Clinical phenotypes and incidence of acute or recent hepatitis C virus infection and bacterial sexually transmitted infections among MSM with HIV

Juan Berenguer[a,b,c], Pablo Ryan[b,c,d,e], Luis Ramos-Ruperto[c,f,g], Luz Martín-Carbonero[c,f,g], Leire Pérez-Latorre[a,b,c], Ignacio De Los Santos[c,h,i], Adriana Pinto[c,j,k], María J. Vivancos[c,l,m], Eva Orviz[c,n,o], Beatriz Álvarez[p], José Sanz[q], Pilar Ruiz-Seco[r,s], Rafael Torres[t], Marta De Miguel[u], Herminia Esteban[u], Inmaculada Jarrín[c,v], Salvador Resino[c,w], José M. Bellón[a,b,c], Juan González-García[c,f,g] and on behalf of the GeSIDA 12121-RIS EPICLIN 08_2021 ATHENS Study Group

Objective: Risk of acute/recent hepatitis C virus infection (ARHCV) and bacterial sexually transmitted infections (STIs) among MSM (MSM-HIV) is heterogeneous. We aimed to identify clinical phenotypes and assess their association with incident ARHCV and bacterial STIs.

Design: A prospective multicenter cohort study.

Methods: Between 2022 and 2024, MSM-HIV were recruited from 10 centers in Madrid and followed for 12 months with HCV and bacterial STI screening. App-based questionnaires captured behavioral and mental health data. Thirty-eight variables were analyzed using principal component analysis and hierarchical clustering to derive clinical phenotypes.

Results: A total of 529 participants were included (median age 41 years). Three phenotypes were identified: CP1 ($n = 328$, 62.0%), CP2 ($n = 133$, 25.1%), and CP3 ($n = 68$, 12.9%), representing different levels of sexual risk, substance use, and prior STI/HCV history. ARHCV incidence was 0.94, 0.72, and 11.76 per 100 person-years in CP1, CP2, and CP3, respectively, and was higher in CP3 than in CP1 (incidence rate ratio [IRR] 12.49, 95% confidence interval [CI] 3.00–73.08) and CP2 (16.25, 2.18–720.93). Bacterial STI incidence was 33.29, 60.83, and 61.76 per 100 person-years, respectively,

[a]Hospital General Universitario Gregorio Marañón, [b]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), [c]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), [d]Hospital Universitario Infanta Leonor, [e]Grupo de Estudio de Infecciones de transmisión sexual de SEIMC (GEITS), [f]Hospital Universitario La Paz, [g]Instituto de Investigación Sanitaria Hospital La Paz (IdiPAZ), [h]Hospital Universitario de la Princesa, [i]Instituto de Investigación Sanitaria del Hospital de la Princesa (IIS-PRINCESA), [j]Hospital Universitario 12 de Octubre, [k]Instituto de Investigación Sanitaria Hospital 12 de Octubre (I+12), [l]Hospital Universitario Ramón y Cajal, [m]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), [n]Hospital Clínico San Carlos, [o]Instituto de Investigación Sanitaria del Hospital Clínico de San Carlos (IdISSC), [p]Hospital Universitario Fundación Jiménez Díaz, Madrid, [q]Hospital Universitario Príncipe de Asturias, Alcalá de Henares, [r]Hospital Universitario Infanta Sofía (FIIB HUIS-HUHEN), San Sebastián de los Reyes, [s]Universidad Europea de Madrid, Madrid, [t]Hospital Universitario Severo Ochoa, Leganés, [u]Fundación SEIMC-GeSIDA, [v]Centro Nacional de Epidemiología – Instituto de Salud Carlos III (ISCIII), Madrid, and [w]Centro Nacional de Microbiología – Instituto de Salud Carlos III (ISCIII), Majadahonda, Spain.

Correspondence to Juan Berenguer, MD, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Doctor Esquerdo 46, 28007 Madrid, Spain.

E-mail: jbb4@me.com
Received: 15 April 2026; revised: 24 June 2026; accepted: 27 June 2026.

DOI:10.1097/QAD.0000000000004614

and was higher in CP2 (IRR 1.83, 95% CI 1.36–2.46) and CP3 (IRR 1.86, 95% CI 1.27–2.68) than in CP1.

Conclusion: Clinical phenotypes stratified ARHCV and bacterial STI incidence among MSM-HIV. ARHCV was concentrated in a small high-exposure subgroup, whereas bacterial STIs were more frequent in intermediate and high-exposure phenotypes. Phenotype-based approaches may help guide risk stratification and prevention in HIV care.

AIDS 2026, **40**:000–000

Keywords: chemsex., clinical phenotyping, hepatitis C virus, MSM, sexually transmitted infections

Introduction

Hepatitis C virus (HCV) transmission in sexual contexts among MSM has been recognized for more than two decades [1]. Although scale-up of direct-acting antivirals (DAAs) in high-income settings may have reduced incidence through a treatment-as-prevention effect [2,3], acute or recent HCV infection or reinfection (ARHCV) remains a relevant co-occurring condition in this population. Cases continue to be reported among MSM with HIV and increasingly among MSM without HIV, particularly those using HIV preexposure prophylaxis (PrEP) [4,5]. In parallel, bacterial sexually transmitted infections (STIs), particularly those caused by *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), and *Chlamydia trachomatis* (chlamydia), represent a growing public health concern worldwide and disproportionately affect MSM [6].

Determinants of ARHCV and bacterial STIs overlap and are driven by sexual exposure and sexualized drug use (chemsex). HCV transmission has been associated with condomless receptive anal intercourse (CRAI) with multiple partners, sexualized injecting drug use (slamsex), practices associated with rectal mucosal trauma, and concurrent STIs as potential biological cofactors [4,7–9]. Bacterial STI transmission among MSM has similarly been linked to high partner turnover, CRAI, and frequent asymptomatic extragenital infections, which sustain transmission and reinfection [8,10,11].

Evidence on determinants of ARHCV and bacterial STIs among MSM largely derives from regression analyses of individual exposures. However, infection risk reflects combinations of correlated behavioral, substance use, and clinical factors that cluster within individuals. Approaches that capture how these features co-occur within individuals are needed to define clinically meaningful subgroups. Although several studies have used clustering methods to identify subgroups among MSM and examine their association with HIV or STI outcomes, these studies have been cross-sectional and evaluated prevalent rather than incident outcomes [12–14]. To our knowledge, no studies have defined multidimensional clinical phenotypes associated to incident HCV or STI outcomes in this population. We therefore applied a data-driven approach in a prospective cohort of MSM with HIV, integrating sexual behavior, substance use, clinical variables, and systematic HCV and bacterial STI testing to identify phenotypes associated with incident infection risk.

