	Participants do not accept screening	*p*-Value
n	683	556 (81.4%)	127 (18.6%)	
Gender, (%)				
Male	580 (84.9)	475 (85.4)	105 (82.7)	0.434
Woman	103 (15.1)	81 (14.6)	22 (17.3)	
Age (years). Median (IQR)	48 (39–56)	48 (40–57)	44 (37–52)	0.002
Smoker, *n* (%)	204 (29.8)	172 (30.9)	32 (25.2)	0.212
Substance, *n* (%)				
Alcohol	552 (80.9)	459 (82.7)	93 (73.6)	0.014
Cocaine	346 (50.7)	280 (50.5)	66 (52)	0.758
Cannabis	268 (39.3)	212 (38.2)	56 (44.1)	0.220
Synthetic drug	40 (5.9)	31 (5.6)	9 (7.1)	0.516
Opiates	154 (22.4)	118 (21.1)	36 (28.3)	0.077

n, number of individuals; IQR, interquartile range; *p*, *p*-value.

Step 4: Treatment of HCV, assessment of the degree of liver fibrosis and follow-up

Patients with HCV infection were clinically assessed in a single-act consultation that included the performance of transient liver elastography (TLE) and in which HCV treatment was initiated. The choice of treatment regimen was made at the discretion of the clinician (16–18). In patients diagnosed with hepatic cirrhosis, an analysis was additionally performed in the same act that included, among other determinations, levels of alpha-fetoprotein and albumin and a coagulation study. Hepatic ultrasound was planned, and patient follow-up was scheduled in coordination with the hepatology service of our hospital. In those patients who did not attend the scheduled appointment, the process of reconciliation of the appointment was repeated in collaboration with the DAC health personnel until they complied. All patients received treatment for 60 days following the initial visit.

After the start of treatment, a contact telephone number was provided to the patients for comments, questions or incidents, and a telephone follow-up was carried out at least every 2 weeks by the responsible tutor until the end of the treatment. In each telephone contact, adherence to treatment and possible adverse effects were evaluated and reinforced. A visit was planned at the end of treatment that included the determination of HCV-RNA. Additionally, patients were offered the possibility of making additional medical visits to reinforce adherence and identification of adverse effects; in these visits, HCV-RNA was determined.

Step 5: Assessment of sustained viral response

The sustained viral response assessment (SVR) visit was reconciled and scheduled at 12 weeks after the end of treatment. An active search was conducted for patients who did not attend the appointment for SVR assessment, and contact was repeated until their attendance was obtained.

Variables and definition

The primary outcome variable of the study was SVR, defined by reaching undetectable HCV-RNA in serum 12 weeks after the end of treatment. The secondary variables were conducting HCV screening, defined as the completion of the single-act visit for patient assessment (Step 2), and initiation of HCV treatment, defined as taking at least one dose of the treatment prescribed by the clinician. End of treatment response (ETR) was defined as undetectable viral load after completion of therapy.

HCV infection screening was performed using a "one-step" diagnostic algorithm in which in all samples positive for antibodies against HCV, HCV RNA and its genotype were determined by quantitative techniques (19). Patients with a liver stiffness value >9.5 kPa were considered to have advanced fibrosis, and those patients with an RH value >12.9 kPa were considered cirrhotic (20).

Statistical analysis

A descriptive analysis of the data was performed, expressing continuous variables as medians (Q1–Q3) and categorical variables as percentages (95% CI).

The primary outcome variable (SVR) was evaluated through the following analyses: (i) intention-to-treat analysis: All patients with HCV infection included in the study were included in the analysis, considering losses as failures of the strategy. (ii) Modified intention-to-treat analysis: All patients with HCV infection who received at least one dose of treatment were included in the analysis. (iii) Analysis by protocol: Only HCV-infected patients who completed the study protocol were included in the analysis.

The secondary outcome variable 1 was measured by the percentage of patients screened for HCV with respect to the population evaluated (number of people screened/total number of people evaluated × 100).

The secondary outcome variable 2 was measured by calculating the percentage of patients diagnosed with HCV infection who started treatment with respect to the total number of patients diagnosed (number of patients diagnosed who started treatment/total number of diagnosed × 100).

Ethical aspects

This study was designed and performed according to the Helsinki Declaration. The Andalusian Ethical Committee approved the study protocol.

Results

Population

During the study period, 683 people met the inclusion criteria in the study, of whom 556 (81.4%) agreed to participate and 127 refused. The characteristics of the population identified according to whether they agreed to participate in the study are shown in Table 1. Three patients were identified with unknown HIV infection, one of whom was coinfected with hepatitis C. All patients presented asymptomatic HIV infection with lymphocyte counts <500 cells/ml and HIV-RNA >10,000 cop/ml. All patients started antiretroviral treatment. Nine patients with serological criteria for latent syphilis were identified and received treatment with penicillin G benzathine according to routine clinical practice.

Patients with HCV infection

Of the 556 patients who agreed to participate in the study, 33 (5.9%) had active HCV infection. The characteristics of these patients are shown in Table 2. Of the 33 patients infected with HCV, three were lost to follow-up once the diagnosis of HCV infection was made, before their clinical situation or the degree of liver fibrosis was evaluated and before HCV treatment. The characteristics of the 30 patients who continued in follow-up are shown in Table 2. Of the 30 patients, seven (23.3%) had advanced fibrosis, and of these, four (16.6%) had liver cirrhosis. One of the cirrhotic patients had hepatic space-occupying lesions at the baseline evaluation and was diagnosed with hepatocarcinoma.

Rate of treatment uptake and SVR

Of the 33 patients diagnosed with active hepatitis C virus infection, 30 (90.90%, 95% CI 76.43–96.86%) started anti-HCV treatment. Of the 30 patients who started treatment, two were lost to follow-up, and 28 reached the end of treatment response (93.33%, 95% CI 78.68–98.15%). The two patients lost to follow-up were followed up and evaluated until week 4, presenting HCV-RNA of 17 and 826 IU/ml at this time. Of the 28 patients who reached ETR, 26 were evaluated at week 12 posttreatment, and all reached SVR. Therefore, the SVR rate obtained in the study was 78.78% (95% CI 62.25–89.32%) in the intention-to-treat analysis, 86.66% (95% CI 70.32–94.69%) in the modified intention-to-treat analysis and 100% (95% CI 87.13–100%) in the per-protocol analysis.

TABLE 2 Characteristics of patients diagnosed with HCV infection.

Characteristics	(*N* = 33)
Age (years), median (IQR)	50 (46.5–57)
Male gender, *n* (%)	30 (90.9)
Genotype, *n* (%)	
1a	16 (48.5)
1b	1 (3)
3	4 (12.1)
4	5 (15.2)
Not genotyped	7 (21.2)
Degree of fibrosis, *n* (%)	30
Advanced fibrosis	4 (13.3)
Cirrhosis	5 (13.3)
Cirrhosis plus hepatocarcinoma	1 (3.3)
Treatment initiation, *n* (%)	30 (90.9)
Glecaprevir/pibrentasvir	15 (50)
Sofosbuvir/velpatasvir	15 (50)
Treatment outcome, *n* (%)	30 (100)
Loss to follow-up during therapy	2 (6.6)
Reach RFT	28 (93.3)
Loss to follow-up after ETR	2 (7.1)
Patients reaching SVR	26 (92.8)

Advanced fibrosis defined as Transient Liver Elastography (TLE) value 9–12.5 kPa; Cirrhosis defined as a TLE value > 12.5 kPa.
ETR, end of treatment response; SVR, sustained viral response.

Discussion

The screening strategy and HCV treatment support evaluated in our study achieved high rates of screening (81.4%) and SVR (86.6% in the modified intention-to-treat analysis) in DAC users. Our results suggest that a strategy based on a tutored intervention (patient navigator intervention), the work of a multidisciplinary team, patient education intervention and the use of the HCV diagnostic algorithm "in a single step" could be useful in the management of a population, such as DAC patients, in whom it is extremely difficult to make both the diagnosis and to achieve completion of the treatment.

Drug users who are unaware of being infected with HCV, in addition to being a serious health problem for individuals, is a serious public health problem and an important barrier to the control and elimination of HCV (21). The greatest difficulty in curing HCV infection among drug users lies in the difficulty of keeping them in treatment. Thus, Ford et al. (22) studied a high proportion (85%; *n* = 435) of patients with active hepatitis C (85%; *n* = 435) identified through a screening program. However, only six of them completed the treatment successfully. In this scenario, multiple strategies were

identified to improve health care for people at high risk of hepatitis C infection (23). *Patient guardianship* has been associated with significantly increased adherence at the beginning and follow-up of treatment among patients with HCV infection compared to the standard of care in a randomized study, which included 1,353 patients (769 in the usual care group and 584 in the patient care group, respectively) (24). The guardianship group had significantly higher probabilities of adherence to care and initiation of treatment within the first 6 months. This study was the first to demonstrate that patient care compared to usual care increases the proportion of patients linked to health care. Our study supports the usefulness of this intervention in people with chronic HCV infection who use drugs.

The "one-step diagnosis of HCV" intervention used in our study is an intervention that simplifies and optimizes the diagnosis of HCV infection. RNA tests in the same sample used for the HCV antibody test significantly improved the acceptance of HCV RNA tests, reducing the number of visits for the patient and the time until diagnosis and minimizing the loss of patients during follow-up (25). For these reasons, this intervention should be considered an essential element in HCV screening strategies in populations with a high risk of infection and a low probability of adherence to the health system. Thus, this intervention has become the standard diagnostic method in Spain for hepatitis C (19). Patient education improves engagement in care in the context of other chronic diseases (26–29). Similarly, educational interventions regarding HCV infection and its treatment could increase the knowledge of the disease and, with it, the motivation of patients to be involved in their care. This could have contributed in our study to improving HCV screening rates and treatment adherence of infected patients. Another essential element of the strategy evaluated in our study was the coordination of the different health agents involved. This coordination is essential to optimize the effectiveness of health resources in the care of people who consume drugs because they reduce the fragmentation of care and facilitate the linkage of patients to them. The usefulness of this intervention has not been demonstrated in the context of HCV infection, but it has been observed in the context of other chronic diseases (30) and in drug users in a methadone maintenance program (31).

Whether the potential pharmacological interactions due to the consumption of drugs of abuse, alcohol or opioid replacement therapies could reduce the efficacy of HCV treatment with AAD is speculation (32). In our study, in the per-protocol analysis, 100% of patients achieved SVR. The four patients who started treatment and did not reach SVR were lost to follow-up (two of them after reaching ETR). These results support the findings of other studies that suggest that the response to HCV treatment with AAD in drug users can be comparable to that of the general population, provided that adequate adherence to treatment is ensured (33, 34).

On the other hand, it is important to note that 30% (n = 9) of patients with HCV infection in whom the degree of liver fibrosis could be assessed had advanced liver fibrosis at the time of diagnosis and that 16.6% had liver cirrhosis (one of them with hepatocarcinoma). The high percentage of patients with advanced liver disease observed in our study indicates the convenience of including a comprehensive assessment of patients, including the degree of liver fibrosis, in HCV screening and treatment programs in drug users. Some strategies, such as *test-and-treat,* suffer from this, despite the advantages of bringing screening closer to the comfort zone of the users. Therefore, strategies that do not include advanced liver disease screening are insufficient for the comprehensive management of hepatitis C in this population. This high percentage of patients with advanced disease, in turn, indicates the significant delay of the health system for the diagnosis of HCV infection in DAC users. Correcting this diagnostic delay is essential to achieve control of HCV both in this population and in the general population.

Our study has some limitations that require us to interpret its results with caution. First, this is a study conducted in DAC that did not have access to screening tests for HCV during the study. This meant that the initial phase of the strategy was focused on achieving the screening of a high proportion of patients. Therefore, our results cannot be extrapolated to DAC in other areas with access to HCV screening. However, in our health environment, access to HCV treatment is universal and free for the entire population, so our results cannot be extrapolated to areas in which access to HCV treatment for drug users is not guaranteed. Part of our study was conducted during the COVID-19 pandemic, and it is not possible to know the impact that this circumstance may have had on the results. Finally, our study was conducted in patients treated in DAC, and we have been able to access them by taking advantage of their link to these centers. Therefore, our results cannot be extrapolated to drug users who are not linked to the health system.

In conclusion, our study suggests that the implementation of strategies based on personalized intervention models can contribute to the control of HCV infection in DAC users.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics and Clinical Trials Committee (CEIC) of Andalusia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AR and AR-J designed the study. BF, DC-A, MG, ML-B, MV, JR-É, AA-A, LM-L, and LC identified candidate patients in DACs and recruited individuals. DC-M, ÁC, IP-V, and AR were the patient reference tutors in the Infectious Disease Unit. DC-M, LR-T, and IR-C collected database. DC-M, AR-J, and AR analyzed statistics data, interpreted the results, and draft the paper. All authors revised the draft critically for important intellectual content, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CHAPTER 2

Corona-Mata D, Rivero-Juárez A, Camacho Á, Ruiz-Torres L, Ruiz-Cáceres I, Pérez AB, de la Fuente Darder B, Cáceres-Anillo D, Castro-Granados MG, Lizaur-Barbudo M, Cabrera-Gisbert MV, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A. **Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addiction Centres**. Front Public Health. 2024 Jan 16;11:1258095. doi: 10.3389/fpubh.2023.1258095. PMID: 38292385; PMCID: PMC10824845.

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Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addiction Centres

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Background and aims: Persons with substance use disorder are at increased risk for hepatitis B virus (HBV) infection. Although most of them are attached to social health centers, the vaccination rate in this group is low. In this context, we designed a study to evaluate the prevalence of users of drug addiction centers (DAC) not immunized against hepatitis B and to compare the rate of vaccination against hepatitis B with the rate of immunization against SARS-Cov-2 in 2 years of follow-up.

