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Comunicaciones orales

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Sesión de Comunicaciones Orales 1
27 de noviembre - 10:15-12:05h

CO-01. VIROLOGIC OUTCOMES OF LAMIVUDINE/DOLUTEGRAVIR IN VIROLOGICALLY SUPPRESSED PERSONS WITH EXPECTED OR CONFIRMED RESISTANCE TO LAMIVUDINE (VOLVER CLINICAL TRIAL-GESIDA 11820)

Rosa de Miguel Buckley[1], Juan Martin-Torres[2], Jose Luis Blanco Arévalo[3], Luz Martín-Carbonero[1], Angela Gutiérrez Liarte[4], Esperanza Cañas-Ruano[5], Laura Bermejo-Plaza[2], Félix Gutiérrez Rodero[6], Alfonso Cabello Úbeda[7], Miguel Cervero Jiménez[8], Leire Pérez Latorre[9], Jesús Troya García[10], Jesús Santos González[11], Ignacio Álvarez Rodríguez[12], Maria Jiménez González[13], Pedro Gil[14], Rafael Delgado[2], Jose Ramón Arribas[1], Federico Pulido[2] and VOLVER-GESIDA 11820 Study Group

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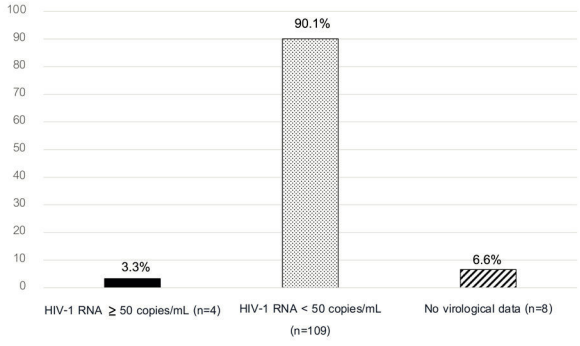
Objectives: We investigated the efficacy of dolutegravir/lamivudine as a maintenance treatment for people with HIV and previous lamivudine resistance, not detected in proviral DNA Sanger genotyping.
Methods: Open-label, single arm, multicentric clinical trial including virologically suppressed participants with historical lamivudine resistance (confirmed by genotypic testing or suspected based on prior virological failure while receiving XTC), no prior integrase resistance and CD4+ > 200 cells/mm^3 whose ART was changed to dolutegravir/lamivudine. Participants were eligible if Sanger proviral DNA sequencing at screening did not detect lamivudine resistance mutations. The primary endpoint was the proportion of participants with HIV-1 RNA viral load [VL] ≥ 50 copies/mL at 48 weeks in the intention-to-treat-exposed (ITT-e) population using the US Food and Drug Administration (FDA) snapshot algorithm. NCT04880785.
Results: 121 participants, 114 with historical lamivudine resistance mutations, mean virological suppression of 9 years (Table). At 48 weeks, 4 participants had a VL ≥ 50 copies/mL (3.3%, 95%CI: 0.91%-8.2% FDA-Snapshot ITT-e): 1 confirmed virologic withdrawal (VL≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test), 1 precautionary virologic withdrawal (3 consecutive VL between 50-200 copies/mL) and 2 excluded for other reasons prior to week 48 with last VL ≥ 50 copies/mL (Figure). Of these 4 participants, plasma population sequencing was successful in 2 at the time of rebound without integrase mutations nor re-emergence of M184V/I or K65R. There were no virologic data for 8 (6.6%) participants: 1 lost to follow-up, 1 protocol deviation, 2 investigator criteria, 3 adverse events, and 1 consent withdrawal. The remaining 109 participants (90.1%, 95%CI: 83-95%) had VL < 50 copies/mL at week 48.

	All (n = 121)
Sex, Male (%)	86 (71.1%)
Age, median (IQR)	56.2 (51.8, 59.8)
CD4+ Baseline (cells/mm3), median (IQR)	675 (516, 819)
ART duration (years), median (IQR)	23.4 (17.5, 27.1)
Number of previous ART regimens, median (IQR)	8 (6, 12)
Suppressed plasma HIV RNA (years), median (IQR)	9.2 (3.7, 14.4)
Confirmed prior 3TC resistance (%)	114 (94.2%)
M184V mutation (%)	107 (88.4%)
M184I/undefined (%)	7 (5.8%)
Suspected prior 3TC resistance (%)	7 (5.8%)
Time since genotype with 3TC resistance (years) median (IQR)	15.2 (14.9, 15.3)
3TC o FTC at baseline (%)	66 (54.5%)
Prior exposure to INSTIs (%)	67 (55.4%)
Prior exposure to DTG (%)	38 (56.7%)

Efficacy at 48 weeks FDA- Snapshot ITT-e



Conclusions: After excluding lamivudine mutations in proviral DNA by population sequencing, dolutegravir/lamivudine effectively maintained virological suppression in persons with HIV and prior history

of lamivudine resistance. Notably, no treatment-emergent resistance was observed.

CO-02. ENSAYO CLÍNICO BIC-NOW: BICTEGRAVIR/EMTRICITAVINA/TENOFOVIR ALAFENAMIDA COMO TRATAMIENTO DE PRIMERA LÍNEA EN PACIENTES VIH NAÏVE EN UN MODELO DE ATENCIÓN DE INICIO RÁPIDO

Carmen Hidalgo Tenorio[1], Sergio Sequera[1], Antonio Collado Romacho[2], David Vinuesa[3], Maria Jesus Vivancos[4], Ignacio de los Santos[5], Patricia Sorni[6], Noemi Cabello[7], Marta Montero[8], Alberto Terrón[9], Onofre Martínez[10], Mohamed Omar Mohamed-Balgahata[11], Pablo Ryan[12], María José Galindo[13], Rosario Javier Martínez[1], Miguel Angel López-Ruz[1] y Coral García-Vallecillos[1]