Materials and methods

Study design and participants

This analysis leveraged data from ATHENS (Acute/recent infecTions and reinfections by Hepatitis C virus in mEN having Sex with men), a prospective, multicenter cohort study conducted in the Madrid region between May 2022 and February 2024. ATHENS enrolled MSM with HIV and MSM using PrEP to investigate the epidemiology and risk factors for ARHCV and bacterial STIs [4]. The present analysis was restricted to MSM with HIV because behavioral and psychological data were collected in this group using a self-administered mobile app questionnaire.

Participants were recruited from ten public hospitals in Madrid through two sources: the Cohort of the Spanish HIV Research Network (CoRIS) and the Madrid Coinfection Registry (Madrid CoRE). CoRIS is a prospective multicenter cohort initiated in 2004 that enrolls individuals newly diagnosed with HIV who are antiretroviral therapy (ART) naive at entry [15]. Madrid CoRE is a mandatory registry established in 2014 that includes all individuals treated for HCV with DAAs within Madrid's public hospital network [16] and was incorporated into ATHENS to support the study of HCV reinfections.

For this substudy, we included MSM with HIV enrolled in CoRIS since 2014 and those registered in Madrid CoRE after achieving sustained virological response (SVR) following DAA therapy; individuals appearing in both data sources were assigned to Madrid CoRE.

Study visits were scheduled at baseline, month 6 (±2 months), and month 12 (±2 months). All participants provided written informed consent, and study data were pseudonymized before analysis.

Data collection and laboratory procedures

Baseline demographic and clinical data were retrieved from the CoRIS and Madrid CoRE databases and completed using REDCap-based case report forms [17] hosted by the SEIMC/GeSIDA Foundation, as detailed in Supplementary Appendix 1, https://links.lww.com/QAD/D965. Variables included sociodemographic characteristics, ART history, CD4 cell counts, HIV RNA levels, and prior diagnoses of bacterial STIs and HCV infection.

Behavioral and psychological data were collected at each study visit using a self-administered mobile app questionnaire covering the preceding two months (Supplementary Appendix 2, https://links.lww.com/QAD/D965). Domains included sexual behavior, substance use, and mental health indicators, assessed using the Hospital Anxiety and Depression Scale (HADS), the adult attention deficit hyperactivity disorder (ADHD) scale, and the Barratt Impulsiveness Scale.

Testing for HCV and bacterial STIs was performed at all scheduled study visits irrespective of symptoms, and additionally when clinically indicated. HCV testing consisted of antibody screening followed by RNA testing when antibodies were detected, except in participants with a history of HCV infection or previously positive serology, for whom HCV RNA testing was performed directly.

Gonorrhea and chlamydia were tested using nucleic acid amplification tests on pharyngeal and rectal swabs and on urethral swabs or first catch urine specimens. Syphilis was assessed using both treponemal and nontreponemal serological tests. All HCV and STI diagnostic testing was performed locally at the participating hospitals using the assays and commercial platforms routinely employed in each site's clinical microbiology laboratory. Standard blood panels, including liver enzyme measurements, were also obtained.

Acute/recent hepatitis C virus infection and sexually transmitted infection definitions

ARHCV was defined according to the NEAT-ID (European Treatment Network for HIV, Hepatitis and Global Infectious Diseases) consensus criteria for recently acquired primary HCV infection or reinfection in MSM [7]. Events required newly detectable HCV RNA. Primary infection was defined as detectable HCV RNA preceded within the previous 12 months by a documented negative HCV RNA or anti-HCV IgG test. Reinfection was defined as newly detectable HCV RNA following documented spontaneous clearance or treatment-induced SVR. When available, reinfection was further supported by identification of a different HCV genotype after resolution of the prior infection.

Gonorrhea and chlamydia episodes were defined as laboratory-confirmed detection at any anatomical site, irrespective of symptoms. Syphilis episodes were identified by clinicians at each site based on clinical and serological criteria, according to established guidelines [8]. All laboratory-confirmed STIs identified during follow-up were treated according to standard clinical practice. Distinct STI episodes were defined as infections involving a different pathogen or occurring after documented treatment of a previous episode; infections identified at different study visits were considered distinct episodes, even when involving the same pathogen and anatomical site.

During the study period, DAAs were widely available, and treatment for ARHCV was typically initiated on the day of diagnosis. Doxycycline postexposure prophylaxis (DoxyPEP) for bacterial STI prevention was not implemented in the study setting.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. To identify clinical phenotypes among MSM with HIV, we used a multistep approach combining dimensionality reduction and unsupervised clustering, followed by analyses of associations with ARHCV or bacterial STIs.

We initially considered 38 variables grouped into six predefined domains, selected *a priori* based on a conceptual framework and existing evidence on determinants of sexually transmitted HCV and bacterial STIs among MSM (Supplementary Table 1, https://links.lww.com/QAD/D965): sociodemographic characteristics, infection history, mental health, drug use, route of drug use, and sexual behavior. Variables on drug use and sexual behavior referred to the preceding 2 months.

Principal component analysis (PCA) was performed to derive uncorrelated components summarizing the multivariate structure of the dataset. Sampling adequacy was assessed using the Kaiser–Meyer–Olkin (KMO) measure and Bartlett's test of sphericity. Variables with individual KMO values <0.60 were excluded prior to analysis. Components were retained according to the Kaiser criterion (eigenvalues >1). Component loadings were examined to interpret and label the components, with absolute values at least 0.40 considered meaningful contributors.

Hierarchical agglomerative clustering was applied to component scores using Euclidean distance and Ward's linkage method. The number of clusters was determined based on inspection of dendrograms and statistical criteria, including the silhouette index. Cluster robustness was evaluated using k-means clustering as a sensitivity analysis.

Differences in component scores across clusters were assessed using Kruskal–Wallis tests.

Incidence rates were expressed per 100 person-years (PY) and calculated as the total number of incident infections during follow-up divided by person-time from baseline to the last follow-up visit or study end, with 95% confidence intervals (CIs) assuming a Poisson distribution. Incidence rate ratios (IRRs) and 95% CIs were calculated using exact conditional methods based on the Poisson distribution. Analyses were conducted in R version 4.4.1 and Stata version 18 (StataCorp, College Station, Texas, USA).