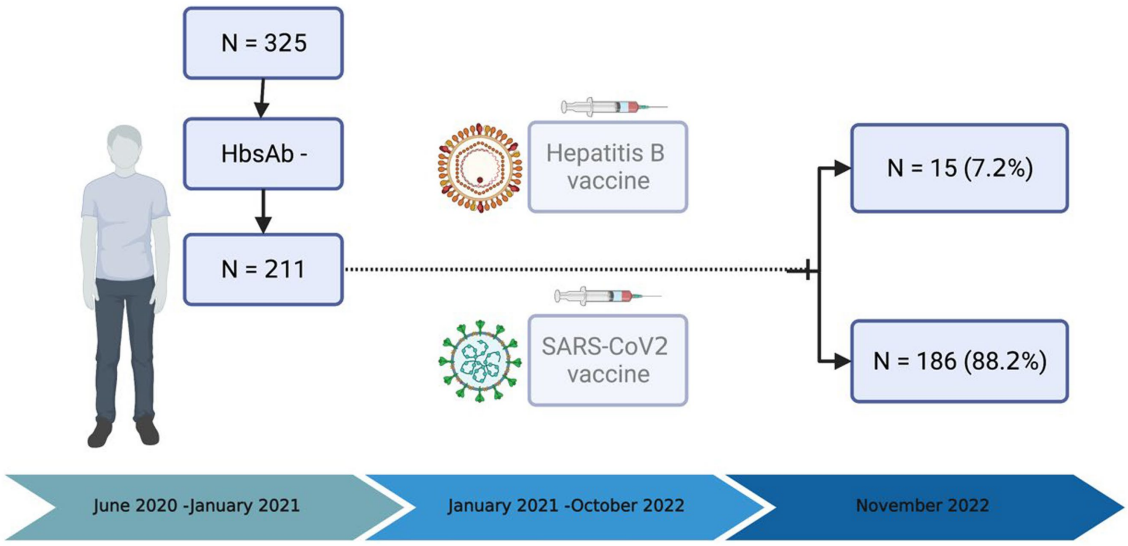
Design: Retrospective study that included individuals attended at DAC. Patients were screened at baseline (June 2020–January 2021) for HBV immunization. Individuals with HBsAb < 10 IU/mL were recommended to receive hepatitis B vaccine, during follow-up (January 2021–October 2022). At the end of follow-up, the HBV vaccination rate among candidates was determined and compared with the vaccination rate against SARS-Cov-2 in this population in the same period.

Findings: A total of 325 subjects were surveyed and tested. At baseline, the 65% (211/325) of were candidates to initiate vaccination and were advisor to HBV vaccination. During the follow-up 15 individuals received at least one dose of HBV vaccine, supposing a vaccination rate of 7.2%. In the same period, 186 individuals received at least one dose against SARS-Cov-2, representing a vaccination rate of 83%. The comparison between vaccination rates reached statistically significant ($p < 0.001$).

Conclusion: Our study manifests a low rate of immunization against HBV in DAC users, despite a high level of immunization for SARS-Cov-2 during the same period in the same population. Consequently, the lack of immunization against HVB in this population might be related with health policy issue more than to individuals linked to care and awareness. A similar approach for vaccination intended for SARS-CoV2 should be applied in high-risk population to warrant the success of immunization program against other preventable diseases such as HBV.

KEYWORDS

hepatitis B virus, COVID-19 disease, SARS-CoV-2, drugs addiction, vaccination, prevention



GRAPHICAL ABSTRACT
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Introduction

Hepatitis B infection is a major cause of liver disease worldwide. WHO estimates that 296 million people were living with chronic hepatitis B virus (HBV) infection in 2019, with 1.5 million new infections occurring each year. Moreover, the problem is aggravated by the high rates of underdiagnosis of this disease. It is estimated that only 10% of the infected population has been diagnosed (1). HBV infection can progress to chronicity and develop liver cirrhosis and complications, ranked as a major cause of end-stage liver disease and death (2). Although there are drugs capable of inhibiting viral replication, HBV is considered an infectious disease with a high risk of chronicity, and vaccination is the only way to prevent its clinical impact. Since 1981, vaccination strategies have been implemented in groups at risk of infection and later extended to the general population (3). WHO recommends vaccination schedules at birth and in early childhood. Thus, it is estimated that 80% of the world's population reaches a vaccination coverage with 3 doses against hepatitis B (4). The contribution of hepatitis B vaccination in preventing infection and reducing hidden hepatitis B has been massive (5).

Despite the availability of an effective vaccine, the prevalence of hepatitis B infection remains high, in part due to hidden infection, late diagnosis, difficulty in accessing treatment, and non-immunization in certain groups of individuals at higher risk of hepatitis B infection (6). People with substance use disorders and people linked to Drugs and Addiction Centers (DACs) constitute a high-risk group for acquiring and spreading HBV infection or have severe complications and therefore may establish a major barrier to the WHO's 2030 goal of elimination of the disease (7) especially those who inject drugs. A recent meta-analysis found that 15.6 million people in 2015 were injecting drugs throughout the world. Of them, 9% (5.1%–13.2%) suffer from chronic HBV infection (8). Identifying HBV unimmunized DAC users and achieving high vaccination rates in them is an essential strategy to eliminate hepatitis B. It is known that access to this population, follow-up and treatment is complicated, so vaccination rates are low. Some studies show low rates of complete hepatitis B vaccination in individuals attending drug dependence centers, especially in younger populations or those with longer vaccination schedules (6 month regimens) (9). Ensuring user adherence to the health system and fostering an understanding of the importance of preventing infections, such as hepatitis B, can be pivotal. However, the health system plays a critical role by shouldering the responsibility of providing adequate information and explaining the risks associated with not achieving immunization. Vaccination compliance is a fundamental milestone in the healthcare system. This example can be illustrated by the SARS-Cov-2 vaccination strategy.

Mass vaccination of the population against SARS-Cov-2 was a decisive tool for the control of the pandemic in the world. This was due to the fact that the information campaigns managed to arouse a high level of interest in being vaccinated in a large part of the population. Moreover, the high impact on mortality of SARS-Cov-2 and the confidence placed in obtaining an effective vaccine for the prevention of a disease that had an outbreak and repercussions on the lives of everyone had an added value for the acceptance of people to follow the preventive measures recommended by the health authorities and get vaccinated. In this scenario, we propose to evaluate the vaccination initiation rates against Hepatitis B in DAC users and compare them with the vaccination rates obtained against SARS-Cov-2 in this same population.

Materials and methods

Study design and population

Retrospective analysis of a study designed to screen and diagnose viral hepatitis in individuals linked to Drugs and Addiction Centres (DAC) from Cordoba (Southern Spain). This analysis aims to assess hepatitis B vaccination rates based on the standard strategy recommended for vaccination, and to compare them with the SARS-CoV-2 rates obtained through the intensive strategy involving health authorities' intervention from June 2020 to November 2022.

The study subjects had previously participated in a study evaluating a comprehensive strategy for detecting and treating hepatitis C infection in Cordoba (10). The healthy volunteers were included in the present study.

At baseline, individuals were screened for hepatitis B serology between June 2020 and January 2021. This screening includes hepatitis B surface antigen tests, total hepatitis B surface antibody, and hepatitis B core antibody. Patients without HBV immunity (defined as anti-HBsAb antibody titer < 10 IU/mL) were referred to reference DAC with the recommendation of HBV vaccination.

Individuals at risk (not immunized to hepatitis B) were recommended to receive vaccination against HVB from baseline up to November 2022 (end of the study). The Infectious Diseases Unit informed the participant of the need to be vaccinated against HBV and recommended to request an appointment at their reference center to complete the vaccination. In our country, vaccination against HBV in adults is covered by the National and Regional Health System, free of charge, in those users at risk of immunosuppression, high risk of infection and dissemination, occupational risk or comorbidities with risk of chronic liver disease with a vaccination schedule of three doses, administered in month 0, 2, and 6 from the prescription (11).

Simultaneously, due to the global pandemic situation of the disease, the Health Authorities supported by the National Government carried out an intensive and universal vaccination strategy against SARS-CoV2. The general population was stratified and prioritized according to risk factors for severe COVID-19 infection and vaccinated in a staggered manner from the availability of the first vaccines in January 2021. The vaccination points were managed by the Preventive and Epidemiology Services, coordinated with the Primary Care Health Districts. Special vaccination teams were created, composed mostly of nursing staff, who, through municipal and health censuses, prioritized the population according to government guidelines. Vaccination was free of charge (12). Adults belonging to this cohort were summoned by census at health centers and vaccination points since June 2021.

The Public Andalusian Health system has a single, universal, and digitized registry of users' medical records, as well as of the vaccines administered. All the health data of individuals are collected in it, and health providers have access to it to afford the best possible health care. To assess the acceptance of this population to receive vaccines, we compared the rate of hepatitis B vaccination with the rate of vaccination against SARS-CoV-2 in the same period.

Variables and definition

The primary endpoint of the study was the initiation of HBV vaccination, defined as receiving at least one dose of the vaccine during the study period in candidate individuals. We decided to assess vaccination acceptance by reviewing their electronic vaccination records. The objective was to know how many had complied with the recommendation to vaccinate after counseling. This measure was objective for all and could be assessed by analyzing the vaccination records. Baseline variables including age (categorized into upper or lower 40 years), gender and history of drug use were registered. Patients with a history of injection drug use were on Opioid Substitute Therapy (OST).

Statistical analysis

A comprehensive examination of the data involved a descriptive analysis, wherein categorical variables were depicted in terms of their frequencies with 95% confidence interval. Frequencies were compared by Chi-square test or Fisher's test and those with statistical significance (defined by $p < 0.05$) were included in a binary logistic regression analysis. We categorized variable "Age" as either more or less than 40 years old, because we assume that people younger than 40 years were immunized by vaccination following the national calendar of vaccination system in our country (born after 1982). Variables associated in the univariate analysis were included in a logistic regression multivariate analysis, adjusted by age and gender. All data analyses were performed using the SPSS statistical software package release 22·0 (IBM, Armonk, New York, United States).

Ethical aspects

This study was designed and performed according to the Helsinki Declaration. The Andalusian Ethical Committee approved the study protocol. Samples were collected and cryopreserved at −80°C in the Andalusian Health System Biobank (National Register Reference: B.0001601).

Findings

Population

A total of 325 participants were enrolled in the study and underwent hepatitis B screening. Two hundred and eleven participants were not immunized against HBV (65%) and were considered candidates for immunization. We considered non-immunized those who presented anti-HBs concentration less than 10mIU/mL. No cases of active hepatitis B were detected. Baseline characteristic between immune and non-immune individuals is shown in Table 1. The median age of participants was 46 years old (38–54 Q1–Q3). The immunization rate among individuals younger than 40 years was higher than among older people (54.9% vs. 27.4%; $p \leq 0.001$). Following multivariate analysis adjusting for gender, age emerged as the sole variable that achieved statistical significance (adjusted HR 2.96, CI95% 1.77 to 4.95, $p < 0.001$). None of the drugs were associated with immunization status.

Hepatitis B and SARS-CoV2 vaccination rate

From June 2020 to January 2021, there were 211 candidates for immunization to HBV and SARS-CoV2. Of them, only 15 participants

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TABLE 1 Baseline characteristics of participants according to their immune status against hepatitis B.

Variable	Category	Global 325 (100%)	No immune 211 (64.9%)	Immune 114 (35.1%)	*p*	HR	*P adjust*	*HR adjust*
Sex	Male	277 (85.2)	179 (64.6)	98 (35.4)	0.78	1.1 (0.5–2.1)	0.78	0.91 (0.46–1.79)
	Female	48 (14.8)	32 (66.7)	16 (33.3)		1		1
Age	<40 years	91 (28)	41 (45.1)	50 (54.9)	<0.001	0.3 (0.2–0.5)	<0.001	2.96 (1.77–4.95)
	≥40 years	234 (72)	170 (72.6)	64 (27.4)		1		1
Drug use								
Tobacco	Yes	109 (33.5)	69 (63.3)	40 (36.7)	0.66	1.1 (0.7–1.8)		
	No	216 (66.5)	142 (65.7)	74 (34.3)		1		
Synthesis drug	Yes	15 (4.6)	11 (73.3)	4 (26.7)	0.48	0.6 (0.2–2.1)		
	No	310 (95.4)	200 (64.5)	110 (35.5)		1		
Cocaine	Yes	177 (54.5)	110 (62.1)	67 (37.9)	0,25	1.3 (0.8–2.1)		
	No	140 (45.5)	101 (68.2)	47 (31.8)		1		
OST	Yes	72 (22.2)	44 (61.1)	28 (38.9)	0.44	1.2 (0.7–2.1)		
	No	253 (77.8)	167 (66)	86 (34)		1		
Alcohol	Yes	265 (81.5)	173 (65.3)	92 (34.7)	0.77	0.9 (0.5–1.6)		
	No	60 (18.5)	38 (63.3)	22 (36.7)		1		
Cannabis	Yes	130 (40)	73 (56.2)	57 (43.8)	0.007	1.9 (1.2–3.1)		1
	No	195 (60)	138 (70.8)	57 (29.2)		1	0.07	0.64 (0.39–1.04)

received at least one dose of the hepatitis B vaccine (7.2%), and 9 of them were fully vaccinated (4.5%). No differences were found between the variables studied and the individuals who received vaccination or not (Table 2).

During the same period, 186 participants (88.2%) received at least one dose of SARS-Cov-2 vaccine, of whom 176 were fully vaccinated (83.4%). Significant differences in vaccination rates were observed between HBV and SARS-CoV-2 vaccines recipients, both for those receiving at least one dose (7.2% vs. 88.2%; $p < 0.001$) and those who were fully vaccinated (4.5% vs. 83.42%; $p < 0.001$).

Discussion

Vaccination against HBV should be a prioritized to eradicate this viral hepatitis and fulfill the WHO objective stablished for 2030 (13). In this context, the WHO the prioritization of hepatitis B vaccination in populations at high risk of infection. Among them, DAC-users constitute a difficult to access population. Different strategies have been tested to achieve vaccination of this group. The admission of DAC-users in closed institutions such detoxification centers represent a great opportunity to complete vaccination. Thus, in a study conducted in patients admitted to an opiate detoxification clinic, an 82% HBV vaccination rate was achieved with an accelerated vaccination schedule (14). This strategy would not be applicable to most DAC-users and, moreover, would only be effective in admissions so prolonged that vaccination schedules could be completed. Loss of follow-up of patients after discharge from a closed institution is common among DAC-users and is a major barrier to HBV vaccination strategies (15). In a study conducted in Brazil, among 553 crack users institutionalized in DAC, only 22% of patients completed a 21-day accelerated vaccination schedule. The main reason for such a small percentage was loss of follow-up of patients after discharge (median hospitalization time, 15 days) (16). Finally, several studies have suggested that strategies involving financial incentives for patients can improve vaccination rates in CAD users, although this cannot be extrapolated to other settings (15, 17, 18). In our study, after two-year follow-up, only 7.6% of those unimmunized against hepatitis B received at least one dose of vaccine. These results illustrate the difficulties to achieve high vaccination rates in DAC-users.

It has been observed that in situations where patients are connected to the health system, vaccination rates increase as the follow-up time is longer. Thus, in a cohort of HIV patients with 3 years of follow-up, hepatitis B vaccination rates of 9.6% were achieved (19), and in others with 7 and 10 years of follow-up, rates of 31.4% and 61.9%, were achieved, respectively (20, 21). In this context, after 20 years of follow-up, rates of 75.2% were obtained in a Needle Exchange Program (NEP) cohort (22). In any case, the vaccination rates obtained are far from optimal. Given the high risk of acquiring the infection and transmitting it to their environment among DAC-users, the objective should be to vaccinate the entire non-immunized population in the shortest period possible. All this suggests that one of the main reasons for vaccination failure in DAC-users is loss to follow-up and inability to contact patients after the loss of contact with the health care setting. However, attributing exclusively to this reason the responsibility for the failure of HBV vaccination strategies in CAD-users may be erroneous and constitute an obstacle to the design of strategies that accurately address the problem. In our experience, resources focused to support and treat substance disorders have limitations in collaborating with the Health System the follow-up of their users. These programs are external and founded by other associations or institutions. This situation complicates to identify risk factors for the healthcare providers and hinders the ability to screen or offer preventive measures for substance use disorders and Addiction Centers. It is strinking that the 88% of the DAC users included in our study received at least one dose of

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TABLE 2 Characteristics of participants according to vaccination against hepatitis B during the follow-up.