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Objetivos: Para reducir el número de nuevos diagnósticos de VIH, se han implementado varias estrategias, incluyendo la PrEP o el inicio rápido de la terapia antirretroviral. antirretroviral. Los objetivos de este estudio fueron analizar en pacientes *naïve* la eficacia, seguridad, satisfacción y adherencia de BIC/FTC/TAF en un modelo de inicio rápido.
Métodos: Ensayo clínico de fase IV, multicéntrico, abierto, de un solo brazo realizado entre diciembre de 2020 y junio de 2022. La adherencia al tratamiento se evaluó mediante el cuestionario SMAQ. Número EudraCT: 2019-003251-11.
Resultados: Se incluyeron 208 participantes con una edad media de 35,6 años; el 87,6% eran hombres, con un recuento medio de CD4 de 393,5 células/uL (el 22% tenía < 200 cél/uL de CD4), carga viral (CV) de 5,6 log cop/mL (43,5% CV > 100.000 cop/mL), y 22,2% estaban en estadio SIDA definido por los CDC. El 4,3% tenía coinfección por VHB. BIC/FTC/TAF se inició en el 100% de los sujetos el día en que acudieron por primera vez al especialista en VIH. 8,2% de las PVVIH se perdieron durante el seguimiento; 1,9% y 0,96% de los ARV se cambiaron debido a intolerancia/toxicidad, e interacciones farmacológicas (quimioterapia y tratamiento antituberculoso), respectivamente. La eficacia (CV < 50 cop/mL a los 48 semana) en ITT fue del 87,9%, mITT 96,8% y PP 98,9%. El perfil lipídico no se vio afectado [CT/HDL (basal vs. 48 semana) 3,8 (IQR: 3,3-4,5 vs. 3,7(IQR: 3,2-4,4), p = 0,09]. El peso, el índice de masa corporal y el perímetro abdominal aumentaron basal vs. 48 sem) (74,2 Kg (IQR: 62,3-84) vs. 76,5(IQR: 67,8-88,5) [p = 0,0001]; 24,5(IQR: 22,1-27,7) vs. 25 (IQR: 22,8-28,6) [p = 0,0001]; 84 (IQR: 76,5-93) vs. 87 (IQR: 80-96,5) cm [p = 0,0001], respectivamente). Durante el seguimiento, no hubo cambios cínicamente relevantes en la adherencia [100% (100-100) vs. 100% (90-100), p = 0,0001], ni en la satisfacción [90% (80-95) vs. 90% (80-95), p = 0,41].
Conclusiones: BIC//FTC/TAF es una opción adecuada, eficaz, duradera, segura y satisfactoria para el inicio rápido del TAR en individuos naïve infectados por el VIH. El tratamiento se asoció a un pequeño aumento del peso corporal, índice de masa y circunferencia abdominal. Este estudio fue financiado por Gilead Sciences.
Investigación patrocinada por el investigador ISR-ES-19-10727.

CO-03. UTILIDAD DE LOS ÍNDICES DE ESTEATOSIS Y FIBROSIS EN EL DIAGNÓSTICO DE ESTEATOSIS HEPÁTICA METABÓLICA Y SU RELACIÓN CON EVENTOS CARDIOVASCULARES

Maria Luisa Montes Ramírez, Carmen Busca Arenzana, Antonio Olveira, Marta Abadía, Jose Ignacio Bernardino, Luz Martín-Carbonero, Eulalia Valencia, Rafael Micán, Rosa de Miguel, José Ramón Arribas y Juan González-García

Hospital Universitario La Paz, Madrid.

Objetivos: Múltiples estudios muestran asociación entre la fibrosis hepática causada por la evolución de la esteatosis hepática metabólica (EHmet) y el riesgo cardiovascular. Recientemente un estudio retrospectivo de personas sin VIH demostró un aumento de eventos cardiovasculares mayores (ECVM) en personas con índices TyG > 8,8 y FIB-4 > 1,3. Nuestro objetivo fue describir las PVIH a las que se aplican los índices de esteatosis y fibrosis, los diagnósticos realizados y los ECVM recogidos en esta población
Métodos: Análisis retrospectivo de todas las PVIH a las que se solicitó un análisis de índices de esteatosis y fibrosis desde junio de 2021 a junio de 2023 en una cohorte de 4.000 sujetos en seguimiento regular. Se calcularon los índices de esteatosis HSI y TyG y para fibrosis FIB-4, APRI y NAFLD-FS. Se registraron todos los eventos cardiovasculares mayores ECVM (IAM, Ictus, enfermedad arterial periférica) y la ateromatosis carotídea (AC) recogidos en las historias clínicas.
Resultados: Se solicitó un estudio de índices a un total de 372 sujetos con sospecha de EHmet cuyas características se resumen en la tabla. La prevalencia de esteatosis por índices fue del 67,8-81,7% y de fibrosis de 38-50%. Solo el 11% de los sujetos tuvieron TyG y FIB-4 normales y un 43% tuvieron ambos índices elevados. En este subgrupo con índices elevados un 8,7% (IC95% 5-14) había tenido un ECVM y en un 21% de ellos se realizó un eco-ddopler de troncos supraórticos encontrándose ateromatosis carotídea en el 100%.