This study followed the STROBE reporting guideline for cohort studies (Supplementary Table 2, https://links.lww.com/QAD/D965).

Ethical considerations

The study was conducted in accordance with the Declarations of Helsinki and was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón (GESIDA 12151, minutes 14/2021, July 5, 2021). All participants provided written informed consent, and procedures complied with local regulations on confidentiality and data protection.

Results

Participant characteristics

Among 733 MSM with HIV enrolled in the ATHENS cohort, 540 (73.7%) completed at least one app-based questionnaire. Baseline characteristics were similar between completers and noncompleters, except for a slightly higher CD4 cell count among completers; baseline HCV prevalence did not differ (Supplementary Table 3, https://links.lww.com/QAD/D965). After excluding 11 participants with missing data for the principal component analysis, 529 participants were included in the final analysis.

In this analytic sample, the median age was 41 years, 88.3% self-identified as White, and 61.8% were born in Spain. A history of an AIDS-defining condition was reported in 11.0%. Most participants were receiving ART (99.8%); the median $CD4^+$ cell count was 804 cells/μl, and 94.3% had undetectable HIV RNA (<50 copies/ml). Baseline characteristics, including prior bacterial STIs, prior HCV infection, and behavioral risk factors, are summarized in Table 1, stratified by cohort of origin.

Dimensionality reduction

Of the 38 variables initially considered, 16 did not meet sampling adequacy criteria (individual KMO <0.60) and were excluded prior to PCA. PCA was conducted on the remaining 22 variables and identified six principal components (PCs) summarizing the main patterns of variation in the dataset and together explaining 59.2% of the total variance. The variables retained, together with their component loadings and individual KMO values, are shown in Fig. 1. The overall KMO was 0.79, indicating good sampling adequacy.

PC1 showed high loadings for any drug use, mephedrone and GHB use, drug ingestion and snorting, and CRAI, reflecting a combined pattern of chemsex-related

Table 1. Baseline characteristics of study participants by cohort of origin.

Characteristic	CoRIS (*N* = 348)	Madrid CoRE[a] (*N* = 181)	All (*N* = 529)
Demographics			
Age, years, median (IQR)	37.5 (31–45)	48 (41–55)	41 (33–49)
Born in Spain, *n* (%)	207 (59.5)	120 (66.3)	327 (61.8)
White, *n* (%)[b]	309 (88.8)	158 (87.3)	467 (88.3)
HIV-related variables			
Prior AIDS-defining conditions, *n* (%)	31 (8.9)	27 (14.9)	58 (11.0)
Antiretroviral therapy, *n* (%)	347 (99.7)	181 (100)	528 (99.8)
$CD4^+$ cell count, cells/μl, median (IQR)	807 (614–998)	796 (586–998)	804 (612–998)
HIV RNA <50 copies per ml, *n* (%)	326 (93.7)	173 (95.6)	499 (94.3)
Risk practices for STIs and HCV[c]			
CRAI, *n* (%)	226 (64.9)	123 (68.0)	349 (66.0)
Chemsex, *n* (%)	89 (25.6)	88 (48.6)	177 (33.4)
Slamsex, *n* (%)	12 (3.4)	29 (16.0)	41 (7.8)
Prior history of HCV/STIs			
HCV infection, *n* (%)	9 (2.6)	181 (100)	190 (35.9)
Any bacterial STI, *n* (%)	238 (68.4)	166 (91.7)	404 (76.4)
Syphilis, *n* (%)	204 (58.6)	157 (86.7)	361 (68.2)
Gonorrhea, *n* (%)	98 (28.2)	66 (36.5)	164 (31.0)
Chlamydia, *n* (%)	71 (20.4)	49 (27.1)	120 (22.7)

CoRIS, Cohort of the Spanish HIV Research Network; Madrid CoRE, Madrid Coinfection Registry; IQR, interquartile range; CRAI, condomless receptive anal intercourse; HCV, hepatitis C virus; STI, sexually transmitted infection.
[a]Madrid CoRE includes individuals who were treated for HCV infection and achieved sustained virological response after DAA therapy.
[b]Race was self-reported; categories available were White, Black, Other.
[c]Risk practices in the previous 2 months.