Variable	Category	Global *N* = 211 (100%)	Unvaccinated HBV *N* = 196 (92.8)	Vaccinated HBV *N* = 15 (7.2)	*p*	HR	*P adjust*	*HR adjust*
Sex	Male	179 (84.8)	168 (93.9)	11 (6.1)	0.25	0.46 (0.13–1.54)	0.18	0.43 (0.12–1.48)
	Female	32 (15.2)	28 (87.5)	4 (12.5)		1		1
Age	<40 years old	41 (19.4)	39 (95.1)	2 (4.9)	0.74	1.61 (0.35–7.45)	0.65	1
	≥40 years old	170 (80.6)	157 (92.4)	13 (7.6)		1		1.4 (0.3–6.7)
Drug use								
Tobacco	Yes	69 (32.7)	66 (95.7)	3 (4.3)	0.39	0.42 (0.13–1.8)		
	No	142 (67.3)	130 (91.5)	12 (8.5)		1		
Synthesis drugs	Yes	11 (5.2)	10 (90.9)	1 (9.1)	0.56	1.3 (0.16–11.14)		
	No	200 (94.8)	186 (93)	14 (7)		1		
Cocaine	Yes	110 (52.1)	102 (92.7)	8 (7.3)	0.99	1.05 (0.37–3,02)		
	No	101 (47.9)	94 (93.1)	7 (6.9)		1		
OST	Yes	44 (20.9)	41 (93.2)	3 (6.8)	0.99	0.94 (0.25–3.5)		
	No	167 (79.1)	155 (92.8)	12 (7.2)		1		
Alcohol	Yes	173 (82)	158 (91.3)	15 (8.7)	0.078	1.09 (1.05–1.15)	0.99	1
	No	38 (18)	38 (100)	0		1		1
Cannabis	Yes	73 (34.6)	68 (93.2)	5 (6.8)	0.99	0.94 (0.31–2.87)		
	No	138 (65.4)	128 (92.8)	10 (7.2)		1		
SARS-Cov-2 vaccine								
Vaccinated 1 doses	Yes	186 (88.15)	172 (92.5)	14 (7.5)	0.99	1.95 (0.25–15.5)		
	No	25 (11.85)	24 (96)	1 (4)				
Vaccinated > 2 doses	Yes	176 (83.41)	162 (92)	14 (8)	0.47	2.94 (0.37–23.1)		
	No	35 (16.6)	34 (97.1)	1 (2.9)				

SARS-Cov-2 vaccine (83% completed vaccination) in the same observation time. This rate is comparable to those observed in the general population in Spain (23, 24). This fact suggests that it is possible to achieve high vaccination rates in DAC-users if appropriate strategies are employed.

The COVID-19 pandemic outbreak had an unexpected impact affecting all levels of the population worldwide. The rapid spread of the infection, due to transmission by air through Flügge droplets at close proximity (1 m) and Wells nuclei forming aerosols over longer distances, coupled with the elevated mortality rates observed during the two first waves (as of November 2023, 771,820,937 confirmed cases of COVID-19 and 6,978,175 reported deaths to WHO) (23), has, in our opinion, played a significant role in fostering widespread acceptance of vaccination among the general population. This way of transmission contrasts with hepatitis B transmission, which is predominantly by unprotected sexual intercourse and blood transmission (sharing syringes is a high risk in people with a history of drug abuse). We believe that these differences in risk perception could alter the population's interest in protecting themselves from hepatitis B, even in the face of the high morbidity and mortality associated with chronic infection. Meanwhile, the measures implemented by governments to curb the outbreak, which originated in China and were subsequently adopted globally following the WHO's declaration of a global health alert (including social restrictions and quarantine policies), had a profound impact on the population. These measures directly affected people's lives, as they realized that taking precautions for their protection (such as using masks, adhering to hygiene measures, and getting vaccinated) had both social and economic repercussions for the general population and themselves. In Spain, the strategy to achieve high vaccination rates against SARS-Cov-2 included two essential elements: raising public awareness of the benefits of vaccination and facilitating access to vaccination. Achieving adequate awareness of the benefits of HBV vaccination in unimmunized DAC-users is an essential element in achieving high vaccination rates in this population, and to achieve this objective it is necessary to ensure that the health caregivers of the DAC-users themselves are also aware of it. Our findings suggest that clinicians should make a special effort to encourage HBV-unvaccinated patients to get vaccinated against HBV.

Our study has several limitations. It is retrospective with the limitations that this implies. The population studied is small, so our results should be interpreted with caution. Finally, our study was conducted in an area of universal and free health care, so our results may not necessarily be extrapolable to other populations with different socio-health care characteristics.

In conclusion, we found a high percentage of DACs-user unimmunized against HBV and the vaccination rates observed at 2 years was very low. This is a troubling finding that may compromise the goal of elimination of HBV infection proposed by WHO. The low vaccination rates against HBV contrast with the high vaccination rates against SARS-Cov-2 in the same population and at the same observation time, denoting that it is possible to achieve high

vaccination rates in this population. Consequently, a similar approach for vaccination intended for SARS-CoV2 should be applied in high-risk population to warrant the success of immunization program against other preventable diseases such as HBV.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité de Ética para la Investigación Biomédica de Andalucía (CEIC)—Nodo Córdoba. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DC-M: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. AR-J: Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. ÁC: Data curation, Investigation, Methodology, Writing – review & editing. LR-T: Data curation, Writing – review & editing. IR-C: Data curation, Writing – review & editing. AP: Writing – review & editing. BF: Writing – review & editing. DC-A: Writing – review & editing. MGC-G: Writing – review & editing. MVC-G: Writing – review & editing. JR-É: Writing – review & editing. AA-A: Writing – review & editing. LM-L: Writing – review & editing. LC: Writing – review & editing. IP-V: Investigation, Writing – original draft, Writing – review & editing, Data curation. AR: Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. ML-B: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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CHAPTER 3

Corona-Mata D, Pérez-Valero I, Camacho A, Gutiérrez Liarte Á, Montero-Alonso M, Alemán MR, Ruiz-Seco P, Pérez González A, Riera M, Jarrin I, Rivero-Juárez A, Rivero A. **Effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters**. Int J Antimicrob Agents. 2024 Jan;63(1):107016. doi: 10.1016/j.ijantimicag.2023.107016. Epub 2023 Oct 26. PMID: 37890734.

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Effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in HIV late presenters

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ABSTRACT

Objectives: The efficacy of BIC/FTC/TAF in HIV late presenters initiating antiretroviral therapy (ART) has not been sufficiently evaluated.
Methods: The aim of this study was to assess the effectiveness and tolerability of BIC/FTC/TAF compared to other first-line antiretroviral regimens in treatment-naïve adult individuals from the CoRIS Cohort starting ART with CD4 counts <200 cells/mm^3 and/or AIDS-defining conditions between January 1st 2019 and November 30th 2020. Logistic regression models were used to estimate odds ratios (ORs) of association between initial regimen and achievement of viral suppression (VS) (primary objective), defined as HIV RNA <50 cop/mL, and immunological recovery (IR) (secondary objective), defined as CD4 count >200 cells/mm^3, at weeks 24 and 48 after initiation of ART.
Results: We evaluated 314 individuals (84.7% men, median age 40 years). Of them, 158 initiated with BIC/FTC/TAF. At inclusion, 117 had an AIDS-defining condition. In multivariable analyses, individuals with AIDS-defining conditions initiating ART with BIC/FTC/TAF achieved higher rates of VS at 24 weeks than other regimens (aOR: 0.2; 95% CI: 0.06–0.64) and, at 48 weeks, than DTG/ABC/3TC (aOR: 0.06; 95% CI: 0.01–0.76) and DTG + TDF/3TC (aOR: 0.2; 95% CI: 0.47–0.9). No other differences in VS or IR were observed. At 24 and 48 weeks after ART initiation, treatment discontinuations were lower with BIC/FTC/TAF than with other regimens (3.2% and 7.6% vs. 24.4% and 37.8%, respectively; $P < 0.005$).
Conclusion: Our results suggest that BIC/FTC/TAF could be a preferred regimen as initial therapy in HIV late presenters because of its high effectiveness and good tolerability.

1. Introduction

Bictegravir (BIC) is an integrase inhibitor with high antiviral potency and a high genetic barrier to resistance. Its pharmacokinetic profile allows its administration once a day without the need of a booster [1]. As initial therapy, BIC in combination with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF) has demonstrated high efficacy and a favourable safety and tolerability profile [2,3], being non-inferior to dolutegravir (DTG)-containing regimens at 48, 96, and 144 weeks of follow-up [4,5]. Therefore, BIC/FTC/TAF is considered a preferred regimen as initial antiretroviral therapy (ART) in current HIV clinical guidelines [6,7].

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Late presentation of HIV infection, defined by the presence of a CD4+ cell count <200 cells/mm^3 or AIDS-defining conditions, remains a major problem among people living with HIV [8,9]. Many ART regimens have demonstrated to decrease their efficacies when they are used in this context [10–12]. This loss of performance is especially noticeable in late presenters with AIDS-defining conditions because drug interactions between antiretroviral drugs and drugs necessary for the treatment of AIDS-defining conditions are common and may result in greater or lesser exposure to drugs, which may increase the frequency and/or severity of toxicities and affect the therapeutic response [13]. These considerations underscore the importance of evaluating the effectiveness of each ART regimen in late presenters [14].

The performance of BIC/FTC/TAF as initial ART in late presenters has been insufficiently evaluated. The number of late presenters included in the pivotal BIC/FTC/TAF studies was small (GS-US-380–1489: 36 patients and GS-1490: 44 patients). As is common in initial phase 3 trials for new HIV drugs, patients with serious infections or AIDS-related diseases were excluded from these clinical trials [2,3]. In addition, data from real-world observational studies analysing this scenario are limited. Therefore, it is important to add more evidence regarding the efficacy and safety of BIC/FTC/TAF as an initial therapy in late presenters. To this end, we developed the following study.

2. Methods

2.1. Study design

We developed a study, nested in the Cohort of the Spanish AIDS Research Network (CoRIS) [15], to evaluate the effectiveness and tolerability of BIC/FTC/TAF in comparison with other regimens as initial ART in late presenters.

2.2. Study population

We selected all HIV late presenters (defined by CD4 count <200 cells/mm^3 or a previous or ongoing AIDS-defining condition) enrolled in the CORIS who started ART between January 1st 2019 and November 30th 2020. Of them, we excluded for all the analyses those who started ART in the context of a clinical trial or with no follow-up after initiation of ART.

2.3. Outcomes

The primary outcome was the proportion of individuals achieving viral suppression (VS), defined as HIV RNA viral load <50 copies/mL at 24 and 48 weeks (±12 weeks) after ART initiation. Secondary outcomes included the proportion of individuals achieving immunological recovery (IR), defined as CD4 count >200 cells/mm^3 at 24 and 48 weeks (±12 weeks) after ART initiation, the time to VS during the first 48 weeks after ART initiation, and the proportion of individuals who discontinued their initial regimen, including reasons for discontinuation, during the first 24 and 48 weeks of ART. Outcomes were analysed both in the entire study population and in subgroups categorized by the presence or absence of AIDS-defining conditions.

Discontinuation reasons were categorized into the following: treatment failure, adverse events (AE), availability of simplified treatment, drug interaction, patient's preference, cost reduction, toxicity prevention, other, and unknown.

For the analyses of VS and IR at 24 and 48 weeks after ART initiation, we included only cases with available data within the assessment window. When multiple measurements were available within that window, we used the most recent one. We conducted two types of analyses: intention-to-treat (ITT) and on-treatment (OT). In the ITT analysis, outcomes were assessed based on the initial regimen, disregarding subsequent changes; thus, participants were assumed to have remained on their initial regimen once started. In the OT analysis, individuals who changed their initial regimen before 24 or 48 weeks were excluded from the analysis.

2.4. Statistical analysis

Our primary analysis was to compare outcomes between participants initiating ART with BIC/FTC/TAF and those on alternative regimens. As a secondary analysis, to elucidate potential differences between alternative regimens, we compared outcomes between participants initiating ART with regimens prescribed to more than 5% of participants and those on BIC/FTC/TAF. We used logistic regression models to estimate odds ratios (ORs) of association between the initial regimen and the achievement of VS and IR at weeks 24 and 48 after ART initiation.

For the analyses of time to VS within the initial 48 weeks after ART initiation, an individual's follow-up commenced at ART initiation and concluded at the occurrence of VS, death, the last study contact, or after 48 weeks, whichever happened first. We applied the multiple decrement method to compute the cumulative incidence of VS and used proportional hazards models on the sub-distribution hazard to estimate sub-distribution hazard ratios (sHR) for VS, considering deaths before VS as competing events.

Multivariable models were adjusted for potential confounding factors, including sex (male, female), age at ART initiation (<30, 30–49, ≥50 years), transmission category (men who have sex with men [MSM], heterosexual, other/unknown), educational level (no or compulsory education, secondary or university education, unknown), country of origin (Spain, foreign-born), CD4 cell count (<50, ≥50 cells/mm^3, unknown) viral load (<100,000, >100,000 copies/mL, unknown) within 6 months before ART initiation, and the presence of AIDS at baseline (no, yes).

To account for clustering of individuals within centres, we applied robust methods to estimate standard errors and calculate 95% CIs and *P* values. Wald tests were used to derive *P* values.

2.5. Ethical approval and informed consent

The CoRIS was approved by the Clinical Research Ethics Committee of the Gregorio Marañón General University Hospital. All patients agree to participate in CoRIS by signing an informed consent form. This study was approved by the Comité de Ética de la Investigación Provincial de Córdoba.

2.6. Role of the funding source

This work was funded by an Investigator Sponsored Research (ISR) grant from Gilead Sciences (IN-ES-380–6277) awarded to AR. Gilead Science were not in position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

3. Results

Between January 1st 2019 and November 30th 2020, 357 late presenters initiated ART within the CORIS. Among them, 314 individuals were eligible for our study, while 43 were excluded (41 who initiated ART within a clinical trial and 2 who lacked follow-up after ART initiation). Of the participants, 117 (37.7%) had AIDS-defining conditions. A total of 158 participants initiated ART with BIC/FTC/TAF and 156 with other regimens (Table S1). Baseline characteristics were similar between participants who initiated ART with BIC/FTC/TAF and those who initiated with other regimens (Table 1).

Table 1
Sociodemographic and clinical characteristics at antiretroviral therapy (ART) initiation according to initial ART regimen.