		Total 372	TyG y FIB4 altos 161
Edad[a]		56 (49-60)	59 (55-64)
Mujer[b]		73 (19,6)	18 (17,4)
Nadir CD4[c]		203 (87-304)	172 (75-273)
Años VIH[a]		23 (13-31)	28 (21 (33)
HSH[b]		155 (42)	55 (34)
Heterosexual[b]		84 (23)	33 (21)
UDVP[b]		115 (31)	68 (42)
Estadio C3[b]		70 (21,7)	45 (30,8)
VHC/RVS[b]		34/100	44/100
HOMA ≥ 2,5[b]		33 (57,9)	19 (73,1)
DM/GAA[b]		104 (29)	61 (39)
IMCa		28 (25-31)	28 (25-31)
CD4/CD8[a]		0,9 (0,6-1,3)	0,8 (0,6-1,2)
HDL-C[a]		40 (35-51)	39 (33-49,5)
LDL-C[a]		397 (81-117)	194,5 (77,5-112)
Triglicéridos[a]		132 (96-185)	145 (109-203)
HSI> 36[b]		246 (67,8)	111 (71,2)
TyG (esteatosis) ≥ 8,38[b]		304 (81,7)	161 (100)
TyG (insulinorresistencia) ≥ 4,68[b]		216 (58,1)	117 (72,7)
NAFLD-FS ≥ -1,455[b]		138 (38,0)	107 (68,6)
FIB-4 > 1,3[b]		188 (50,5)	161 (100)
TyG-FIB4 normal[b]		41 (11)	-
TyGalto-FIB4 normal[b]		143 (38,4)	-
TyGnormal-FIB4 alto[b]		27 (7,3)	-
TyG-FIB4 altos		161 (43,3)	161 (100,0)
Evento CV[c]		21;5,6 (3,6-8,3)	14;8,7 (5,1-13,8)
	AIT	3;14,3 (4,2-33,4)	2;14,3 (3,1-38,5)
	AIT/EAP	1;4,8 (0,5-20,2)	1;7,1 (0,8-28,8)
	EAP	4;19,0 (6,8-39,2)	2;14,3 (3,1-38,5)
	IAM	9;42,9 (23,7-63,8)	6;42,9 (20,3-68,1)
	Ictus	4;19,0 (6,8-39,2)	3;21,4 (6,4-46,9)

[a]Mediana (p25-p75); [b]N(%); [c]N;%(IC95%)

Conclusiones: En PVIH con elevada prevalencia de EHMet el uso de los índices de esteatosis y fibrosis TyG y FIB-4 permite identificar a una población con riesgo cardiovascular elevado. Es necesario incorporar la evaluación de la EHMet como parte de la estratificación de RCV con el objetivo de maximizar las intervenciones preventivas.

CO-04. INCIDENCE OF NON-AIDS CANCERS IN ADULTS LIVING WITH HIV IN SPAIN

Marta Rava[1], Inés Suárez-García[2], Félix Gutiérrez[3], José A. Pérez-Molina[4], Santiago Moreno[4], Ángela Gutiérrez Liarte[5], Xabier Kortajarena Urkola[6], Marta Montero Alonso[7], Dácil García Rosado[8], David Dalmau Juanola[9], José Ramón Blanco[10], Elena Tapia Moral[11], Victor Asensi[12], Inma Jarrín[1] and Cohorte Coris[13]

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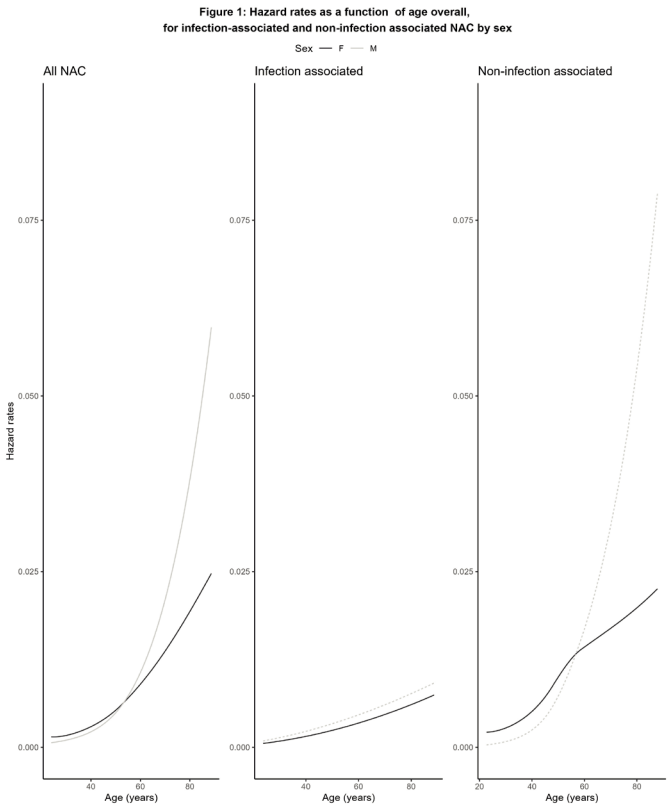
Objectives: To estimate the incidence of non-AIDS cancers (NACs) and to examine the association between age and NACs risk in males and females living with HIV from the CoRIS cohort.
Methods: We included antiretroviral-*naïve* people with HIV (PLWH) aged ≥ 18 years at enrolment, recruited between January 1, 2004, and November 30, 2022. Our endpoint was the first incident primary NAC diagnosis. We grouped the first NAC as infection-associated (Hodgkin lymphoma, liver, anal, stomach, gynaecological, penile and conjunctival cancers) and non-infection-associated. Oral cavity, head and neck, oropharyngeal as well as cancers of unknown primary site could not be classified as infection or non-infection associated and were classified as 'other'. We calculated incidence rates (IR) per 1,000 person-years (py) for all NACs, separately for infection and non-infection associated NACs and by cancer type. We applied flexible parametric survival models to study NACs hazard rates variation with age overall and stratified by sex.
Results: We considered 18,983 CoRIS participants: 85.6% were males, median age at enrollment was 35.2 (1^{st}-3^{rd} quartile: 28.8; 43.1) years and the most frequent transmission route was males having sex with other males (MSM) (62.9%). During 123,088.7 py of follow-up, 478 individuals developed a NAC, with an IR of 3.88 × 1,000 py (95%CI: 3.55, 4.25). NAC IR was 3.82 × 1,000 py (95%CI: 3.46, 4.22) in males and 4.21 × 1,000 py (95%CI: 3.4, 5.21) in females. The majority of all incident NACs (65%) was non-infection associated, with an IR of 2.50 × 1,000 py (95%CI: 2.24, 2.80), while the IR for the infection associated NACs was 1.24 × 1,000 py (95%CI: 1.06, 1.46). The most frequent types of NAC were lung (IR: 0.69 × 1,000 py; 95%CI: 0.56, 0.86), Hodgkin's lymphoma (0.62 × 1,000 py; 95%CI: 0.49, 0.77) and prostate cancer (0.25 × 1,000 py; 95%CI: 0.18, 0.36). Infection-associated NAC rates increased slowly with age and were similar in males and females (Figure). Non-infection-associated NAC hazard rates were slightly lower in males than in females at younger ages but around the age of 60 years the hazards in males increased steeply and exceeded those of females.