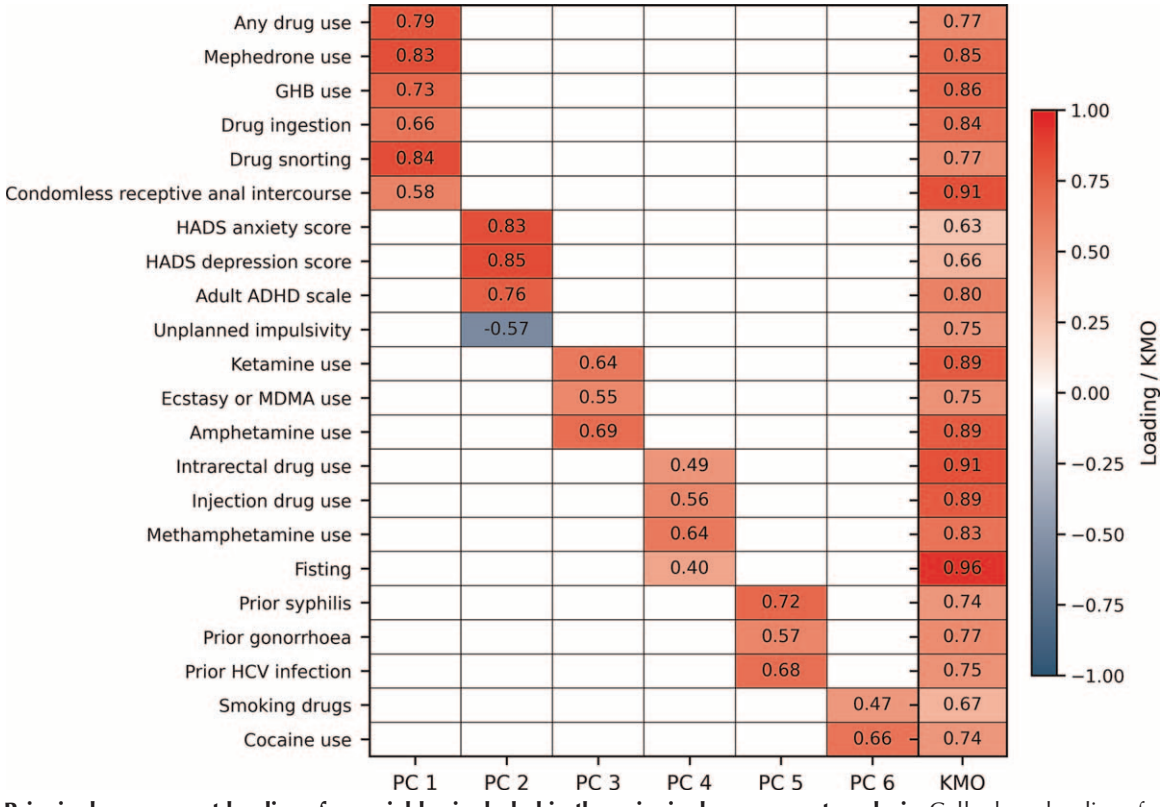

Fig. 1. Principal component loadings for variables included in the principal component analysis. Cells show loadings for the six retained principal components used to derive clinical phenotypes; blank cells indicate absolute loadings < 0.40. Negative loadings indicate inverse contributions to the corresponding component. Sampling adequacy is summarized by the KMO statistic for each variable and overall. ADHD, attention-deficit/hyperactivity disorder; GHB, gamma-hydroxybutyrate; HADS, Hospital Anxiety and Depression Scale; HCV, hepatitis C virus; KMO, Kaiser–Meyer–Olkin; MDMA, 3,4-methylenedioxymethamphetamine; PC, principal component.

substance use and sexual risk behavior. PC2 was characterized by self-reported anxiety and depression, adult ADHD, and impulsivity, reflecting psychological vulnerability. PC3 loaded on ketamine, MDMA/ecstasy, and amphetamine use, consistent with recreational party drug use. PC4 was defined by intrarectal and injection drug use, methamphetamine use, and fisting, indicating high-intensity chemsex and higher-risk sexual practices. PC5 loaded on prior syphilis, prior gonorrhea, and prior HCV infection, capturing a history of bacterial STIs and HCV. PC6 loaded on smoking drugs and cocaine use, suggesting smoked stimulant use.

For interpretability, PCs were labelled as follows: PC1, chemsex-associated drug use and sexual risk behavior; PC2, psychological vulnerability; PC3, party drug use; PC4, high-intensity chemsex and higher-risk sexual practices; PC5, history of STIs and HCV; and PC6, smoked stimulant use.

Identification of clinical phenotypes

Hierarchical clustering was used to identify clinical phenotypes. Among the evaluated clusterg solutions, the two, three, and four-cluster models showed similar average silhouette widths (0.23, 0.25, and 0.25, respectively). The three-cluster solution was selected because it provided the best balance between interpretability and parsimony (Fig. 2a). A sensitivity analysis using k-means produced a similar grouping in the two-dimensional component space, supporting the robustness of the phenotype structure (Fig. 2b).

Median PC scores by phenotype are shown in Table 2. Clinical phenotype 3 ($n = 68$, 12.9%) showed the highest alignment with chemsex-associated drug use and sexual risk behavior (PC1) and high-intensity chemsex and higher-risk sexual practices (PC4), together with positive alignment for history of STIs and HCV (PC5), defining a high-intensity risk phenotype characterized by converging behavioral risk factors and a history of prior STI and HCV infection. Clinical phenotype 2 ($n = 133$, 25.1%) occupied an intermediate but distinct position, with positive alignment for chemsex-associated drug use and sexual risk behavior (PC1) and smoked stimulant use (PC6) yet marked negative alignment with high-intensity chemsex and higher-risk sexual practices (PC4) and party drug use (PC3), consistent with engagement in chemsex without escalation to the highest-intensity risk configuration. In contrast, clinical phenotype 1 ($n = 328$, 62.0%) showed consistently negative or near-zero alignment

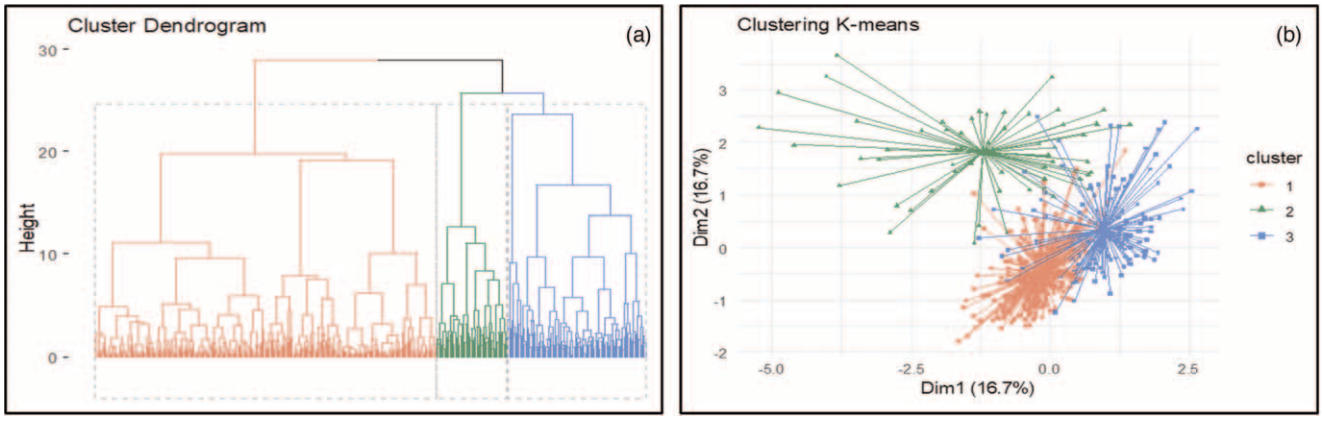

Fig. 2. Clustering of clinical phenotypes among MSM with HIV. (a) shows the hierarchical clustering dendrogram (primary analysis) based on the retained principal components (PC1-PC6). (b) shows the k-means clustering solution (sensitivity analysis) projected onto the two-dimensional principal component space. Three clinical phenotypes were consistently identified across both methods: clinical phenotype 1 (red), clinical phenotype 2 (green), and clinical phenotype 3 (blue). CP, clinical phenotype.

across behavioral components, reflecting a comparatively lower-risk behavioral profile. Psychological vulnerability (PC2) did not differ across phenotypes ($P = 0.698$), suggesting that phenotypic differentiation was more strongly associated with behavioral exposure patterns than with the psychological measures assessed.