	BIC/FTC/TAF N = 158	Other regimens N = 156	*P* value
Sex [N (%)]			0.790
Male	133 (84.2)	133 (85.3)	
Female	25 (15.8)	23 (14.7)	
Age, years [N (%)]			
Median (IQR)	40 (33–51)	40 (33–52)	0.622
<30	28 (17.7)	24 (15.4)	0.836
30–49	85 (53.8)	88 (56.4)	
≥50	45 (28.5)	44 (28.2)	
Transmission category [N (%)]			0.224
Men who have sex with men	86 (54.4)	82 (52.6)	
Heterosexual	59 (37.3)	53 (34.0)	
Injection drug users	1 (0.6)	3 (1.9)	
Other/Unknown	12 (7.6)	18 (11.5)	
Country of origin [N (%)]			0.282
Spain	78 (49.4)	76 (48.7)	
Other in Western Europe	14 (8.9)	11 (7.0)	
Eastern Europe	5 (3.2)	0	
sub-Saharan Africa	5 (3.2)	8 (5.1)	
Northern Africa	1 (0.6)	3 (1.9)	
Latin America	54 (34.2)	56 (35.9)	
Other	1 (0.6)	2 (1.3)	
Educational level [N (%)]			0.069
No/compulsory education	22 (13.9)	20 (12.8)	
Upper secondary/university	98 (62.0)	80 (51.3)	
Unknown	38 (24.0)	56 (35.9)	
CD4 count, cells/mm3 [N (%)]			
Median (IQR)	103 (51–154)	97 (42–171)	0.978
<50	37 (23.4)	40 (25.6)	0.024
≥50	115 (72.8)	98 (62.8)	
Unknown	6 (3.8)	18 (11.5)	
Viral load, copies/mL [N (%)]			
Median (IQR)	249,621 (86,500–851,138)	273,000 (65,000–690,000)	0.510
<100,000	40 (25.3)	44 (28.2)	0.305
≥100,000	109 (69.0)	97 (62.2)	
Unknown	9 (5.7)	15 (9.6)	
AIDS diagnosis [N (%)]			0.066
No	107 (67.7)	90 (57.7)	
Yes	51 (32.3)	66 (42.3)	

3.1. Viral suppression

Viral suppression at 24 and 48 weeks after ART initiation was assessed in 147 (93.0%) and 137 (86.7%) of participants who initiated ART with BIC/FTC/TAF and in 140 (89.7%) and 127 (81.4%) of participants who initiated ART with other regimens, respectively. The reasons for exclusion from these analyses are detailed in Table S2. The proportion of participants achieving VS with BIC/FTC/TAF or alternative regimens was comparable at both 24 and 48 weeks after ART initiation (Fig. 1). Crude (ORc) and adjusted (ORa) odds ratios for achieving VS were also similar between BIC/FTC/TAF (used as reference) and other regimens, both at week 24 (ORc [95% CI]: 0.65 [0.3–1.43]; ORa: 0.61 [0.27–1.36]) and week 48 (ORc: 0.69 [0.31–1.54]; ORa: 0.61 [0.27–1.42]) after ART initiation. Nearly identical results were observed in the OT analyses (not shown) and in the subgroup of participants without AIDS-defining conditions (VS at week 24: 69% vs. 71.1%; VS at week 48: 82.8% vs. 82.9%).

Conversely, participants with AIDS-defining conditions achieved higher rates of VS with BIC/FTC/TAF compared to other regimens at both 24 and 48 weeks after ART initiation (Fig. 1). This difference remained statistically significant after adjusting for relevant confounders at week 24 (ORa [95%CI]: BIC/FTC/TAF (reference) vs. 0.2 [0.06–0.64]; $P = 0.007$ for other regimens) but not at week 48 ($P = 0.058$). We also evaluated the relationship between the initial ART and the achievement of VS, comparing BIC/FTC/TAF to each alternative regimen. At week 24, we observed lower ORa for the association between VS and DTG/ABC/3TC (ORa [95%CI]: BIC/FTC/TAF (reference) vs. 0.17 [0.04–0.68; $P = 0.012$) or DRV/COBI/FTC/TAF (ORa [95%CI]: BIC/FTC/TAF (reference) vs. 0.8 [0.01–0.52]; *P* value = 0.008). Similarly, at week 48, comparable results were found for DTG/ABC/3TC (ORa [95% CI]: BIC/FTC/TAF (reference) vs. 0.06 [0.01–0.76]; $P = 0.03$) and DTG + FTC/TDF (ORa [95% CI]: BIC/FTC/TAF (reference) vs. 0.2 [0.47–0.9]; $P = 0.035$).

3.2. Time to viral suppression

The median time to achieve VS from ART initiation was 17 weeks (IQR: 9–41) for participants who initiated ART with BIC/FTC/TAF and 25 weeks (13–48+) for those initiating with any other regimen: 20 (10–47) in DTG+FTC/TDF, 22 (8–48+) in DTG/ABC/3TC, and 45 (25–48+) in DRV/COBI/FTC/TAF (Fig. 2).

In our multivariable analyses, initiating ART with a regimen other than BIC/FTC/TAF was associated with a lower likelihood of achieving VS within the first 48 weeks after ART initiation (adjusted sHR: 0.69; 95% CI: 0.52–0.92; $P = 0.011$). However, in a comparative analysis of individual regimens, DRV/COBI/FTC/TAF was the only regimen that showed a significantly lower likelihood of VS compared to BIC/FTC/TAF (adjusted sHR: 0.36; 95% CI: 0.21–0.59; $P < 0.001$). Similar results were observed among participants initiating ART with AIDS-defining conditions (adjusted

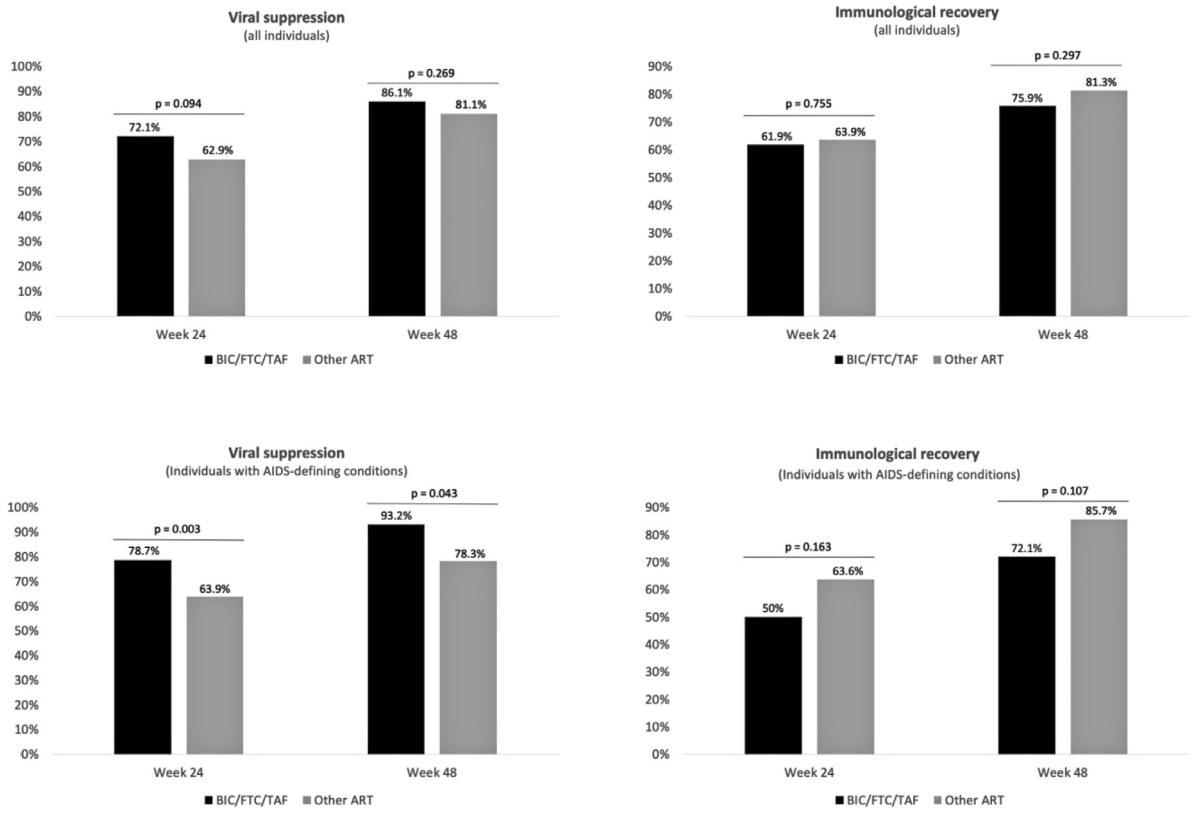

Figure 1. Viral suppression and immunological recovery at 24 and 48 weeks after ART initiation.

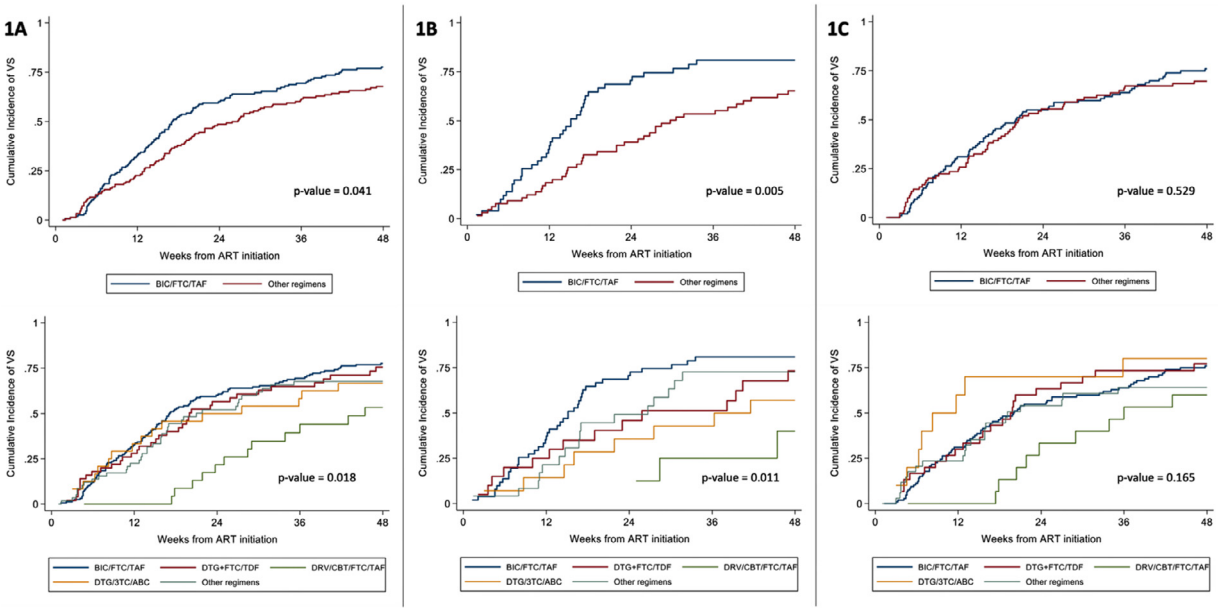

Figure 2. Time to VS during the first 48 weeks after ART initiation according to initial regimen for (1A) all individuals, (1B) individuals with AIDS-defining conditions and (1C) individuals without AIDS-defining conditions.

sHR: 0.49; 95% CI: 0.29–0.85; $P = 0.011$). In a comparative analysis of individual regimens performed within the subgroup of participants with AIDS-defining conditions, BIC/FTC/TAF demonstrated a significantly higher likelihood of achieving VS compared to DRV/COBI/FTC/TAF (adjusted sHR: 0.18; 95% CI: 0.07–0.45; $P < 0.001$) and DTG/ABC/3TC (adjusted sHR: 0.34; 95% CI: 0.13–0.88; $P = 0.026$).

3.3. Immunological recovery

We evaluated the achievement of IR at 24 and 48 weeks after ART initiation in 147 (93.0%) and 133 (84.2%) participants who initiated ART with BIC/FTC/TAF and in 135 (86.5%) and 123 (78.8%) who initiated ART with alternative regimens, respectively. The reasons for exclusion from these analyses are detailed in Table S2.

Table 2
Treatment discontinuations during the first 24 and 48 weeks after initiation of antiretroviral therapy (ART) and reason for discontinuation, according to initial regimen.

	BIC/FTC/TAF N = 158	No BIC/FTC/TAF					*P* value[a]
		DTG+FTC/TDF N = 50	DTG/ABC/3TC N = 24	DRV/CBT/FTC/TAF N = 24	Other regimens N = 58	Total N = 156	
During the first 24 weeks							
Treatment changes [N (%)]	5 (3.2)	20 (40.0)	2 (8.3)	3 (12.5)	13 (22.4)	38 (24.4)	<0.001
Reason for treatment change [N (%)]							
Treatment failure	0	0	0	0	2 (3.4)	2 (1.3)	0.153
Adverse event	3 (1.9)	8 (16.0)	1 (4.2)	2 (8.3)	3 (5.2)	14 (9.0)	0.006
Simplified treatment available	0	6 (12.0)	0	1 (4.2)	1 (1.7)	8 (5.1)	0.004
Drug interaction	0	0	1 (4.2)	0	0	1 (0.6)	0.313
Patient's wish/decision	2 (1.3)	0	0	0	1 (1.7)	1 (0.6)	0.569
Cost reduction	0	1 (2.0)	0	0	0	1 (0.6)	0.313
Toxicity prevention	0	4 (8.0)	0	0	5 (8.6)	9 (5.8)	0.002
Other	0	1 (2.0)	0	0	1 (1.7)	2 (1.3)	0.153
During the first 48 weeks							
Treatment changes [N (%)]	12 (7.6)	30 (60.0)	4 (16.7)	5 (20.8)	20 (34.5)	59 (37.8)	<0.001
Reason for treatment change [N (%)]							
Treatment failure	2 (1.3)	1 (2.0)	1 (4.2)	0	2 (3.4)	4 (2.6)	0.401
Adverse event	4 (2.5)	8 (16.0)	1 (4.2)	2 (8.3)	3 (5.2)	14 (9.0)	0.014
Simplified treatment available	1 (0.6)	13 (26.0)	1 (4.2)	1 (4.2)	5 (8.6)	20 (12.8)	<0.001
Drug interaction	0	0	1 (4.2)	1 (4.2)	0	2 (1.3)	0.153
Patient's wish/decision	4 (2.5)	0	0	0	1 (1.7)	1 (0.6)	0.181
Cost reduction	0	1 (2.0)	0	0	0	1 (0.6)	0.313
Toxicity prevention	0	5 (10.0)	0	0	6 (10.3)	11 (7.1)	0.001
Other	1 (0.6)	2 (4.0)	0	0	2 (3.4)	4 (2.6)	0.172
Unknown	0	0	0	1 (4.2)	1 (1.7)	2 (1.3)	0.153

[a] *P* value for the difference in percentages between BIC/FTC/TAF and no BIC/FTC/TAF.