Conclusions: Non-infection associated cancers represent the majority of the incident NACs in PLWH, with higher incidence in males than in females mainly around 60 years of age. Risk of developing an infection-associated NAC was similar in males and females.

CO-05. CRIBADO DE CÁNCER COLORRECTAL (CCR) Y ANAL EN PERSONAS CON VIH (PCVIH). RESULTADOS DE LA EVALUACIÓN BASAL DEL ENSAYO MULTICÉNTRICO ESPAÑOL IMPAC-NEO

Mar Masiá[1], Leandro López[2], Antonia Castillo Navarro[3], Helena Albendin[3], Ana Carina Silva[4], Joseba Portu[5], Ester Saez de Adana[5], Lucio Jesús García-Fraile Fraile[6], Ignacio de los Santos[6], Antonio Rivero[7], Enrique Bernal[8], Ana González-Cordón[9], Onofre Juan Martínez[10], Francisco J. Vera Méndez[10], Juan Flores[11], Dácil Rosado[12], Marta Montero-Alonso[13], Mariona Tasias[13], Guillem Sirera[14], Melani Novas[14], Miguel Torralba[15], Juan Macías[16], Inmaculada González[17], Vicente Boix[18], Miguel García-Deltoro[19], Neus Gómez-Muñoz[19], María Jesús Vivancos[20], Paula Dios[21], Joaquín Bravo[22], José Ramón Blanco[23], Marta Fernández-González[2], Sergio Padilla[2], Esteban Martínez[9] y Félix Gutiérrez[1]

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Objetivos: La historia natural del CCR y anal puede modificarse mediante el tratamiento temprano de las lesiones precursoras de carcinoma invasivo: pólipos de alto riesgo en el CCR y lesiones intraepiteliales escamosas de alto grado (HSIL) en el anal. Presentamos los resultados del cribado basal de CCR y anal en los participantes en el estudio multicéntrico español para cribado de cáncer en PCVIH (IMPAC-Neo).
Métodos: El IMPAC-Neo es un ensayo aleatorizado en el que se está evaluando la eficacia, seguridad y eficiencia de dos estrategias de cribado para la detección precoz de neoplasias, que incluyen cribado basal de CCR mediante test de determinación de sangre oculta en heces (SOH) en hombres y mujeres entre 40 y 75 años, y cribado anal mediante citología en hombres que tienen sexo con hombres y en mujeres con citología cervical anormal, verrugas genitales o relaciones sexuales anales. Se presentan los resultados de las pruebas realizadas a la entrada en el estudio y las lesiones precancerosas detectadas.
Resultados: Se han reclutado hasta la actualidad 1.275 participantes (edad media, 55 años; 79% hombres; mediana de linfocitos CD4, 714 cls/uL; 98% carga viral < 200 copias/mL; 48% fumadores; 20% coinfección por VHC). Se presentan los datos de 789 participantes (edad media, 54 años; 82% hombres; mediana de linfocitos CD4 754 cls/uL) en el cribado de CCR y de 375 (edad media, 54 años; sexo al nacer, 84,5% hombres; mediana de linfocitos CD4 753 cls/uL) del cribado anal. El test de SOH resultó positivo en 68 participantes (8,6%). En ellos, tras realización de 47 estudios endoscópicos, se detectaron 29 lesiones precancerosas en 11 personas (1,4% del total de los cribados). La citología anal fue positiva en 146 (11,4%) de los participantes en el cribado anal. Se realizaron un total de 87 anoscopias de alta resolución en las que se detectaron 20 HSIL en 15 participantes (4% del total de los cribados) y 40 lesiones intraepiteliales de bajo grado (LSIL) en 34 participantes. Se documentaron 3 eventos adversos relacionados con las pruebas endoscópicas (hemorragia y/dolor), en todos ellos de intensidad leve.
Conclusiones: En los participantes del ensayo IMPAC-Neo el cribado basal de CCR y anal establecido en el protocolo fue viable y seguro. Se detectó un número considerable de lesiones precancerosas que fueron más prevalentes en la mucosa anal.

CO-06. REVEALING THE ROLE OF TISSUE-RESIDENT NK CELLS IN HIV INFECTION USING EXPLANT TISSUE MODELS

David Perea Pérez[1], Nerea Sánchez-Gaona[1], Ana Gallego-Cortés[1], Stefania Landolfi[2], Fèlix Pumarola[2], Núria Ortiz[2], Inés Llano[2], Juan Lorente[2], Vicenç Falcó[2], Meritxell Genescà[1] and María José Buzón[1]