Infections across clinical phenotypes

Across the study period, including prevalent diagnoses at baseline and incident diagnoses during follow-up, 24 participants (4.5%) were diagnosed with ARHCV, and 332 bacterial STI episodes were recorded among 212 participants (40.1%), comprising 114 episodes of syphilis, 121 of gonorrhea, and 97 of chlamydia.

Incident infections during follow-up are summarized in Table 3. ARHCV incidence was 0.94 per 100 PY in phenotype 1, 0.72 per 100 PY in phenotype 2, and 11.76 per 100 PY in phenotype 3. The IRR was 12.49 (95% CI 3.00–73.08; $P < 0.001$) for phenotype 3 versus phenotype 1 and 16.25 (95% CI 2.18–720.93; $P = 0.001$) for phenotype 3 versus phenotype 2.

For bacterial STIs overall, incidence was 33.29 per 100 PY in phenotype 1, 60.83 per 100 PY in phenotype 2, and 61.76 per 100 PY in phenotype 3. The IRR was 1.83 (95% CI 1.36–2.46; $P < 0.001$) for phenotype 2 versus phenotype 1, 1.86 (95% CI 1.27–2.68; $P = 0.001$) for phenotype 3 versus phenotype 1, and 1.02 (95% CI 0.68–1.49; $P = 0.927$) for phenotype 3 versus phenotype 2.

Discussion

In this prospective multicenter cohort of MSM with HIV in Madrid (2022–2024), conducted in a context of broad access to DAAs and during a period when DoxyPEP was not implemented, three data-driven phenotypes stratified 12-month incidence of ARHCV and bacterial STIs. ARHCV incidence was concentrated in the phenotype characterized by high-intensity chemsex and practices associated with rectal mucosal trauma, whereas bacterial STI incidence was lowest in the lowest-exposure phenotype and higher in the two phenotypes with greater behavioral exposure.

Table 2. Median principal component scores by clinical phenotypes identified through hierarchical clustering.

Principal component (label)	Clinical phenotype 1 ($n = 328$, 62.0%)	Clinical phenotype 2 ($n = 133$, 25.1%)	Clinical phenotype 3 ($n = 68$, 12.9%)	*P*
PC1 (chemsex-associated drug use and sexual risk behavior)	−0.61 (−0.97 to −0.35)	0.99 (0.42 to 1.48)	1.41 (0.94 to 1.72)	<0.001
PC2 (psychological vulnerability)	−0.20 (−0.78 to 0.63)	0.05 (−0.74 to 0.61)	−0.15 (−0.85 to 0.79)	0.698
PC3 (party drug use)	−0.07 (−0.26 to 0.17)	−0.45 (−0.86 to 0.93)	−0.63 (−1.11 to −0.09)	<0.001
PC4 (high-intensity chemsex and higher-risk sexual practices)	−0.07 (−0.42 to 0.28)	−0.88 (−1.19 to −0.34)	1.66 (0.99 to 2.37)	<0.001
PC5 (history of STIs and HCV)	−0.19 (−1.25 to 0.71)	0.02 (−0.64 to 0.77)	0.49 (−0.35 to 1.20)	0.002
PC6 (smoked stimulant use)	−0.29 (−0.69 to 0.14)	0.42 (−0.34 to 1.72)	−0.34 (−1.03 to 0.61)	<0.001

Values are median (IQR). *P* values were derived from Kruskal–Wallis tests comparing PC scores across phenotypes. Higher PC scores indicate greater alignment with the pattern captured by each component, whereas negative values indicate inverse alignment.
HCV, hepatitis C virus; IQR, interquartile range; PC, principal component; STI, sexually transmitted infection.

Table 3. Incidence of acute/recent hepatitis C virus infection infection and bacterial sexually transmitted infections across clinical phenotypes.

	Follow-up (PY)	Incident events	Incidence per 100 PY (95% CI)	IRR (95% CI)[a]	*P*	IRR (95% CI)[b]	*P*
Clinical phenotype 1 (*N*=328)							
Acute HCV	318.4	3	0.94 (0.19–2.75)	Reference	—	—	—
Any STI	318.4	106	33.29 (27.26–40.27)	Reference	—	—	—
Syphilis	318.4	36	11.31 (7.92–15.65)	Reference	—	—	—
Gonorrhea	318.4	34	10.68 (7.40–14.92)	Reference	—	—	—
Chlamydia	318.4	36	11.31 (7.92–15.65)	Reference	—	—	—
Clinical phenotype 2 (*N*=133)							
Acute HCV	138.1	1	0.72 (0.02–4.03)	0.77 (0.02–9.57)	0.884	Reference	—
Any STI	138.1	84	60.83 (48.52–75.31)	1.83 (1.36–2.46)	<0.001	Reference	—
Syphilis	138.1	31	22.45 (15.25–31.86)	1.99 (1.19–3.30)	0.006	Reference	—
Gonorrhea	138.1	33	23.90 (16.45–33.56)	2.24 (1.34–3.72)	0.001	Reference	—
Chlamydia	138.1	20	14.48 (8.85–23.37)	1.28 (0.70–2.27)	0.376	Reference	—
Clinical phenotype 3 (*N*=68)							
Acute HCV	68.0	8	11.76 (5.08–23.18)	12.49 (3.00–73.08)	<0.001	16.25 (2.18–720.93)	0.001
Any STI	68.0	42	61.76 (44.51–83.49)	1.86 (1.27–2.68)	0.001	1.02 (0.68–1.49)	0.927
Syphilis	68.0	7	10.29 (4.14–21.21)	0.91 (0.34–2.07)	0.855	0.46 (0.17–1.06)	0.051
Gonorrhea	68.0	23	33.82 (21.44–50.75)	3.17 (1.78–5.54)	<0.001	1.42 (0.79–2.49)	0.206
Chlamydia	68.0	12	17.65 (9.12–30.83)	1.56 (0.74–3.07)	0.193	1.22 (0.54–2.62)	0.585

[a]IRRs comparing clinical phenotype 2 versus 1 and clinical phenotype 3 versus 1.
[b]IRRs comparing clinical phenotype 3 versus 2.
ARHCV, acute or recent hepatitis C virus infection; CI, confidence interval; IRR, incidence rate ratio; PY, person-years; STI, sexually transmitted infection.