The proportion of late presenters achieving IR at both time points was comparable between the study groups (Fig. 1). Both ORc and ORa for achieving IR were similar between BIC/FTC/TAF (used as reference) and alternative regimens, both at week 24 (ORc [95% CI]: 1.08 [0.66–1.78]; ORa: 1.22 [0.67–2.22]) and week 48 (ORc: 1.38 [0.72–2.65]; ORa: 1.72 [0.79–3.73]) after ART initiation. Rates of IR were also similar among participants with or without AIDS-defining conditions (Fig. 1), even after adjusting for significant confounders. Comparable results were obtained in the OT analyses (not shown).

3.4. Treatment discontinuations

The rate of treatment discontinuations within the initial 24 weeks after ART initiation was significantly lower among individuals commencing ART with BIC/FTC/TAF (3.2%) compared to those starting on alternative regimens (24.4%) ($P < 0.001$). This difference was primarily driven by lower percentages of discontinuations attributed to adverse events (1.9% vs. 9.0%, $P = 0.006$), treatment simplification (0% vs. 5.1%, $P = 0.004$), and toxicity prevention (0% vs. 5.8%, $P = 0.002$) (Table 2). A comprehensive breakdown of the types of AE leading to first-line regimen discontinuation and substitution regimens is provided in Table 3. The results for discontinuations within the initial 48 weeks after initiation of ART were consistent with those observed during the first 24 weeks (Table 2 and 3). Similar findings were observed among participants who initiated ART with and without AIDS-defining conditions (details not shown).

4. Discussion

In the CORIS real-world European cohort, late presenters who initiated ART with BIC/FTC/TAF demonstrated substantial achievement to VS and IR at both 24 and 48 weeks of follow-up. Compared to alternative regimens, initiating ART with BIC/FTC/TAF in late presenters was associated with a shorter time to VS and lower rates of ART discontinuation, primarily attributed to its enhanced safety and tolerability profile.

Our findings further support the robust efficacy and favourable safety profile observed among the late presenters who participated in BIC/FTC/TAF phase 3 clinical trials. In the GS-US-380–1489 and 1490 clinical trials, 99% of late presenters initiating ART with BIC/FTC/TAF achieved VS after 48 weeks of follow-up [2,3]. As anticipated from clinical trials settings, this percentage was slightly higher than the 86.1% observed in our study.

In the real world, only two cohort studies have evaluated the performance of BIC/FTC/TAF as initial therapy in late presenters. The first study examined the effectiveness and persistence of recommended 3-drug regimens in treatment-naïve individuals with CD4 cell counts <200/mm^3 enrolled in the US OPERA cohort at two different time points: July 31st 2019 [16] and December 31st 2021 [17]. The second study compared the virological effectiveness and discontinuation patters of BIC/FTC/TAF vs. DTG/ABC/3TC in late presenters initiating ART in Taiwan [18]. In contrast, our study conducted in Europe, has been the first to analyse the performance of BIC/FTC/TAF in late presenters initiating ART with AIDS-defining conditions.

In both of those cohorts, initiating ART with BIC/FTC/TAF was linked to lower rates of ART discontinuation when compared to alternative regimens. This finding aligns within our study results. Like the Taiwanese cohort, we observed that differences in the rate of initial ART discontinuation between BIC/FTC/TAF and alternative regimens was primarily attributed to a reduced proportion of AE associated with BIC/FTC/TAF leading to ART discontinuation.

However, it's worth nothing that in the OPERA cohort, this association was not identified [16]. Nevertheless, caution should be exercised when interpreting this lack of association, as 56% of the

Table 3
Treatment discontinuations due to adverse events (AEs) during the first 24 weeks after initiation of antiretroviral therapy (ART) and substitution regimen, according to initial regimen.

	BIC/FTC/TAF N = 158	No BIC/FTC/TAF					*P* value[a]
		DTG+FTC/TDF N = 50	DTG/ABC/3TC N = 24	DRV/CBT/FTC/TAF N = 24	Other regimens N = 58	Total N = 156	
Any adverse event [N (%)]	3 (1.9)	8 (16.0)	1 (4.2)	2 (8.3)	3 (5.2)	14 (9.0)	0.006
Renal	0	4 (8.0)	0	0	2 (3.4)	6 (3.8)	0.013
Skin	0	1 (2.0)	0	1 (4.2)	0	2 (1.3)	0.153
Gastrointestinal	1 (0.6)	0	0	1 (4.2)	0	1 (0.6)	0.993
Neuropsychiatric	0	2 (4.0)	0	0	0	2 (1.3)	0.153
Liver	1 (0.6)	0	0	0	0	0	0.320
Other	1 (0.6)	1 (2.0)	1 (4.2)	0	1 (1.7)	3 (1.9)	0.308
Substitution regimen [N (%)]	DTG/ABC/3TC	DTG/ABC/3TC	DRV/COBI/FTC/TAF	DTG/ABC/3TC	DTG/3TC	DTG/ABC/3TC	
	1 (33.3)	3 (37.5)	1 (100.0)	1 (50.0)	1 (33.3)	4 (28.6)	
	DRV/COBI/FTC/TAF	DRV/COBI/FTC/TDF		BIC/FTC/TAF	EFV+3TC/ABC	BIC/FTC/TAF	
	1 (33.3)	2 (25.0)		1 (50.0)	1 (33.3)	2 (14.3)	
	DTG/RPV	BIC/FTC/TAF			No ART	DRV/COBI/FTC/TDF	
	1 (33.3)	1 (12.5)			1 (33.3)	2 (14.3)	
		DRV+RTV+FTC/TDF				DTG/3TC	
		1 (12.5)				2 (14.3)	
		DTG/3TC				DRV/COBI/FTC/TAF	
		1 (12.5)				1 (7.1)	
						DRV+RTV+FTC/TDF	
						1 (7.1)	
						EFV+3TC/ABC	
						1 (7.1)	
						No ART	
						1 (7.1)	

[a] *P* value for the difference in percentages between BIC/FTC/TAF and no BIC/FTC/TAF.

participants had unknown reasons for ART discontinuation. Regardless of the specific cause, the available evidence suggests the high durability of BIC/FTC/TAF as an initial therapy option for late presenters [17].

Two other significant findings from these two studies, which our study also confirmed, are the comparable likelihood of achieving VS after 48 weeks of ART initiation in late presenters commencing ART with BIC/FTC/TAF or DTG-based regimens, and the higher likelihood of achieving VS after 48 weeks of ART initiation in late presenters starting ART with BIC/FTC/TAF compared to those initiating with DRV/COBI/FTC/TAF. Pending the results of the LAPTOP trial [19], the available evidence suggests that late presenters should initiate ART with integrase inhibitors-based ART rather than DRV/COBI/FTC/TAF.

Another observation from the OPERA cohort was a lower likelihood of achieving a CD4 count >200 cells/mm^3 with DRV and DTG-based regimens compared to BIC/FTC/TAF [17]. These results, which were not initially found in their earlier analyses [16], have not been confirmed in our study, possibly due to the lower number of individuals included in our study.

Our study is the first to assess the effectiveness and the tolerability of BIC/FTC/TAF as initial ART in late presenters with AIDS-defining conditions. In this critical scenario, where achieving VS as early as possible is paramount to prevent subsequent complications, our findings indicated that BIC/FTC/TAF, when compared other regimens, was associated with higher rates of VS at 24 weeks after ART initiation, an increased likelihood of achieving VS within the first 48 weeks after ART initiation, and greater ART persistence during the initial 48 weeks after ART initiation.

Interestingly, late presenters with AIDS-defining conditions achieved a higher percentage of VS with BIC/FTC/TAF as initial therapy compared to those without such conditions. The exact reason for this discrepancy remains uncertain. Drawing from a study by Sax P. et al, which demonstrated an association between higher VS rates and greater adherence at 24 weeks after ART initiation [20], it is plausible that late presenters with AIDS-defining conditions exhibited higher adherence rates compared to their counterparts without AIDS-defining conditions. Unfortunately, we cannot confirm this hypothesis because our study did not provide adherence data.

Nevertheless, regardless of the underlying cause, the proportion of VS achieved with BIC/FTC/TAF as initial ART in late presenters was notably distinct from that seen with other regimens, including recommended DTG-based regimens. The significant disparity supports our conclusion that the likelihood of achieving VS with BIC/FTC/TAF is superior to that of DTC/3TC/ABC and DTG + FTC/TDF at 48 weeks after ART initiation in late presenters with AIDS-defining conditions. Based on our comprehensive findings, we advocate for considering BIC/FTC/TAF as the preferred initial ART regimen for individuals with AIDS-defining conditions.

This study boasts several strengths. The CORIS, a large prospective cohort, is highly representative of the HIV population diagnosed with HIV since 2014 in Spain. Consequently, the participants included in this study offer a robust reflection of contemporary late presenters initiating ART. This provides us with a precise understanding of real-world prescription practices and the associated health outcomes within our clinical context. Additionally, our study benefits from the exceptional data quality maintained within the CORIS database. The incidence of unavailable data and estimated data entry errors remained minimal, ensuring the accuracy and reliability of our statistical analyses.

This study is not without its limitations. Despite the generous time window for the 24 and 48-week results (±12 weeks), ca. 5% of the participants lacked HIV viral load or CD4 cell count data during these periods. This was primarily due to a reduction in blood draws, a consequence of the COVID-19 pandemic. While we did

not identify significant differences in baseline characteristics between included and excluded individuals (except for a higher percentage of MSM among the included individuals), we cannot rule out the possibility that those without available data might exhibit different rates of VS or IR, although this seems less unlikely. Another limitation pertains to the relatively narrow eligibility and follow-up timeframe since BIC/FTC/TAF's approval in Spain in June 2018. Nevertheless, the number of participants initiating ART with BIC/FTC/TAF in our study was sufficient to evaluate the study outcomes. Additional analyses with larger participant cohorts and extended follow-up periods may potentially reveal differences between BIC/FTC/TAF and other preferred regimens, such as DTG/3TC, if they indeed exist.

In summary, BIC/FTC/TAF stands out as an excellent choice for initiating therapy in HIV late presenters, particularly among those with AIDS-defining conditions. This is attributed to its remarkable effectiveness in swift HIV replication and its minimal incidence of ART discontinuations.

Declarations

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Competing interests: DC reports to be the recipient of a Rio-Hortega (CM22/00176) grant from the by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union from 2023 to 2024 and honoraria for educational presentations and travel support for educational meetings from ViiV Healthcare, Gilead Sciences, and Janssen Cilag. IPV reports an Investigator Sponsored Research grant from Gilead Sciences (IN-ES-380–5729); educational grants from ViiV Healthcare and Gilead Sciences; and honoraria for educational presentations, travel support for educational meetings, and consulting fees from Gilead Sciences, ViiV Healthcare, Janssen, and MSD. AR reports an Investigator Sponsored Research grant from Gilead Sciences (IN-ES-380–6277) to support this work and honoraria for educational presentations, travel support for educational meetings, and consulting fees from Gilead Sciences, ViiV Healthcare, Janssen, and MSD. ARJ reports to be the recipient of a Miguel Servet Research Contract awarded by the Ministerio de Ciencia, Promoción y Universidades of Spain (CP18/00111). PRS reports honoraria for educational presentations and travel support for educational meetings from Gilead Sciences and Janssen Cilag. All other authors declare no competing interests.

Ethical approval: Comité de Ética de la Investigación Provincial de Córdoba. PEIBA 5096.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107016.

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Table S1: Description of initial regimens prescribed between January 1, 2019 and November 30, 2020

Initial regimen	N (%)
BIC/FTC/TAF	158 (50.3)
DTG+FTC/TDF	50 (15.9)
DTG/ABC/3TC	24 (7.6)
DRV/COBI/FTC/TAF	24 (7.6)
EVG/COBI/FTC/TAF	11 (3.5)
RAL+FTC/TDF	11 (3.5)
DTG/3TC	10 (3.2)
DTG+FTC/TAF	9 (2.9)
EFV/FTC/TDF	7 (2.2)
RAL+FTC/TAF	4 (1.3)
RAL+3TC/ABC	2 (0.6)
DRV+RTV+FTC/TDF	1 (0.3)
EFV+FTC/TAF	1 (0.3)
RAL+ETR/FTC	1 (0.3)
RPV+FTC/TAF	1 (0.3)

Table S2: Selection of the study population for the ITT and OT analyses of VS and IR at 24 and 48 weeks after ART initiation

	At 24 (±12) weeks			At 48 (±12) weeks		
	Total N = 314	**BIC/FTC/TAF N = 158**	**Other regimens N = 156**	**Total N = 314**	**BIC/FTC/TAF N = 158**	**Other regimens N = 156**
Overall exclusions						
Death before the assessment window	5 (1.6)	1 (0.6)	4 (2.6)	11 (3.5)	3 (1.9)	8 (5.1)
AIDS-related death	3 (1.0)	1 (0.6)	2 (1.3)	8 (2.5)	2 (1.3)	6 (3.8)
Death to non-AIDS infection	0	0	0	1 (0.3)	1 (0.6)	0
Death due to MI or other ischemic heart disease	1 (0.3)	0	1 (0.6)	1 (0.3)	0	1 (0.6)
Death due to other causes	1 (0.3)	0	1 (0.6)	1 (0.3)	0	1 (0.6)
Last visit to the centre before the assessment window	6 (1.9)	2 (1.3)	4 (2.6)	16 (5.1)	9 (5.7)	7 (4.5)
No visit in the assessment window	10 (3.2)	3 (1.9)	7 (4.5)	14 (4.5)	5 (3.2)	9 (5.8)
Exclusions for VS analyses						
	6 (1.9)	5 (3.2)	1 (0.6)	9 (2.9)	4 (2.5)	5 (3.2)

Available visit in the assessment window but missing viral	**287 (91.4)**	**147 (93.0)**	**140 (89.7)**	**264 (84.1)**	**137 (86.7)**	**127 (81.4**)
load	39 (13.6)	4 (2.7)	35 (25.0)	59 (22.3)	10 (7.3)	49 (38.6)
ITT analyses	**248 (79.0)**	**143 (90.5)**	**105 (67.3)**	**205 (65.3)**	**127 (80.4)**	**78 (50.0)**
Treatment discontinuation before 24 or 48 weeks, as appropriate[1]						
OT analyses	11 (3.5)	5 (3.2)	6 (3.8)	17 (5.4)	8 (5.1)	9 (5.8)
	282 (89.8)	**147 (93.0)**	**135 (86.5)**	**256 (81.5)**	**133 (84.2)**	**123 (78.8)**
Exclusions for IR analyses	38 (13.5)	4 (2.7)	34 (25.2)	59 (23.0)	10 (7.5)	49 (39.8)
Available visit in the assessment window but missing CD4	**244 (77.7)**	**143 (90.5)**	**101 (64.7)**	**197 (62.7)**	**123 (77.8)**	**74 (47.4)**
ITT analyses						
Treatment discontinuation before 24 or 48 weeks, as appropriate[1]						
OT analyses						

ITT: Intention to treat. OT: On treatment. VS: virological suppression. IR: immunological recovery. MI: myocardial infarction.