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Introduction: Tissue-resident NK cells participate in immune clearance of tumor and infections within tissues. However, the function of NK cells in different tissues against HIV-infected cells is complex and can vary depending on the tissue microenvironment. Here, we have characterized NK cells present in relevant tissues, particularly their memory-like and residency properties, and assessed their functionality in killing HIV-infected cells in tissue models of HIV infection.
Methods: We obtained tissue resections from tonsils (n = 33) and gut (mainly colon) (n = 29) from routine surgeries. Flow cytometry was used to quantify the expression of residency markers (CD49a, CD69, and CD103), the memory-related marker NKG2C, and Killer-cell immunoglobulin-like receptors (KIRs) (KIR2DL1, S1, L2, L3, S2). Additionally, we assessed the natural cytotoxicity potential by measuring CD107a and IFN-γ expression after co-culturing tissue cells with HLA-negative K562 cells (n = 11 for tonsil and gut). Furthermore, using tonsil (n = 7) and gut (n = 8) explant models, we characterized NK cells following ex vivo HIVBAL infection for 5-7 days.
Results: In both tissue types, the predominant NK cell phenotype was characterized by $CD56^+$ and $CD16^-$ expression; however, the $CD16^+$ subset more frequently displayed the residency markers CD49a and CD103, as well as KIRs and NKG2C. Notably, within these tissues, the gut exhibited a higher frequency of cells expressing triple residency and memory markers. Nevertheless, it was exclusively in tonsillar NK cells that we observed natural cytotoxicity, and this phenomenon was closely linked to the co-expression of CD69 and CD49a on these NK cells. Following a 5-7 days of HIV challenge, expansion of distinct NK cell populations was evident in both tissues. Specifically, tonsils had an expansion of $CD16^+$ $CD69^+$ $CD49a^+$ $CD103^-$ $KIRs^+$ NK cells ($p = 0.032$), yet the presence of $CD69^+$ $CD49a^-$ NK cells expressing KIRs correlated with lower levels of HIV infection. Conversely, in the gut, the $CD16^-$ $CD103^+$ population expanded significantly ($p = 0.001$), and the fraction of this subset expressing $NKG2C^+$ correlated with reduced levels of HIV infection in this tissue.
Conclusions: This study underscores the tissue-specific nature of NK cell responses and the potential importance of distinct NK cell subsets in the context of HIV infection, offering valuable insights for future research and therapeutic strategies.

CO-07. ANALYSIS OF EXTRACELLULAR VESICLES IN PLWH AND THEIR ROLE IN THE IMMUNE ACTIVATION: ASSOCIATION WITH HIV RESERVOIR IN THE BRAIN AND NEUROCOGNITIVE IMPAIRMENT

Sara Bachiller[1], Joana Vitallé[1], Lluís Camprubí-Ferrer[2], Carmen Gasca-Capote[1], Francisco Ostos[1], Isabel Gallego[1], Alberto Pérez-Gómez[1], María Reyes Jiménez-León[1], Cristina Roca-Oporto[1], Nuria Espinosa[1], María Jesús Rodríguez-Hernández[1], Mohammed Rafii-El-Idrissi-Benhnia[1], Tomas Deierborg[2], Luis Fernando López-Cortés[1] and Ezequiel Ruiz-Mateos[1]

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Objectives: Although effective antiretroviral therapies (ART) have improved the quality and living conditions of people living with HIV (PLWH), this population undergoes a chronic persistent low-grade immune activation and inflammation affecting different organs and systems, including the central nervous system (CNS). Several factors may cause this inflammation, including residual HIV replication in tissues, immune dysregulation, or increased inflammatory/viral spread through extracellular vesicles (EVs), among other factors. This work aims to analyze the mechanisms underlying neuroinflammation-induced cognitive dysfunction associated with (i) innate immunity parameters, (ii) a specific EVs cargo profile, and (iii) HIV-reservoir in brain tissue.
Methods: 88 PLWH (> 50 years and > 24 months on ART with undetectable viral load) were stratified into cognitive impairment (CI) or non-CI based on the memory alteration test (M@T) score and associated with both immunological and clinical parameters (e.g. T-cell counts, monocytes). Multiparametric flow cytometry analyses were performed on 22 participants (11 Non-CI and 11 CI) to determine the phenotype and function of monocytes, T-cells and dendritic cells. EVs and neuronal-derived EVs (NDEVs) were isolated from plasma samples and characterized for size (Zetasizer), surface composition (western blot, WB) and inflammation, neurodegeneration/cognitive

impairment-related cargo (ELISA and MesoScale). HIV mRNA and protein levels in EVs was measured by ddPCR and, WB and *in situ* by confocal microscopy in different brain regions of a historical cohort of PLWH on and off ART.
Results: Memory alterations were detected in 20% of the participants. CD4+ T-cell counts and CD4+ nadir were associated with memory impairment. In plasma, IL-12 was related to M@T score. Alterations in monocyte phenotype and function (CX3CR1+, TLR4), CD8+ T-cells (CD38+HLA-DR+) and dendritic cells (CD1c+, CD141+) were associated with memory dysfunction. Characterization of EVs revealed differences in size, CD81 surface concentration and pro-inflammatory cargo related to memory alterations. Interestingly, the presence of HIV was also detected in EVs of 3 participants. In relation to brain alterations, neurofilament (NEFL) levels in NDEVs were associated with memory dysfunction. Although at a lower level than in PLWH off ART, p24 expression, increased neurodegeneration (MAP-2) and astrocyte activation (GFAP) were found in PLWH on ART, following a brain region-dependent distribution.
Conclusions: In PLWH: Immunological alterations were related to memory alterations. The size, surface composition, and proinflammatory cargo of EVs were associated with CI. NEFL levels were increased in NDEVs related to participants with memory alterations. The expression of p24, MAP-2 and GFAP followed a brain region-dependent distribution in PLWH on ART.