The phenotypes captured behavioral exposures consistently associated with sexual transmission of HCV and acquisition of bacterial STIs among MSM, including CRAI in the context of chemsex [8,18–22]. The highest-risk phenotype was distinguished by injecting or intrarectal drug use together with behaviors linked to rectal mucosal trauma, including fisting, and a higher prevalence of prior STI and HCV infection, consistent with cumulative exposure within highly connected sexual transmission networks. This profile aligns with proposed mechanisms of sexual transmission of HCV involving repeated exposure to infectious semen or blood, rectal mucosal disruption, and transmission within densely interconnected sexual networks [4,8,9,23]. Nevertheless, the wide confidence intervals around the ARHCV IRRs reflect the limited number of ARHCV events observed during follow-up and indicate that these estimates should be interpreted with caution.

The higher bacterial STI incidence observed in the two more exposed phenotypes further supports the concentration of these infections within defined behavioral contexts among MSM [8,10,18,24,25].

Psychological measures did not differentiate phenotypes. This may reflect limited variability among MSM engaged in care or the inability of the instruments to capture psychosocial determinants more directly associated with infection risk, such as sexual compulsivity, minority stress, or syndemic conditions that may increase vulnerability to STIs [11,26]. Longitudinal studies incorporating broader psychosocial assessments are warranted to assess whether mental health influences changes in behavioral patterns over time.

Nearly two-thirds of participants were classified within the lowest-exposure phenotype, with low ARHCV incidence and comparatively lower bacterial STI rates during follow-up. This distribution highlights substantial heterogeneity of behavioral risk among MSM with HIV and suggests that uniform screening and prevention strategies may not reflect the variability in exposure observed in clinical practice. In this context, a phenotype-based approach could support pragmatic risk stratification in routine care without formal principal component analysis. A brief structured assessment focusing on recent CRAI, engagement in chemsex, and markers of high-intensity practices such as methamphetamine use, injection or intrarectal drug use, or fisting may approximate the phenotype structure and help align screening and prevention efforts with level of exposure. De-intensification in lower-exposure groups should not compromise case detection or equitable access to testing.

This study should be interpreted in light of several methodological considerations. Behavioral and drug use data were self-reported and referred to the preceding 2 months, which may have resulted in some underreporting or imprecision, although the short reporting window likely reduced longer-term recall error. Selection bias cannot be excluded because around one quarter of eligible participants did not complete the questionnaires; however, completers and noncompleters were broadly comparable, making substantial selection bias unlikely. Phenotypes were derived among MSM with HIV from a single region, and inclusion of participants from Madrid CoRE, all of whom had a history of HCV infection, may have increased the representation of higher-risk phenotypes. Accordingly, our findings would benefit from external validation before

extrapolation to other settings. The present analysis did not include MSM using PrEP, another population at substantial risk of ARHCV and bacterial STIs. However, in the original ATHENS study, ARHCV and bacterial STI risk were concentrated among individuals with persistent high-risk sexual behaviors and chemsex practices, irrespective of HIV status, suggesting that similar phenotype structures may also be present among MSM without HIV [4,27]. As with any unsupervised data-driven method, results depend on analytic choices and the variables included.

Notwithstanding these considerations, the study has important strengths. The prospective cohort design included structured follow-up and systematic microbiological screening irrespective of symptoms, including extragenital STIs. The integration of sexual behavior, substance use, mental health, and clinical history enabled identification of multidimensional phenotypes. In addition, the phenotype structure remained stable in sensitivity analyses, supporting the robustness of the clustering.

In summary, behavioral heterogeneity among MSM with HIV can be characterized through data-driven phenotyping with clear clinical relevance. The concentration of ARHCV within a high-intensity exposure profile and the graded distribution of bacterial STIs across phenotypes support moving beyond uniform screening strategies. Incorporating brief, structured behavioral assessment into routine HIV care may enable more precise, risk-informed prevention while maintaining equitable access to testing. Further validation will determine the generalizability and practical impact of this approach across settings.

Acknowledgements

The ATHENS Study Group author contributors: ⋆

Hospital General Universitario Gregorio Marañón: Leire PÉREZ-LATORRE, Teresa ALDÁMIZ-ECHEVARRÍA, Cristina DÍEZ, Francisco TEJERINA, Chiara FANCIULLI, Francisco PARRAS, Camila A FREDES, Pilar CATALÁN, Margarita RAMÍREZ-SCHACKE, Isabel GUTIÉRREZ, Saray CARRETERO, Juan C LÓPEZ, José M BELLÓN, Juan BERENGUER.

Hospital Universitario La Paz: María M ARCOS, José R ARRIBAS, Víctor ARRIBAS, José I BERNARDINO, Carmen BUSCA, Juan M CASTRO, Ana DELGADO-HIERRO, Alejandro DÍEZ-VIDAL, Alejandro de GEA, Rosa de MIGUEL, Rafael MICÁN, Luz MARTÍN-CARBONERO, Rocío MONTEJANO, María L MONTES, Carlos M OÑORO, Luis RAMOS-RUPERTO, María J ROLDÁN, Joanna CANO, Eulalia VALENCIA, Juan GONZÁLEZ-GARCÍA.

Hospital Universitario Infanta Leonor: Jorge VALENCIA, Guillermo CUEVAS, Mariano MATARRANZ, Jesús TROYA, Pablo RYAN.

Centro Sanitario Sandoval: Mar VERA, Oskar AYERDI, Teresa PUERTA, Carmen RODRÍGUEZ, Begoña BAZA, Jorge PÉREZ, María FERRERAS-FORCADA, Mónica GARCÍA-LOTERO, Alberto DELGADO-IRIBARREN, Jorge Del ROMERO.

Hospital Universitario de La Princesa: Lucio GARCÍA-FRAILE, Azucena BAUTISTA, Carmen SÁEZ, Ana M BARRIOS, Ángela GUTIÉRREZ-LIARTE, Marianela CIUDAD, María AGUILERA, Violeta SAMPÉRIZ, Javier PÉREZ-SERRANO, Ignacio De los SANTOS.

Hospital Universitario 12 de Octubre: Adriana PINTO, María De LAGARDE, Laura BERMEJO-PLAZA, Federico PULIDO, Rafael RUBIO.

Hospital Universitario Ramón y Cajal: María J VIVANCOS, Santos Del CAMPO, José L CASADO, Fernando DRONDA, Ana MORENO, María J PÉREZ-ELÍAS, Sergio SERRANO-VILLAR, Javier MARTÍNEZ-SANZ, Matilde SÁNCHEZ-CONDE, José A PÉREZ-MOLINA, Jorge DÍAZ, Santiago MORENO.

Hospital Clínico San Carlos: Eva ORVIZ, Reynaldo HOMEN, María J NÚÑEZ, Noemí CABELLO, Juncal PÉREZ-SOMARRIBA, Ana MUÑOZ, Javier RODRÍGUEZ-AÑOVER, Vicente ESTRADA.