All percentages are calculated over the total number of individuals in each group, except those for [1]Treatment discontinuation before 24 or 48 weeks, as appropriate, that are calculated over the total number of individuals included in the ITT analyses.

DISCUSSION

The scientific works presented in this doctoral thesis were designed to improve knowledge in the clinical management of viral infections caused by the Hepatitis C Virus, Hepatitis B Virus, and HIV infection in drug users. The results obtained in the presented scientific papers have allowed us to make some general and specific considerations that can be incorporated into routine clinical practice. We will discuss the results separately in 3 sections corresponding to each of the presented scientific papers.

- Section 1.- Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers.

- Section 2.- Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addictions Centres.

- Section 3.- Effectiveness and safety of bictegravir plus emtricitabine and tenofovir alafenamide in HIV late presenters.

Note: The bibliographic references cited in each of the sections correspond to those referenced in the References section of each of the articles presented

Section 1.- Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers

The screening strategy and HCV treatment support evaluated in our study achieved high rates of screening (81.4%) and SVR (86.6% in the modified intention-to-treat analysis) in DAC users. Our results suggest that a strategy based on a tutored intervention (patient navigator intervention), the work of a multidisciplinary team, patient education intervention and the use of the HCV diagnostic algorithm "in a single step" could be useful in the management of a population, such as DAC patients, in whom it is extremely difficult to make both the diagnosis and to achieve completion of the treatment.

Drug users who are unaware of being infected with HCV, in addition to being a serious health problem for individuals, is a serious public health problem and an important barrier to the control and elimination of HCV(21) The greatest difficulty in curing HCV infection among drug users lies in the difficulty of keeping them in treatment. Thus, Ford et al. (22) studied a high proportion (85%; n = 435) of patients with active hepatitis C (85%; n = 435) identified through a screening program. However, only 6 of them completed the treatment successfully. In this scenario, multiple strategies were identified to improve health care for people at high risk of hepatitis C infection(23) Patient guardianship has been associated with significantly increased adherence at the beginning and follow-up of treatment among patients with HCV infection compared to the standard of care in a randomized study, which included 1353 patients (769 in the usual care group and 584 in the patient care group, respectively) (24). The guardianship group had significantly higher probabilities of adherence to care and initiation of treatment within the first 6 months. This study was the first to demonstrate that patient care compared to usual care increases the proportion of patients linked to health care. Our study supports the usefulness of this intervention in people with chronic HCV infection who use drugs.

The “one-step diagnosis of HCV” intervention used in our study is an intervention that simplifies and optimizes the diagnosis of HCV infection. RNA tests in the same sample used for the HCV antibody test significantly improved the acceptance of HCV RNA tests, reducing the number of visits for the patient and the time until diagnosis and minimizing the loss of patients during follow-up(25). For these reasons, this intervention should be considered an essential element in HCV screening strategies in populations with a high risk of infection and a low probability of adherence to the health system. Thus, this intervention has become the standard diagnostic method in Spain for hepatitis C (19). Patient education improves engagement in care in the context of other chronic diseases(26–29). Similarly, educational interventions regarding HCV infection and its treatment could increase the knowledge of the disease and, with it, the motivation of patients to be involved in their care. This could have contributed in our study to improving HCV screening rates and treatment adherence of infected patients. Another essential element of the strategy evaluated in our study was the coordination of the different health agents involved. This coordination is essential to optimize the effectiveness of health resources in the care of people who consume drugs because they reduce the fragmentation of care and facilitate the linkage of patients to them. The usefulness of this intervention has not been demonstrated in the context of HCV infection, but it has been observed in the context of other chronic diseases(30) and in drug users in a methadone maintenance program(31).

Whether the potential pharmacological interactions due to the consumption of drugs of abuse, alcohol or opioid replacement therapies could reduce the efficacy of HCV treatment with AAD is speculation(32). In our study, in the per-protocol analysis, 100% of patients achieved SVR. The four patients who started treatment and did not reach SVR were lost to follow-up (two of them after reaching ETR). These results support the findings of other studies that suggest that the response to HCV treatment with AAD in drug users can be comparable to that of the general population, provided that adequate adherence to treatment is ensured(33,34)

On the other hand, it is important to note that 30% (n = 9) of patients with HCV infection in whom the degree of liver fibrosis could be assessed had

advanced liver fibrosis at the time of diagnosis and that 16.6% had liver cirrhosis (one of them with hepatocarcinoma). The high percentage of patients with advanced liver disease observed in our study indicates the convenience of including a comprehensive assessment of patients, including the degree of liver fibrosis, in HCV screening and treatment programs in drug users. Some strategies, such as test-and-treat, suffer from this, despite the advantages of bringing screening closer to the comfort zone of the users. Therefore, strategies that do not include advanced liver disease screening are insufficient for the comprehensive management of hepatitis C in this population. This high percentage of patients with advanced disease, in turn, indicates the significant delay of the health system for the diagnosis of HCV infection in DAC users. Correcting this diagnostic delay is essential to achieve control of HCV both in this population and in the general population.

Our study has some limitations that require us to interpret its results with caution. First, this is a study conducted in DAC that did not have access to screening tests for HCV during the study. This meant that the initial phase of the strategy was focused on achieving the screening of a high proportion of patients. Therefore, our results cannot be extrapolated to DAC in other areas with access to HCV screening. However, in our health environment, access to HCV treatment is universal and free for the entire population, so our results cannot be extrapolated to areas in which access to HCV treatment for drug users is not guaranteed. Part of our study was conducted during the COVID-19 pandemic, and it is not possible to know the impact that this circumstance may have had on the results. Finally, our study was conducted in patients treated in DAC, and we have been able to access them by taking advantage of their link to these centres. Therefore, our results cannot be extrapolated to drug users who are not linked to the health system.

In conclusion, our study suggests that the implementation of strategies based on personalized intervention models can contribute to the control of HCV infection in DAC users.

Section 2.- Comparison of hepatitis B and SARS-CoV2 vaccination rates in people who attended Drugs and Addictions Centres

Vaccination against HBV should be a prioritized to eradicate this viral hepatitis and fulfil the WHO objective stablished for 2030 (13). In this context, the WHO the prioritization of hepatitis B vaccination in populations at high risk of infection. Among them, DAC-users constitute a difficult to access population. Different strategies have been tested to achieve vaccination of this group. The admission of DAC-users in closed institutions such detoxification centers represent a great opportunity to complete vaccination. Thus, in a study conducted in patients admitted to an opiate detoxification clinic, an 82% HBV vaccination rate was achieved with an accelerated vaccination schedule (14). This strategy would not be applicable to most DAC-users and, moreover, would only be effective in admissions so prolonged that vaccination schedules could be completed. Loss of follow-up of patients after discharge from a closed institution is common among DAC-users and is a major barrier to HBV vaccination strategies (15). In a study conducted in Brazil, among 553 crack users institutionalized in DAC, only 22% of patients completed a 21-day accelerated vaccination schedule. The main reason for such a small percentage was loss of follow-up of patients after discharge (median hospitalization time, 15 days (16) . Finally, several studies have suggested that strategies involving financial incentives for patients can improve vaccination rates in CAD users, although this cannot be extrapolated to other settings (15,17,18). In our study, after two-year follow-up, only 7.6% of those unimmunized against hepatitis B received at least one dose of vaccine. These results illustrate the difficulties to achieve high vaccination rates in DAC-users.

It has been observed that in situations where patients are connected to the health system, vaccination rates increase as the follow-up time is longer. Thus, in a cohort of HIV patients with 3 years of follow-up, hepatitis B vaccination rates of 9.6% were achieved (19), and in others with 7 and 10 years of follow-up, rates of 31.4% and 61.9%, were achieved respectively (20,21). In

this context, after 20 years of follow-up, rates of 75.2% were obtained in a Needle Exchange Program (NEP) cohort (22). In any case, the vaccination rates obtained are far from optimal. Given the high risk of acquiring the infection and transmitting it to their environment among DAC-users, the objective should be to vaccinate the entire non-immunized population in the shortest period possible. All this suggests that one of the main reasons for vaccination failure in DAC-users is loss to follow-up and inability to contact patients after the loss of contact with the health care setting. However, attributing exclusively to this reason the responsibility for the failure of HBV vaccination strategies in CAD-users may be erroneous and constitute an obstacle to the design of strategies that accurately address the problem. In our experience, resources focused to support and treat substance disorders have limitations in collaborating with the Health System the follow-up of their users. These programs are external and founded by other associations or institutions. This situation complicates to identify risk factors for the healthcare providers and hinders the ability to screen or offer preventive measures for substance use disorders and Addiction Centers. It is strinking that the 88% of the CAD users included in our study received at least one dose of SARS-Cov-2 vaccine (83% completed vaccination) in the same observation time. This rate is comparable to those observed in the general population in Spain (23,24). This fact suggests that it is possible to achieve high vaccination rates in DAC-users if appropriate strategies are employed.

The COVID-19 pandemic outbreak had an unexpected impact affecting all levels of the population worldwide. The rapid spread of the infection, due to transmission by air through Plfugge droplets at close proximity (1 meter) and Wells nuclei forming aerosols over longer distances, coupled with the elevated mortality rates observed during the two first waves (as of November 2023, 771,820,937 confirmed cases of COVID-19 and 6,978,175 reported deaths to WHO) (23), has, in our opinion, played a significant role in fostering widespread acceptance of vaccination among the general population. This way of transmission contrasts with hepatitis B transmission, which is predominantly by unprotected sexual intercourse and blood transmission (sharing syringes is a high risk in people with a history of drug abuse). We believe that these

differences in risk perception could alter the population's interest in protecting themselves from hepatitis B, even in the face of the high morbidity and mortality associated with chronic infection. Meanwhile, the measures implemented by governments to curb the outbreak, which originated in China and were subsequently adopted globally following the WHO's declaration of a global health alert (including social restrictions and quarantine policies), had a profound impact on the population. These measures directly affected people's lives, as they realized that taking precautions for their protection (such as using masks, adhering to hygiene measures, and getting vaccinated) had both social and economic repercussions for the general population and themselves. In Spain, the strategy to achieve high vaccination rates against SARS-Cov-2 included two essential elements: raising public awareness of the benefits of vaccination and facilitating access to vaccination. Achieving adequate awareness of the benefits of HBV vaccination in unimmunized DAC-users is an essential element in achieving high vaccination rates in this population, and to achieve this objective it is necessary to ensure that the health caregivers of the DAC-users themselves are also aware of it. Our findings suggest that clinicians should make a special effort to encourage HBV-unvaccinated patients to get vaccinated against HBV.

Our study has several limitations. It is retrospective with the limitations that this implies. The population studied is small, so our results should be interpreted with caution. Finally, our study was conducted in an area of universal and free health care, so our results may not necessarily be extrapolable to other populations with different socio-health care characteristics.

In conclusion, we found a high percentage of DACs-user unimmunized against HBV and the vaccination rates observed at 2 years was very low. This is a troubling finding that may compromise the goal of elimination of HBV infection proposed by WHO. The low vaccination rates against HBV contrast with the high vaccination rates against SARS-Cov-2 in the same population and at the same observation time, denoting that it is possible to achieve high vaccination rates in this population. Consequently, a similar approach for vaccination intended

for SARS-CoV2 should be applied in high-risk population to warrant the success of immunization program against other preventable diseases such as HBV.

Section 3.- Effectiveness and safety of bictegravir plus emtricitabine and tenofovir alafenamide in HIV late presenters

In the CORIS real-world European cohort, late presenters who initiated ART with BIC/FTC/TAF demonstrated substantial achievement to VS and IR at both 24 and 48 weeks of follow-up. Compared to alternative regimens, initiating ART with BIC/FTC/TAF in late presenters was associated with a shorter time to VS and lower rates of ART discontinuation, primarily attributed to its enhanced safety and tolerability profile. Our findings further support the robust efficacy and favourable safety profile observed among the late presenters who participated in BIC/FTC/TAF phase 3 clinical trials. In the GS-US-380–1489 and 1490 clinical trials, 99% of late presenters initiating ART with BIC/FTC/TAF achieved VS after 48 weeks of follow-up [2, 3]. As anticipated from clinical trials settings, this percentage was slightly higher than the 86.1% observed in our study. In the real world, only two cohort studies have evaluated the performance of BIC/FTC/TAF as initial therapy in late presenters. The first study examined the effectiveness and persistence of recommended 3-drug regimens in treatment-naïve individuals with CD4 cell counts < 200/mm3 enrolled in the US OPERA cohort at two different time points: July 31st 2019 [16] and December 31st 2021 [17]. The second study compared the virological effectiveness and discontinuation patters of BIC/FTC/TAF vs. DTG/ABC/3TC in late presenters initiating ART in Taiwan [18]. In contrast, our study conducted in Europe, has been the first to analyse the performance of BIC/FTC/TAF in late presenters initiating ART with AIDS-defining conditions.

In both of those cohorts, initiating ART with BIC/FTC/TAF was linked to lower rates of ART discontinuation when compared to alternative regimens. This finding aligns within our study results. Like the Taiwanese cohort, we observed that differences in the rate of initial ART discontinuation between BIC/FTC/TAF and alternative regimens was primarily attributed to a reduced proportion of AE associated with BIC/FTC/TAF leading to ART discontinuation. However, it's worth nothing that in the OPERA cohort, this as- sociation was not identified

[16]. Nevertheless, caution should be exercised when interpreting this lack of association, as 56% of the participants had unknown reasons for ART discontinuation. Regardless of the specific cause, the available evidence suggests the high durability of BIC/FTC/TAF as an initial therapy option for late presenters [17]. Two other significant findings from these two studies, which our study also confirmed, are the comparable likelihood of achieving VS after 48 weeks of ART initiation in late presenters commencing ART with BIC/FTC/TAF or DTG-based regimens, and the higher likelihood of achieving VS after 48 weeks of ART initiation in late presenters starting ART with BIC/FTC/TAF compared to those initiating with DRV/COBI/FTC/TAF. Pending the results of the LAPTOP trial [19], the available evidence suggests that late presenters should initiate ART with integrase inhibitors-based ART rather than DRV/COBI/FTC/TAF. Another observation from the OPERA cohort was a lower likelihood of achieving a CD4 count > 200 cells/mm3 with DRV and DTG-based regimens compared to BIC/FTC/TAF [17]. These results, which were not initially found in their earlier analyses [16], have not been confirmed in our study, possibly due to the lower number of individuals included in our study.