CO-08. A PHASE IV CLINICAL TRIAL OF THE NONAVALENT HUMAN PAPILLOMAVIRUS VACCINE IN MEN WHO HAVE SEX WITH MEN WITH HIV

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Introduction: Human papillomavirus (HPV) is a viral infection that can lead to anal cancer, whose incidence is dramatically increased in men who have sex with men (MSM) with HIV. HPV vaccine prevents persistent viral infection and progression to dysplasia, but the immunogenicity of the nonavalent vaccine (9vHPV) is understudied in MSM with HIV, and its use in Spain is only recommended in subjects aged less than 26 years.
Methods: This phase IV clinical trial (EudraCT number 2018-000215-24) enrolled 158 MSM with HIV aged 18-35 years at HIV clinics in Madrid, Spain. Participants received 3 doses of the 9vHPV vaccine. Blood samples were collected at baseline, month 7, and month 24 to measure HPV antibodies. Anal samples were collected at baseline and month 7 for 16S rRNA sequencing of the microbiota. We compared HPV antibody levels between age groups and CD4/CD8 ratio strata. We calculated microbiome alpha and beta diversity and compared taxa abundances between groups. Bioinformatics analyses utilized QIIME2 for quality control, taxonomic classification, and diversity analyses. Statistics included regression modeling for immunogenicity and Wilcoxon testing for microbiome comparisons between groups.
Results: From 158 enrolled participants, 119 completed all study visits and were included in the analysis. The cohort comprised MSM with HIV predominantly white, with a median age of 32 years. Participants had been on antiretroviral therapy for an average of 5.8 years. The mean nadir CD4 count was 425 cells/mm^3 and the median CD4 count at recruitment was 731 cells/mm^3. The median CD4/CD8 ratio was 0.85. The 9-valent HPV vaccine induced robust seroconversion (nearly 100%) and increased antibody titers for all HPV vacunal serotypes. Overall, the vaccine demonstrated strong immunogenicity, without significant differences between age groups or CD4/CD8 ratio strata. Regarding the microbiome, alpha diversity metrics were unchanged after vaccination. Microbiome diversity and composition were largely stable before and after vaccination across groups, with subtle taxonomic shifts for some genera.

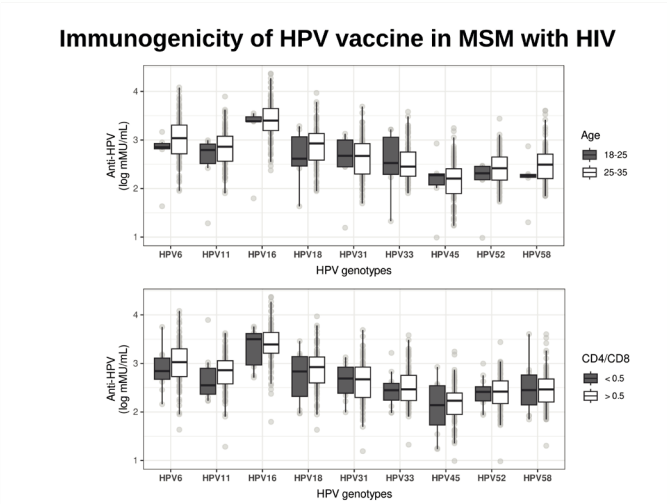

Figure 1. Antibody concentrations in plasma samples by HPV competitive Luminex immunoassay (HPV-9 cLIA) at month 7. In the upper panel, participants were stratified by age. In the lower panel, they were stratified by CD4/CD8 ratio. No statistically significant changes were observed (Wilcoxon test, $p > 0.05$).

Conclusions: We found a robust immunogenicity of 9vHPV in our population including MSM with HIV on ART up to 35 years of age, regardless of other factors that could influence the response. Our study provides evidence to expand guidelines on HPV vaccination in this group.

Sesión de Comunicaciones Orales 2
28 de noviembre - 10:15-12:15h

CO-09. EVALUATION OF URINARY EXOSOME-DERIVED MICRORNAS AS BIOMARKERS OF TENOFOVIR DISOPROXIL FUMARATE-ASSOCIATED (TDF) RENAL TOXICITY IN PEOPLE LIVING WITH HIV-1

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Introduction: The use of antiretroviral drug tenofovir disoproxil fumarate (TDF) may produce tubular proximal renal toxicity, but its relationship with time to toxicity, severity and outcome is controversial and specific biomarkers are still required. The aim of this study was to evaluate the expression profiles of urinary exosome-derived microRNA (miR) as biomarkers of TDF-associated renal toxicity.
Methods: In a longitudinal study, urine samples were collected from 60 virologically suppressed people living with HIV (PWH) receiving TDF. In all cases, different tubular parameters and urinary low-weight molecular proteins (LWMP, beta-2-microglobulin, retinol-binding protein) were compared according to mRNA analyzed. Tubular dysfunction was defined as the presence of at least 2 tubular abnormal-

ities. Urine exosomes were precipitated and a pre-selected panel of miRs were isolated and quantified using miR-specific real-time qPCR.
Results: At inclusion, median time on TDF was 65 months (38-82.6), and mean eGFR was 90.9 ml/min/1.73 m^2 (50.1-122; only 6% of patients with chronic kidney disease CKD diagnosis). A profile of 7 miRs were evaluated. The levels of miR-let-7d, miR-203, and miR-29a were significantly upregulated (p = 0.018, and p = 0.014) according to time on TDF, while miR-127 was negatively correlated (p = 0.033). Moreover, miR-Let-7-d miR-107, and miR-23a positively correlated with tubular and biomarkers parameters, such as fractional excretion of phosphate, glycosuria, albumin/creatinine, β2-microglobuline/creatinine, RBP/creatinine, and protein/creatinine ratios. Thus, miR-let-7d, miR-107, and miR-423 were found to have increased expression in patients with tubular dysfunction and miR-15b was upregulated in urinary exosomes of patients with decreased eGFR (p = 0.028). An increased expression of miR-let-7d predict tubular dysfunction (AUC 0.733), and miR-23a identified those with subsequent eGFR decrease (AUC 0.633), respectively, after a median follow up of 9 months (IQR, 4-13).
Conclusions: This is the first study showing the usefulness of micro-RNA as biomarkers of antiretroviral drug-associated toxicity. Specifically, the expression profile of miRs was significantly altered in urinary exosomes according to time on TDF, changes in tubular parameters and presence of tubular dysfunction, and were associated with further tubular dysfunction and eGFR decrease. Thus, this study confirms that exosome-derived miRs in urine could be used as non-invasive biomarkers for the detection of renal toxicity associated with TDF.