Hospital Universitario Fundación Jiménez Díaz: Beatriz ÁLVAREZ, Laura PRIETO-PÉREZ, Elia ASENSI, Alfonso CABELLO, Miguel GÓRGOLAS.

Hospital Universitario Príncipe de Asturias: José SANZ, Cristina HERNÁNDEZ, María NOVELLA.

Hospital Universitario Infanta Sofía: Pilar RUIZ-SECO, Jorge MAZA, Inés SUÁREZ-GARCÍA, Patricia GONZÁLEZ-RUANO.

Hospital Universitario Severo Ochoa: Rafael TORRES, Miguel CERVERO.

Servicio Madrileño de Salud (SERMAS), Subdirección General de Farmacia y Productos Sanitarios: Beatriz LÓPEZ-CENTENO, Ángela GIL-MARTIN, Daniele ALIOTO, Ainhoa ARANGUREN, María J CALVO-ALCÁNTARA.

Centro Nacional de Epidemiología, Instituto de Salud Carlos III: Marta RAVA, Rebeca IZQUIERDO, Teresa GÓMEZ, Cristina MARCO, Inmaculada JARRÍN.

Centro Nacional de Microbiología, Instituto de Salud Carlos III: Isidoro MARTÍNEZ, Daniel SEPÚLVEDA, Ana VIRSEDA, Rafael AMIGOT, María J MUÑOZ, Salvador RESINO.

Fundación SEIMC/GeSIDA: Beatriz BRAZAL, Marta De MIGUEL, Herminia ESTEBAN.

The authors are indebted to all the patients who participated in this research.

J.B., P.R., and J.G.G. conceived and designed the study. M.D.M. and I.J. curated the databases. J.M.B. cleaned and assembled the analytical dataset and conducted the statistical analyses. L.R.R., L.M.C., L.P.R., I.D.S., A. P., M.J.V., E.O., B.A., J.S., P.R.S., S.R., and R.T. contributed to the investigation. J.B., P.R., and J.G.G. supervised the study, and H.E. coordinated project administration. J.B. drafted the manuscript, and all authors contributed to data interpretation and critically revised the manuscript. J.M.B., M.D.M., H.E., and I.J. accessed and verified the underlying data. J.B., S.R.S., and J.G.G. acquired funding. J.B., P.R., and J.G.G. had final responsibility for the decision to submit for publication; all authors approved the submission.

This work was supported by grants PI20/00474 (JB/PR), PI20/00507 (JGG), and PI20CIII/00004 (S.R.) from Instituto de Salud Carlos III; and by grant GLD21–00121 (J.G.) from GILEAD Fellowship Program Spain. The funders of the study had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication. All authors had access to all the data. The corresponding author had final responsibility for the decision to submit for publication.

During manuscript preparation, the authors used ChatGPT (OpenAI), model GPT-5.2 to improve the readability, grammar, and clarity of the text. The authors reviewed and edited all artificial intelligence assisted text and take full responsibility for the final manuscript.

Data collected for this study, including deidentified participant data and a data dictionary defining each field, can be made available to others upon reasonable request. Additional related documents, such as the study protocol, and REDCap based case report form, will also be provided. These data will be available beginning with the publication of this manuscript. Requests for access can be directed to hesteban@f-sg.org. Data sharing will be subject to approval of a research proposal, a signed data access agreement, and compliance with ethical guidelines to ensure participant confidentiality and data protection.

On behalf of the GeSIDA 12121-RIS EPICLIN 08_2021 ATHENS Study Group: A list of other author contributors is listed in the Acknowledgment section.

Conflicts of interest

P.R. reports payment or honoraria for lectures, presentations, or educational events from Gilead and ViiV Healthcare; support for attending meetings from Gilead; and grants from Gilead. L.R.R. reports honoraria for lectures, presentations, or educational events from Gilead and MSD; and support for attending meetings from Gilead. L.M.C. reports consulting fees and honoraria for lectures from Johnson & Johnson, ViiV Healthcare, and Gilead; and support for attending meetings from Gilead. L.P.L. reports honoraria for lectures, presentations, or educational events from Gilead and MSD; and support for attending meetings from Gilead. I.D.S. reports consulting fees from Johnson & Johnson; honoraria for lectures, presentations, or educational events from Gilead; support for attending meetings and/or travel from Gilead. A.P. reports honoraria for lectures, presentations, or educational events from Gilead, MSD, and ViiV Healthcare; and support for attending meetings from Johnson & Johnson, MSD, and Gilead. M.J.V. reports honoraria for lectures, presentations, or educational events from ViiV Healthcare and Gilead; and support for attending meetings from MSD and ViiV Healthcare. B.A. reports honoraria for educational presentations from Gilead, MSD, Johnson & Johnson, and ViiV Healthcare. J.S. reports honoraria for lectures, presentations, or educational events from MSD, Johnson & Johnson, ViiV Healthcare, and Gilead; and support for attending meetings from Johnson & Johnson, MSD, and Gilead. I.J. reports honoraria for advice or public speaking from Gilead and ViiV Healthcare, and grants from MSD. J.G. G. reports honoraria for advice or public speaking and support for attending meetings from Gilead, and institutional research grants from Gilead, MSD, and ViiV Healthcare. J.B., E.O., P.R.S., R.T., M.D.M., H.E., S. R., and J.M.B. have nothing to disclose.

References

1. Jin F, Dore GJ, Matthews G, Luhmann N, Macdonald V, Bajis S, *et al*. **Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis**. *Lancet Gastroenterol Hepatol* 2021; **6**:39–56.
2. van Santen DK, Sacks-Davis R, Stewart A, Boyd A, Young J, van der Valk M, *et al*. **Treatment as prevention effect of direct-acting antivirals on primary hepatitis C virus incidence: findings from a multinational cohort between 2010 and 2019**. *EClinicalMedicine* 2023; **56**:101810.
3. Sacks-Davis R, van Santen DK, Boyd A, Young J, Stewart A, Doyle JS, *et al*. **Changes in incidence of hepatitis C virus reinfection and access to direct-acting antiviral therapies in people with HIV from six countries, 2010-19: an analysis of data from a consortium of prospective cohort studies**. *Lancet HIV* 2024; **11**:e106–e116.
4. Ryan P, Berenguer J, Ramos-Ruperto L, Vera M, Martin-Carbonero L, Perez-Latorre L, *et al*. **Epidemiology and risk factors for HCV infection among MSM with or at risk of HIV in Madrid (2022-2024)**. *Open Forum Infect Dis* 2025; **12**:ofaf678.
5. Traeger MW, Harney BL, Sacks-Davis R, van Santen DK, Cornelisse VJ, Wright EJ, *et al*. **Incidence and prevalence of hepatitis C virus among HIV-negative gay and bisexual men using HIV**