Our study is the first to assess the effectiveness and the tolerability of BIC/FTC/TAF as initial ART in late presenters with AIDS-defining conditions. In this critical scenario, where achieving VS as early as possible is paramount to prevent subsequent complications, our findings indicated that BIC/FTC/TAF, when compared other regimens, was associated with higher rates of VS at 24 weeks after ART initiation, an increased likelihood of achieving VS within the first 48 weeks after ART initiation, and greater ART persistence during the initial 48 weeks after ART initiation. Interestingly, late presenters with AIDS-defining conditions achieved a higher percentage of VS with BIC/FTC/TAF as initial therapy compared to those without such conditions. The exact reason for this discrepancy remains uncertain. Drawing from a study by Sax P. et al, which demonstrated an association between higher VS rates and greater adherence at 24 weeks after ART initiation [20], it is plausible that late presenters with AIDS-defining conditions exhibited higher adherence rates compared to their

counterparts without AIDS-defining conditions. Unfortunately, we cannot confirm this hypothesis because our study did not provide adherence data.

Nevertheless, regardless of the underlying cause, the proportion of VS achieved with BIC/FTC/TAF as initial ART in late presenters was notably distinct from that seen with other regimens, including recommended DTG-based regimens. The significant disparity supports our conclusion that the likelihood of achieving VS with BIC/FTC/TAF is superior to that of DTC/3TC/ABC and DTG + FTC/TDF at 48 weeks after ART initiation in late presenters with AIDS-defining conditions. Based on our comprehensive findings, we advocate for considering BIC/FTC/TAF as the preferred initial ART regimen for individuals with AIDS-defining conditions. This study boasts several strengths. The CORIS, a large prospective cohort, is highly representative of the HIV population diagnosed with HIV since 2014 in Spain. Consequently, the participants included in this study offer a robust reflection of contemporary late presenters initiating ART. This provides us with a precise understanding of real-world prescription practices and the associated health outcomes within our clinical context. Additionally, our study benefits from the exceptional data quality maintained within the CORIS database. The incidence of unavailable data and estimated data entry errors remained minimal, ensuring the accuracy and re- liability of our statistical analyses.

This study is not without its limitations. Despite the generous time window for the 24 and 48-week results (±12 weeks), ca. 5% of the participants lacked HIV viral load or CD4 cell count data during these periods. This was primarily due to a reduction in blood draws, a consequence of the COVID-19 pandemic. While we did not identify significant differences in baseline characteristics between included and excluded individuals (except for a higher percentage of MSM among the included individuals), we cannot rule out the possibility that those without available data might exhibit different rates of VS or IR, although this seems less unlikely. Another limitation pertains to the relatively narrow eligibility and follow-up timeframe since BIC/FTC/TAF's approval in Spain in June 2018. Nevertheless, the number of participants initiating ART with BIC/FTC/TAF in our study was sufficient to evaluate the study outcomes. Additional analyses with larger participant cohorts and extended follow-up

periods may potentially reveal differences between BIC/FTC/TAF and other preferred regimens, such as DTG/3TC, if they indeed exist. In summary, BIC/FTC/TAF stands out as an excellent choice for initiating therapy in HIV late presenters, particularly among those with AIDS-defining conditions. This is attributed to its remarkable effectiveness in swift HIV replication and its minimal incidence of ART discontinuations.

CONCLUSIONS

1.- The screening strategy and HCV treatment support evaluated in our study achieved high rates of screening (81.4%) and SVR (86.6% in the modified intention-to-treat analysis) in DAC users.

2.- Our results suggest that a strategy based on a tutored intervention (patient navigator intervention), the work of a multidisciplinary team, patient education intervention, and the use of the HCV diagnostic algorithm "in a single step" could be helpful in the management of a population, such as DAC patients, in whom it is extremely difficult to make both the diagnosis and to achieve completion of the treatment.

3.- A high percentage of DACs-user unimmunized against HBV, and the vaccination rates observed at two years were deficient. This is a troubling finding that may compromise the goal of elimination of HBV infection proposed by WHO.

4.- The low vaccination rates against HBV contrast with the high vaccination rates against SARS-Cov-2 in the same population and at the same observation time, denoting that it is possible to achieve high vaccination rates in this population.

5.- A similar approach for vaccination intended for SARS-CoV2 should be applied in high-risk populations to warrant the success of immunization programs against other preventable diseases such as HBV.

6.- In the CORIS real-world European cohort, late presenters who initiated ART with BIC/FTC/TAF demonstrated substantial achievement to VS and IR at 24 and 48 weeks of follow-up.

7.- Compared to alternative regimens, initiating ART with BIC/FTC/TAF in late presenters was associated with a shorter time to VS and lower rates of ART discontinuation, primarily attributed to its enhanced safety and tolerability profile.

8.- Our study is the first to assess the effectiveness and the tolerability of BIC/FTC/TAF as initial ART in late presenters with AIDS-defining conditions. In this critical scenario, where achieving VS as early as possible is paramount to prevent subsequent complications, our findings indicated that BIC/FTC/TAF, when compared to other regimens, was associated with higher rates of VS at 24.

APPENDIX I: OTHER SCIENTIFIC PUBLICATIONS DERIVED FROM THE RESEARCH ACTIVITY DURING THE PHD

Authors: Corona-Mata D; Rivero-Juarez A.
Title: The road to HIV and HCV elimination among people who inject drugs.
Journal: Lancet Gastroenterology & Hepatology. 8 - 6, pp. 497 - 498. 2023. ISSN 2468-1253 DOI: 10.1016/S2468-1253(23)00082-1

Authors: Pérez-Valero I; Corona D; Martínez N; López-Cavanillas M; Lluis C; Luque I
Title: Real-world discontinuations due to neuropsychiatric symptoms in people living with HIV treated with second-generation integrase inhibitors: a systematic review
Journal: Expert review of anti-infective therapy. 21 - 6, pp. 655 - 665. 2023. ISSN 1478-7210 DOI: 10.1080/14787210.2023.2203914

Authors: Casares-Jimenez M; Garcia-Garcia T; Suárez-Cárdenas JM; Perez-Jimenez AB; Martín MA; Caballero-Gómez J; Michán C; Corona-Mata D; Risalde MA; Perez-Valero I; Guerra R; Garcia-Bocanegra I; Rivero A; Rivero-Juarez A; Garrido JJ.
Title: Correlation of hepatitis E and rat hepatitis E viruses urban wastewater monitoring and Clinical Cases.
Journal: Science of the total environment. 908, 2024. ISSN 0048-9697 DOI: 10.1016/j.scitotenv.2023.168203

Authors: Casares-Jimenez M; Rivero-Juarez A; Lopez-Lopez P; Montes ML; Navarro-Soler R; Peraire J; Espinosa N; Alemán-Valls MR; Garcia-Garcia T; Caballero-Gomez J; Corona-Mata D; Perez-Valero I; Ulrich RG; Rivero A.
Title: Rat Hepatitis E virus (Rocahepevirus ratti) in people living with HIV
Journal: Emerging Microbes & Infections. 13 - 1, 2024. ISSN 2222-1751 DOI: 10.1080/22221751.2023.2295389

Authors: Oluremi AS; Casares-Jimenez M; Opaleye OO; Caballero-Gomez J; Ogbolu DO; Lopez-Lopez P; Corona-Mata D; Rivero-Juarez A; Rivero A.
Title: Butchering activity is the main risk factor for Hepatitis E virus (Paslahepevirus balayani) infection in Southwestern Nigeria: A prospective cohort study.
Journal: FRONTIERS IN MICROBIOLOGY. 2023. ISSN 1664-302X DOI: 10.3389/fmicb.2023.1247467

Authors: Vizcarra P; Moreno A; Vivancos MJ; García AM; González RP; Gutiérrez F; Mata DC; Galindo P; Calzado S; Casado JL.
Title: Improving Recognition of Fracture Risk in People with Human Immunodeficiency Virus: Performance and Model Contribution of Two Common Risk Assessment Tools
Journal: AIDS PATIENT CARE AND STDS. 37 - 1, pp. 11 - 21. 2023. DOI: 10.1089/apc.2022.0183

Authors: Frías M; Corona-Mata D; Moyano JM; Camacho-Espejo A; López-López P; Caballero-Gómez J; Ruiz-Cáceres I; Casares-Jiménez M; Pérez-Valero I; Rivero-Juárez A; Rivero A.
Title: Lack of associations of microRNAs with severe NAFLD in people living with HIV: Discovery case-control study
Journal: Frontiers in Endocrinology. 14, 2023. ISSN 1664-2392 DOI: 10.3389/fendo.2023.1230046

Authors: Rivera-Ruiz I; Corona-Mata D; Camacho-Espejo Á
Title: Monkeypox infection presenting as genital lesions.
Journal: Indian Journal of Dermatology Venereology & Leprology. 2023. ISSN 0378-6323
DOI: 10.25259/IJDVL_790_2022

Authors: Ruiz-Cáceres I; Hermida Romero T;Guerra Merino I; Portu Zapirain J; Pérez-Mies B; Sánchez-Conde M; Riaño MA; Rubio R; Fortés Alen J; Vidal González Á; Salas Antón C; Múñez E; Sánchez Sánchez R; Corona-Mata D;

Aldecoa Ansorregui I; Miró JM; Beloqui Pérez de Obanos R; Ibero C; Gómez-Román J; Fariñas MC; Tabuyo Bello T; de Alava E; Cisneros JM; Matías-Guiu X; Rivero A.

Title: Post-mortem findings in Spanish patients with COVID-19.

Journal: Frontiers in Medicine. 2023. ISSN 2296-858X DOI: 10.3389/fmed.2023.1151843

Authors: Gonzalez-Serna A; Corma-Gomez A; Tellez F; Corona-Mata D; Rios-Villegas MJ; Merino D; Galera C; Collado-Romacho AR; De Los Santos I; Cucurull J; Santos M; García-Martín S; Rivero A; Real LM; Macias J.

Title: Response to Glecaprevir/Pibrentasvir in HIV/HCV-coinfected patients in Clinical Practice

Journal: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY. 78 - 10, pp. 2591 - 2596. 2023. ISSN 0305-7453 DOI: 10.1093/jac/dkad278

Authors: Lopez-Lopez P; Frias M; Perez-Jimenez AB; Freyre-Carrillo C; Pineda JA; Fuentes A; Alados JC; Ramirez-Arellano E; Viciana I; Corona-Mata D; Caballero-Gomez J; Garcia-Bocanegra I; Risalde MA; Rivero-Juarez A; Rivero A.

Title: Temporal changes in the genotypes of Paslahepevirus balayani in southern Spain and their possible link with changes in pig trade imports.

Journal: One health. 16, 2023. ISSN 2352-7714 DOI: 10.1016/j.onehlt.2023.100539

Authors: Corma-Gómez A; Cabello A; Orviz E; Morante-Ruiz M; Ayerdi O; Al-Hayani A; Muñoz-Gómez A; Santos IL; Gómez-Ayerbe C; Rodrigo D; Riestra SR; Reus-Bañuls S; Silva-Klug A; Galindo MJ; Santos M; Serrano-Fuentes M; Faro-Míguez N; Pérez-Camacho I; Corona-Mata D; Morano L; López-Ruz MÁ; Montero M; Anaya-Baz B; Merino D; Castillo-Navarro A; Pineda JA; Macías J.

Title: Long or complicated mpox in patients with uncontrolled HIV infection.

Journal: J Med Virol. 2024 Mar;96(3):e29511. ISSN 0146-6615 DOI: 10.1002/jmv.29511

APPENDIX II. SCIENTIFIC COMMUNICATIONS DERIVED FROM THIS DOCTORAL THESIS IN INTERNATIONAL OR NATIONAL MEETINGS

II.A International meetings

Title: High rates of virological suppression after 24 weeks of tenofovir alafenamide/emtricitabine/bictegravir (BIC/FTC/TAF) in people living with HIV (PLWHIV) starting antiretroviral therapy with <200 CD4 cell count
Congress: HIV Drug Therapy
Place: Glasgow, United Kingdom
Date: 23/10/2022 – 26/10/2022
Organizating institution: International AIDS Society
Type of communication: Poster
Authors: I Pérez Valero; D Corona Mata; A Camacho Espejo; C Roca-Oporto; C Tomas; N Cabello; M Cervero Jimenez; M Navarro; A Rivero-Juarez; A Rivero Roman.

Title: Prospective screening of rocahepevirus ratti infection in a patient with acute hepatitis in Spain
Congress: 33nd European Congress of Clinical Microbiology and Infectious Diseases
Place: Copenhague, Denmark
Date: 15/04/2023-18/04/2023
Organizating institution: European Society of Clinical Microbiology and Infectious Diseases
Type of communication: Poster
Authors: Diana CORONA-MATA; Pedro LOPEZ-LOPEZ; Ana Belen PEREZ-JIMENEZ; Carolina FREYRE-CARRILLO; Juan Antonio PINEDA; Antonio AGUILERA; Ana FUENTES; Juan Carlos ALADOS; Gabriel REINA; Encarnacion RAMIREZ-ARELLANO; Isabel VICIANA; Javier CABALLERO-GOMEZ; Antonio RIVERO; Antonio RIVERO-JUAREZ.

Title: Long-term liver events in patients with HCV chronic infection after SVR
Congress: Conference on Retroviruses and Opportunistic Infections
Place: Seattle. United States
Date: 19/02/2023 – 22/02/2023
Organizating institution: AIS-USA
Type of communication: Poster
Authors: Jesica Martin Carmona, Anais Corma-Gomez, Francisco Tellez, Miriam Serrano-Fuentes, Luis Morano, Diana Corona Mata, Maria Jose Rios, Francisco J. Vera Mendez, Isabel Barroso, Rosario Palacios, Ignacio De Los Santos, Paloma Geijo, Arkaitz Imaz, Juan A. Pineda, Juan Macias, GEHEP-011

Title: Long-Term changes in liver stiffness post-SVR in patients with HCV chronic infection
Congress: Conference on Retroviruses and Opportunistic Infections
Place: Seattle. United States
Date: 19/02/2023 – 22/02/2023
Organizating institution: AIS-USA
Type of communication: Poster
Authors: Anais Corma-Gomez, Francisco Tellez, Diana Corona Mata, Luis Morano, Miriam Serrano-Fuentes, Maria Jose Rios, Francisco J. Vera Mendez, Isabel Barroso, Rosario Palacios, Ignacio De Los Santos, Paloma Geijo, Arkaitz Imaz, Dolores Merino, Juan A. Pineda, Juan Macias, Carlos Galera, GEHEP-011

IIB. National meetings

Title: Efectividad, seguridad y tolerabilidad de Bictegravir/Emtricitabina/TenofovirAlafenamida en personas con diagnóstico tardío de VIH
Congress: XIV CONGRESO NACIONAL GeSIDA

Place: A Coruña, Galicia, España

Date: 26/11/2023 - 29/11/2023

Organizating institution: Grupo de Estudio del SIDA GESIDA, SEIMC

Type of communication: Poster

Authors: Ignacio Perez Valero; Diana Corona-Mata; Angela Camacho; Angela Gutierrez; Marta Montero; Maria Remedios Aleman; Pilar Ruiz; Alexandre Perez; Melchor Riera; Inmaculada Jarrin; Antonio Rivero-Juarez; Antonio Rivero.