CO-10. INCIDENCIA DE ITS EN USUARIOS DE PREP. DATOS DEL SISTEMA DE INFORMACIÓN DE PROGRAMAS DE PROFILAXIS PRE-EXPOSICIÓN (SIPREP) AL VIH EN ESPAÑA

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Introducción: El cribado de infecciones de transmisión sexual (ITS) forma parte de control clínico de los usuarios de programas de profilaxis preexposición (PrEP) para el VIH. Nuestro objetivo fue describir las tasas de incidencia de gonococia, clamidia y sífilis e identificar sus factores asociados en una cohorte de usuarios de PrEP en España.
Métodos: Se ha analizado datos del sistema de información de programas de profilaxis preexposición (SIPrEP) al VIH entre noviembre-2019 y mayo-2023. Criterio de inclusión: tener al menos una visita de seguimiento e información sobre el diagnóstico de ITS. Se han calculado las tasas de incidencia de gonococia, clamidia y sífilis (primaria, secundaria o latente precoz) por 100 personas-año (pa) de seguimiento y se han utilizado modelos de regresión de Poisson multivariable para calcular las razones de tasas de incidencia (IRR) según características sociodemográficas y antecedentes de prácticas de riesgo para la inclusión en los programas de PrEP. Para gonococia y clamidia se consideraron episodios diferentes cuando había más de un mes entre episodios. Para sífilis, solo se consideró el primer episodio.
Resultados: Se han analizado datos de 1.864 usuarios de PrEP. La mediana de edad fue de 37 años, el 75,2% eran españoles y el 66,7% tenían estudios secundarios o superiores. El 22,6% consumió drogas en los 3 meses previos a la entrada al programa de PrEP y el 11,6% habían tomado PrEP anteriormente. Las tasas de incidencia fueron 26,34/100 pa (IC95% 23,98-28,92) para gonococia (437 episodios), 23,88/100 pa (21,65-26,35) para clamidia (298 episodios) y 11,30/100 pa (9,72-13,13) para sífilis (170 episodios). En la tabla se muestran los factores asociados significativamente en el análisis multivariable:

	Gonococia	Clamidia	Sífilis
	IRR (IC95%)	IRR (IC95%)	IRR (IC95%)
Tener < 50 años versus ≥ 50	1,78 (1,23-2,57)		
Estudios secundarios/ superiores versus sin estudios/primarios		1,83 (1,14-2,94)	
Haber tenido > 10 parejas sexuales en los últimos 12 meses previos a iniciar PrEP	1,72 (1,47-2,76)		
Antecedentes de una o más ITS bacterianas en los últimos 12 meses previos a iniciar PrEP	1,55 (1,06-2,25)	1,37 (1,13-1,65)	2,06 (1,46-2,91)
Uso previo de PrEP			1,29 (1,02-1,64)
Uso de drogas últimos 3 meses previos a iniciar PrEP	1,66 (1,28-2,17)	1,24 (1,06-1,76)	

Conclusiones: Las tasas de incidencia de ITS entre usuarios de PrEP son elevadas. El riesgo de infección varía según los antecedentes de prácticas de riesgo. El cribado que se realiza en los programas de PrEP representa una oportunidad muy importante para el control de las ITS.

CO-11. MANAGING SYPHILIS IN PEOPLE LIVING WITH HIV: THE KEY ROLE OF THE IMMUNE SYSTEM

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Introduction: There are controversial data about syphilis in people living with HV (PLWH) requiring clarification about time to serological response after treatment, serofast definition, and the factors associated.
Methods: Cohort of PLWH in follow up in a tertiary hospital. Univariate analysis was done to determine factors associated with syphilis presentation and serological outcomes. Survival curve analysis and multivariate Cox regression analysis were applied to compare time to serological cure in different situations.
Results: A total of 318 episodes of syphilis were diagnosed in 173 PLWH between 2016-2022. In the first episode, mean age was 46 yrs (18-79), 95% were MSM, and nadir CD4+ count was 304 cells/μL. At the time of syphilis (58% had latent early stage -16% primary, 20% secondary-), median RPR was 1/32 (IQR, 8-64). Fever (2%) or headache (3%) were rare, and only 4 (2%) had ocular/otosyphilis or CNS symptoms. Of note, a fall in CD4+ count and CD4/CD8 ratio during syphilis episode was observed. Moreover, RPR level at diagnosis was inversely correlated with nadir (p = 0.03) and current CD4+ count (p = 0.002). During follow up, the rate of serological nonresponse decreases from 26% to 12% during the first year of follow up. Indeed, the serological rate of nonresponse at 12 months was 11% (71% response, 18% lost or reinfection). The persistence of serofast status after response was observed in 45% of cases at very low titers (median, 1/4). The time to initial serological response was 6.6 months (95%CI, 5.8-8.4), longer in lower RPR levels at diagnosis, CD4+ nadir count and CD4+ count previous to syphilis episode. However, time to response at 12th month was related with age and nadir CD4+ count. There was no difference in RPR, rate of response and time of response between first and consecutive episodes of syphilis. Neurosyphilis was suspected in 38 cases (22%, in 29 cases due to lack of serological response). A total of 22 lumbar punctures (21 in the first episode) were performed with final diagnosis in 11 cases (9 with pleocytosis, 2 with increased protein level, 2 with a positive VDRL). Again, confirmed neurosyphilis was correlated with higher CD8+ and lower CD4/CD8 count.

Conclusions: We present data about the expected time to initial and follow up response after a syphilis episode and the factors associated. Moreover, we demonstrate the importance of the immune status in the presentation and evolution of syphilis in PLWH.