preexposure prophylaxis (PrEP): a systematic review and meta-analysis. *Open Forum Infect Dis* 2023; **10**:ofad401.
6. World Health Organization. Sexually transmitted infections (STIs). 2024; https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis) [Accessed January 20, 2024].
7. **European Treatment Network for Hiv H, Global Infectious Diseases Consensus P. Recently acquired and early chronic hepatitis C in MSM: recommendations from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel**. *AIDS* 2020; **34**:1699–1711.
8. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, *et al*. **Sexually Transmitted Infections Treatment Guidelines, 2021**. *MMWR Recomm Rep* 2021; **70**:1–187.
9. Fierer DS, Carollo JR, Rodriguez-Caprio G, Radix A, Vail R, Chavez R, *et al*. **Hepatitis C virus reinfection among men who have sex with men with HIV in New York City**. *Clin Infect Dis* 2024; **79**:1420–1427.
10. Torres Silva MS, Torres TS, Coutinho C, Ismerio Moreira R, da Costa Leite I, Cunha M, *et al*. **Bacterial sexually transmitted infections among men who have sex with men and transgender women using oral preexposure prophylaxis in Latin America (ImPrEP): a secondary analysis of a prospective, open-label, multicentre study**. *Lancet HIV* 2024; **11**:e670–e679.
11. Rozenberg FD, Preciado E, Silver M, Hirshfield S. **Longitudinal modeling of bacterial sexually transmitted infections among sexual minority men living with HIV**. *AIDS Behav* 2024; **28**:3984–3993.
12. Smith MK, Stein G, Cheng W, Miller WC, Tucker JD. **Identifying high risk subgroups of MSM: a latent class analysis using two samples**. *BMC Infect Dis* 2019; **19**:213.
13. Blondeel K, Dias S, Furegato M, Seuc A, Gama A, Fuertes R, *et al*. **Sexual behaviour patterns and STI risk: results of a cluster analysis among men who have sex with men in Portugal**. *BMJ Open* 2021; **11**:e033290.
14. Lu F, She B, Zhao R, Li G, Hu Y, Liu Y, *et al*. **Identifying high-risk populations for sexually transmitted infections in chinese men who have sex with men: a cluster analysis**. *Open Forum Infect Dis* 2025; **12**:ofae754.
15. Sobrino-Vegas P, Gutierrez F, Berenguer J, Labarga P, Garcia F, Alejos-Ferreras B, *et al*. **[The Cohort of the Spanish HIV Research Network (CoRIS) and its associated biobank; organizational issues, main findings and losses to follow-up]**. *Enferm Infecc Microbiol Clin* 2011; **29**:645–653.
16. Berenguer J, Gil-Martin A, Jarrin I, Moreno A, Dominguez L, Montes M, *et al*. **All-oral direct-acting antiviral therapy against hepatitis C virus (HCV) in human immunodeficiency virus/HCV-coinfected subjects in real-world practice: Madrid coinfection registry findings**. *Hepatology* 2018; **68**:32–47.
17. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, *et al*. **The REDCap consortium: building an international community of software platform partners**. *J Biomed Inform* 2019; **95**:103208.
18. Raccagni AR, Poli A, Galli L, Spagnuolo V, Bruzzesi E, Muccini C, *et al*. **Association of high-risk sexual behaviours with sexually transmitted infections among men who have sex with men living with HIV**. *Sex Transm Infect* 2023; **99**:120–123.
19. Ramiere C, Charre C, Miailhes P, Bailly F, Radenne S, Uhres AC, *et al*. **Patterns of hepatitis C virus transmission in human immunodeficiency virus (HIV)-infected and HIV-negative men who have sex with men**. *Clin Infect Dis* 2019; **69**:2127–2135.
20. Bradshaw D, Vasylyeva TI, Davis C, Pybus OG, Theze J, Thomson EC, *et al*. **Transmission of hepatitis C virus in HIV-positive and PrEP-using MSM in England**. *J Viral Hepat* 2020; **27**:721–730.
21. Newsum AM, Matser A, Schinkel J, van der Valk M, Brinkman K, van Eeden A, *et al*. **Incidence of HCV reinfection among HIV-positive MSM and its association with sexual risk behavior: a longitudinal analysis**. *Clin Infect Dis* 2021; **73**:460–467.
22. Martinello M, Carson JM, Van Der Valk M, Rockstroh JK, Ingiliz P, Hellard M, *et al*. **Reinfection incidence and risk among people treated for recent hepatitis C virus infection**. *AIDS* 2023; **37**:1883–1890.
23. Hoornenborg E, Coyer L, Boyd A, Achterbergh RCA, Schim van der Loeff MF, Bruisten S, *et al*. **High incidence of HCV in HIV-negative men who have sex with men using preexposure prophylaxis**. *J Hepatol* 2020; **72**:855–864.
24. Jongen VW, Van Der Loeff MFS, Van Den Elshout M, Wijstma E, Coyer L, Davidovich U, *et al*. **Bacterial sexually transmitted infections are concentrated in subpopulations of men who have sex with men using HIV preexposure prophylaxis**. *AIDS* 2023; **37**:2059–2068.
25. Zeggagh J, Bauer R, Delaugerre C, Carette D, Fressard L, Charreau I, *et al*. **Incidence and risk factors for recurrent sexually transmitted infections among MSM on HIV preexposure prophylaxis**. *AIDS* 2022; **36**:1129–1134.
26. Mayer KH, Nelson L, Hightow-Weidman L, Mimiaga MJ, Mena L, Reisner S, *et al*. **The persistent and evolving HIV epidemic in American men who have sex with men**. *Lancet* 2021; **397**:1116–1126.
27. Ramos L, Berenguer J, Ryan P, Vera M, Pérez-Latorre L, De los Santos I, *et al*. Epidemiology of bacterial STIs in MSM with or at risk of HIV in the Region of Madrid (2021-2023). Abstract # 1272. *Conference on Retroviruses and Opportunistic Infections*; 2025; San Francisco, CA. https://www.croiconference.org/abstract/756-2025/.