Title: Comparación de las tasas de inmunización frente a la hepatitis B y el SARS-Cov2 en personas que acuden a centros de atención a drogadicciones

Congress: VIII Congreso Nacional de GEHEP

Place: Cádiz, Andalucía, España

Date: 28/09/2023 - 30/09/2023

Organizating institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)

Type of communication: Poster

Authors: Diana Corona-Mata; Antonio Rivero-Juárez; Ángela Camacho Espejo; Ignacio Pérez Valero; Inmaculada Ruiz Cáceres; Laura Ruiz Torres; Mario Frías; Pedro López López; Javier Caballero Gómez; Ismael Zafra Soto; María Casares Jiménez; Bartolomé De La Fuente Darder; Antonio Rivero Román.

Title: Correlación entre casos de hepatitis aguda por los virus de la Hepatitis E y Rocahepevirus ratti y su presencia en aguas residuales

Congress: II Congreso de la Sociedad Andaluza de Microbiología Clínica y Enfermedades Infecciosas

Place: Córdoba, Andalucía, España

Date: 16/11/2023 - 18/11/2023

Organizating institution: Sociedad Andaluza de Microbiología Clínica y Enfermedades Infecciosas (SAMICEI)

Type of communication: Ponencia oral (comunicación oral)

Authors: M. Casares-Jimenez; T. Garcia-Garcia; J.M. Suarez-Cardenas; A.B. Perez-Jimenez; M.A. Martín; J. Caballero-Gomez; C. Michán; D. Corona-Mata; M.A. Risalde; I. Perez-Valero; R. Guerra; I. Garcia-Bocanegra; A.Rivero; A. Rivero Juarez; J.J. Garrido.

Title: Cambios temporales en los genotipos de paslahepevirus balayani en el sur de España y su posible relación con los cambios en las importaciones comerciales de porcino

Congress: VIII Congreso Nacional de GEHEP

Place: Cádiz, Andalucía, España

Date: 28/09/2023 - 30/09/2023

Organizating institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)

Type of communication: Poster

Authors: María Casares Jiménez; Tránsito García García; José Manuel Suárez Cárdenas; Ana Belén Pérez; María A Martín; Javier Caballero Gómez; Carmen Michán; Diana Corona-Mata; María Angeles Risalde Moya; Ignacio Pérez Valero; Rafael Guerra; Ignacio García Bocanegra; Antonio Rivero Román; Antonio Rivero-Juárez; Juan José Garrido.

Title: Estudio molecular y serológico del virus de la hepatitis E de rata (Rocahepevirus ratti) en personas con infección VIH en España

Congress: VIII Congreso Nacional de GEHEP

Place: Cádiz, Andalucía, España

Date: 28/09/2023 - 30/09/2023

Organizating institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)

Type of communication: Poster

Authors: Antonio Rivero-Juárez; María Casares Jiménez; Pedro López López; María Luisa Montes Ramírez; Roser Navarro Soler; Joaquín Peraire; Nuria Espinosa; María Remedios Alemán Valls; Tránsito García García; Javier

Caballero Gómez; Diana Corona-Mata; Ignacio Pérez Valero; Rainer G Ulrich; Antonio Rivero Román.

Title: Evaluación de la correlación entre casos clínicos y la monitorización en aguas residuales del virus de la hepatitis E y Rocahepevirus ratti
Congress: VIII Congreso Nacional de GEHEP
Place: Cádiz, Andalucía, España
Date: 28/09/2023 - 30/09/2023
Organizating institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)
Type of communication: Poster
Authors: María Casares Jiménez; Tránsito García García; José Manuel Suárez Cárdenas; Ana Belén Pérez; María A Martín; Javier Caballero Gómez; Carmen Michán; Diana Corona-Mata; María Angeles Risalde Moya; Ignacio Pérez Valero; Rafael Guerra; Ignacio García Bocanegra; Antonio Rivero Román; Antonio Rivero-Juárez; Juan José Garrido.

Title: Optimización del diagnóstico molecular de Rocahepevirus ratti en su hospedador
Congress: VIII Congreso Nacional de GEHEP
Place: Cádiz, Andalucía, España
Date: 28/09/2023 - 30/09/2023
Organizating institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)
Type of communication: Poster
Authors: Javier Caballero Gómez; Ignacio García Bocanegra; David Cano Terriza; María Casares Jiménez; Tomás Fajardo Alonso; Rafael Guerra; Ismael Zafra; Adrián Beato Benítez; Diana Corona-Mata; Débora Jiménez Martín; Mario Frías; Antonio Rivero Román; Antonio Rivero-Juárez.

Title: Cinética de anticuerpos de Paslahepevirus balayani en pacientes VIH/VHC cirróticos

Congress: XXVI Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
Place: Santiago de Compostela, Galicia, España
Date: 01/06/2023 - 03/06/2023
Organizating institution: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)
Type of communication: Poster
Authors: Pedro López López; Mario Frías; Gema García Delgado; Diana Corona Mata; Javier Caballero Gómez; María Casares Delgado; María A. Risalde; Inmaculada Ruíz Cáceres; Ignacio García Bocanegra; Ismael Zafra Soto; Ignacio Pérez Valero; Laura Ruíz Torres; José C. Gómez Villamandos; Ángela Camacho; Antonio Rivero Juárez; Antonio Rivero. ISBN 978-84-09-50940-9

Title: Mpox grave en pacientes con infección por el VIH no controlada
Congress: XXVI Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
Place: Santiago de Compostela, Galicia, España
Date: 01/06/2023 - 03/06/2023
Organizating institution: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)
Type of communication: Poster
Authors: A. Corma-Gómez; M. Santos; A. Cabello; M. Morante-Ruiz; A. Al-Hayani; I. De Los Santos; C. Gómez-Ayerbe; D. Rodrigo; S. De La Rosa Riestra; S. Reus-Bañuls; A. Silva-Klug; M.J. Galindo; M. Serrano-Fuentes; N. Faro-Míguez; I. Pérez-Camacho; D. Corona-Mata; L. Morano; M.Á. López-Ruz; M. Montero; D. Merino; A. Castillo-Navarro; J. Macías.

Title: Proteómica y metabolómica como biomarcadores de la enfermedad del hígado graso no alcohólico en pacientes infectadas por VIH: Estudio discovery caso-control

Congress: XXVI Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
Place: Santiago de Compostela, Galicia, España
Date: 01/06/2023 - 03/06/2023
Organizating institution: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)
Type of communication: Poster
Authors: Mario Frías; Antonio Rivero-Juárez; Pedro López-López; Inmaculada Ruiz Cáceres; Diana Corona-Mata; Javier Caballero-Gómez; Antonio Rivero.
ISBN 978-84-09-50940-9

Title: Efficacy of a comprehensive strategy for the detection and treatment of hepatitis C infection in a population attending addiction centers
Congress: XI Congreso Científico de Investigadores en Formación
Place: Córdoba, Andalucía, Spain
Date: 04/05/2023 – 04/05/2023
Organizating institution: Universidad de Córdoba
Type of communication: Ponencia oral (comunicación oral)
Authors: Corona-Mata D, Rivero-Juárez A, Camacho Á, Ruiz-Torres L, Ruiz-Cáceres I, de la Fuente Darder B, Cáceres-Anillo D, de Guía Castro-Granados M, Lizaur-Barbudo M, Victoria Cabrera-Gisbert M, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A

Title: Study on an intensified strategy for the elimination of hepatitis C in drug addiction centers in the province of Cordoba.
Congress: 7o Congreso Nacional del Grupo de Estudio de las Hepatitis Víricas (GEHEP) de la SEIMC Type of communication: Póster
Place: Murcia, Región de Murcia, España
Date: 22/09/2022 - 24/09/2022
Organizing institution: Grupo de Estudio de las¡ Hepatitis Víricas (GEHEP)
Authors: Corona Mata D, Corona-Mata D, Rivero-Juárez A, Camacho Á, Ruiz-

Torres L, Ruiz-Cáceres I, de la Fuente Darder B, Cáceres-Anillo D, de Guía Castro-Granados M, Lizaur-Barbudo M, Victoria Cabrera-Gisbert M, Redondo-Écija J, Aparicio-Aparicio A, Manchado-López L, Cobos L, Pérez-Valero I, Rivero A

Title: Expresión diferencial de proteínas y metabolitos en la enfermedad del hígado graso no alcohólico en pacientes infectadas por VIH: estudio Discovery caso-control
Congress: 7o Congreso Nacional del Grupo de Estudio de las Hepatitis Víricas (GEHEP) de la SEIMC Type of communication: Póster
Place: Murcia, Región de Murcia, España
Date: 22/09/202- 24/09/2022
Organizing institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)
Authors: Frías M; Rivero Juárez A; López-López P; Garcia Delgado G; Corona Mata D; Caballero Gómez J; Rivero A.

Title: Comparación de master mix para la detección del virus de la hepatitis E mediante técnica QPCR pangenotípica
Congress: 7o Congreso Nacional del Grupo de Estudio de las Hepatitis Víricas (GEHEP) de la SEIMC Type of communication: Póster
Place: Murcia, Región de Murcia, España
Date: 22/09/202- 24/09/2022
Organizing institution: Grupo de Estudio de las Hepatitis Víricas (GEHEP)
Authors: Zafra Soto I; Garcia Delgado G; López-López P; Caballero Gómez J; Frías M; Ruiz Torrez L; Ruiz Cáceres I; Corona Mata D; Rivero A; Rivero Juárez A.

APPENDIX III. PROJECTS FUNDED IN COMPETITIVE PUBLIC CALLS IN WHICH THE DOCTORAL STUDENT PARTICIPATES

Project Name: Detección molecular de patógenos no diagnosticados e infradiagnosticados causantes de diarrea de origen desconocido en pacientes inmunodeprimidos y VIH positivos (PATHDUO)
Degree of contribution: Investigador/a
Carrying out entity: Centro Nacional de Microbiología
City Entity Realization: Madrid, Comunidad de Madrid, España
Principal Investigator Names (PI, Co-PI,...): Diana Corona Mata; David Antonio Carmena Jiménez
No. of researchers: 12
Funding entity(ies): Instituto de Salud Carlos III
Entity Type: Public Research Organisation
Type of participation: Team member
Program Name: Acción Estratégica en Salud Intramural
Cod. According to the funder: PI23CIII/00051
Start-end date: 2024 - 2026 **Duration**: 3 years **Total amount**: 132.000 €

Project Name: Magnitude and clinical impact of Orthohepevirus C infection.
Carrying out entity: Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)
City Entity Realization: Córdoba, Andalucía, España
Principal Investigator Names (PI, Co-PI,...): Corona Mata D.; Rivero-Juárez A. (IP)
Funding entity(ies): Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III
Cod. According to the funder: PI22/01098
Start-end date: 2023 - 2025 **Duration**: 3 años

Project Name: Evaluation of Orthohepevirus C infection as an emerging cause of zoonotic disease.
Degree of contribution: Investigador/a
Carrying out entity: Hospital Universitario Reina Sofía, Córdoba
Entity Type: Instituciones Sanitarias Sofía
City Entity Realization: Córdoba, Andalucía, España
Principal Investigator Names (PI, Co-PI,...): Corona D; Rivero A (IP) No de investigadores/as: 20
Funding entity(ies): Instituto de Salud Carlos III
Type of participation: Team Member
Cod. according to funder: PI21/00793
Start-end date: 2021 - 2024
Total amount: 90.750 €

Network Name: CIBER - Enfermedades Infecciosas (CIBERINFEC)
Network ID: CB21/13/00083
Funding entity: Instituto de Salud Carlos III
Entity Type: Organismo Público de Investigación
Start Date: 25/05/2023

APPENDIX IV: CERTIFICATE OF OBTAINING PREDOCTORAL GRANT FOR CLINICAL RESEARCH STAFF "RIO HORTEGA"

During the period of study of her doctoral thesis, the doctoral student obtained a contract with public funding from the Carlos III Health Institute for the development of a training plan in research in health sciences and technologies that will be combined with healthcare activity corresponding to their specialty.

This contract is valid for two years, from 2023-2024 and links the doctoral student to the clinical healthcare activity of the Servicio de Enfermedades Infecciosas del Hospital Universitario Reina Sofía (Córdoba) as well as the research activity carried out at the Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC).

Rosario Perona Abellón
Subdirectora General de Evaluación y Fomento de la Investigación

CERTIFICA

Que según los antecedentes que obran en poder de esta Subdirección General, **Dña. DIANA CORONA MATA,** ha participado como Personal Contratado en los Contratos Rio Hortega-2022 que se relacionan:

Título del Proyecto: **"CONTRATOS RIO HORTEGA"**
- Número de Expediente: CM22/00176
- Duración: 2 años.
- Jefe de Grupo: RIVERO ROMAN, ANTONIO.
- Fecha de inicio: 01/01/2023, con una duración de 2 años.

Y para que así conste, firmo el presente certificado en Madrid,

Subdirección General de Evaluación y Fomento de la Investigación.

Rosario Perona Abellón

APPENDIX V: INTERNATIONAL ROTATION DURING THE PHD

During the study period of her doctoral thesis, the doctoral student did an international rotation at the University of California, San Diego, United States, for a period of 3 months (September to November 2023) under the direction of Dr. Edward Cachay, Professor of Clinical Medicine at the University of California, San Diego (UCSD).

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FAX: 858-822-5362

12 February 2024

Re: Documentation of international scholar visit

To whom it may concern,

It is my pleasure to provide documentation regarding the professional visit of Dr. Diana Corona Mata, an international post-graduate doctoral scholar, from the University of Córdoba to the University of California San Diego (UCSD) for a period of 3 months (September-November 2023).

During her UCSD-sponsored visit, Dr. Corona Mata worked under my professional mentorship and was exposed to our diverse range of clinical HIV programs, including our High Resolution Anoscope program for anal cancer screening. Additionally, she actively participated in two significant research projects at the UCSD Antiviral Research Center alongside Dr. Susan Little. Throughout her tenure, Dr. Corona Mata diligently fulfilled her scholar duties and contributed to two projects focused on HIV epidemiology and sexually transmitted diseases.

Dr. Corona Mata demonstrated exceptional clinical skills and professionalism during her time with us. Her empathetic and compassionate approach to patient care was evident at the bedside. It is worth noting that her scholarly contributions are expected to culminate in the publication of two collaborative manuscripts upon completion of data analysis.

In summary, it was a true pleasure collaborating with Dr. Diana Corona Mata. She consistently exhibited a commitment to excellence in all aspects of her work. Please do not hesitate to contact me if further assistance is needed.

Sincerely,

Edward Cachay MD, MAS
Professor of Clinical Medicine
Division of Infectious Diseases and Global Public Health
University of California at San Diego
Director of UC San Diego Altman Clinical & Translational Research Institute Community Research Partnerships Unit
Pronouns: He/His/him

Owen Clinic: T: 619-543-3995 |F: 619.543.3178
Office: Hillcrest Campus Clinical Teaching Facility Building C, Office C-108 | T: 619.543.3882