CO-12. COHORTE NACIONAL DE MUJERES EMBARAZADAS CON INFECCIÓN POR VIH Y SUS HIJOS EXPUESTOS (2020-2022)

Arantxa Berzosa[1], Asunción Díaz[2], Marta Illán[1], Inmaculada Jarrín[2], Beatriz Lázaro[3], Ana Piqueras[4], Luis Escosa[5], Matilde Bustillo[6], Ana Isabel Menasalvas[7], Luis Manuel Prieto[8], Lola Falcón[9], Dara Boza[10], Laura Calle[11], Eider Oñate[12], Pilar Galán[13], Beatriz Jiménez[14], Rosa Polo[15], María Luisa Navarro[3] y José Tomas Ramos[1]

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Introducción: La tasa de transmisión vertical (TV) de VIH ha disminuido en nuestro medio hasta alrededor del 1%.
Objetivos: Describir la población actual de mujeres embarazadas que viven con VIH (WLHIV) y sus recién nacidos expuestos y analizar la TV de VIH en nuestro país.
Métodos: Se analizaron los partos de WLHIV entre 2020- 2022, incluidos en la Cohorte Nacional de mujeres embarazadas con infección por VIH y sus hijos expuestos en España (61 hospitales, 16 comunidades autónomas).
Resultados: Se registraron 402 gestaciones de WLHIV: mediana de edad 32,9 años (RIQ: 28,7-37,7), 33,1% españolas, 31,8% africanas, 23,5% latinoamericanas; infectadas un 74% por vía sexual, 20,4% vertical. El 80,4% diagnosticadas antes de la gestación, 12,3% durante la misma (0,3% en el parto). 28 y 19 WLHIV presentaban coinfección con VHB y VHC. El 89% fueron gestaciones controladas. El 98% de WLHIV recibió TAR durante el embarazo, presentando carga viral indetectable en el parto el 89,3%. El 59,3% fueron partos vaginales, el 27,6% cesárea electiva y 13,1% urgente. Se incluyeron 414 recién nacidos expuestos (12 embarazos múltiples), 52% varones. Nacieron un 11,1% de recién nacidos pretérmino (2,9% < 32 SEG) y el 9,7% tenían bajo peso para la edad gestacional. Recibieron profilaxis con zidovudina en monoterapia un 86,5% de los expuestos y con triple terapia un 10,9%. Un 0,7% no recibió profilaxis, sin reportar TV. Un recién nacido recibió lactancia materna, tiempo limitado, sin transmisión de infección perinatal. No hubo TV de VHB ni VHC. Se diagnosticaron 3 casos de TV (0,72%; IC95% 0,67-0,76), con PCR positiva a las 48 horas de vida. Dos gestantes (una española, otra de origen guineano), diagnosticadas en tercer trimestre (semana 35 y 36) que recibieron TAR con TDF/FTC/RAL, llegando al parto con CV detectable (18.849 y 273 cp/ml). La tercera gestante, de origen guineano, diagnosticada en semana 28, con tratamiento con TDF/FTC/EFV, con muy mala adherencia al TAR, llegando también al parto con CV detectable (95.000 cp/ml). En todas se realizó cesárea electiva en semana 38. Los recién nacidos (de peso adecuado) recibieron triple terapia y se confirmó el diagnóstico al 4º, 7º y 14º día de vida.
Conclusiones: Las WLHIV en TAR durante el embarazo, tienen buen control de la infección y los recién nacidos expuestos nacen sanos. Aunque la tasa de TV del VIH es muy baja en nuestro medio (0,72%), el objetivo es la eliminación de la misma, siendo prioritario llegar al parto con CV indetectable.

CO-13. SUCCESSIVE SARS-COV-2 VACCINE DOSES ENHANCE AND PROLONG HUMORAL AND CELLULAR IMMUNITY AGAINST VARIANTS OF CONCERN IN PEOPLE LIVING WITH HIV

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Objectives: We evaluated humoral and T-cell immune responses against SARS-CoV-2 variants of concern (VOC) after different COVID-19 vaccination schedules and intercurrent infections in people living with HIV (PWH)
Methods: Prospective cohort study. Peripheral blood mononuclear cells (PBMCs) were collected after successive doses of mRNA vaccines. T cell responses against the spike (S) glycoprotein of wild type SARS-CoV-2 (ancestral Wuhan variant) and mutated S-protein regions found in the Delta and Omicron variants were assessed by flow cytometry analysis. Changes in total and specific memory B cell responses were assessed.
Results: Overall, 163 PWH received successive vaccine doses (63, 38% received only 2 vaccine doses, 81, 50% received 3 doses -in 21 cases with a previous COVID-19 infection-, and 14 received 4 doses). Mean age was 52 yrs (25-59), and nadir CD4+ count was 275 cells/µL (99-475). Bivariate correlations showed a significant association between T-cell responses to the different variants after 2nd, 3rd, and 4th vaccine doses. There were significant improvements in T-cell response against ancestral strain and the different variants after 3rd dose of vaccine ($p < 0.001$). Also, a significant improvement was observed in total MBC and specific IgG-IgA MBC response. Notably, the rate of lack of T-cell response against ancestral, Delta and Omicron strains ranged from 12%, 17%, and 33% for CD4+ T-cell count, and 19%, 22%, 29% for CD8+ after 2 doses of vaccine, that decrease to 4%, 7% and 15% for CD4+ and 4%, 7%, and 11% for CD8+ after 3 doses of vaccine. Of note, the rate of response was similar regardless of intercurrent COVID-19 infection, but with a higher IgG MBC response ($p = 0.059$). An additional 4th dose of vaccine further increases T-cell and MBC response but the number of PWH was low. On the other hand, those PWH with only two doses of vaccine who refused continuation of vaccination had a 45% of lack of response to Omicron strain at the 3rd determination. We did not observe a relation of the magnitude of response according to age, time of HIV infection, CD4+ count nadir, or CD4+ and CD4/CD8 ratio previous to vaccination schedule.
Conclusions: Although a worse response against Delta and Omicron variants is observed in PWH, a successive vaccination schedule produces an important humoral and cellular immune response against VOC, even better to that observed after concurrent COVID-19 infection.

CO-14. EARLY HIV MEDICAL CARE INTERRUPTION AND MORTALITY AND MORBIDITY AMONG HIV-POSITIVE INDIVIDUALS IN SPAIN, 2004-2022

Rebeca Izquierdo[1], Marta Rava[1], Jorge del Romero[2], Santiago Moreno[1], Chiara Fanciulli[3], Carmen Busca[4], Adrià Curran[5], Juan Macias Sánchez[6], Diana Corona-Mata[7], Miguel Cervero[8], Gemma Navarro[9], Rafael Rubio[10], José Antonio Iribarren[11], Inmaculada Jarrín[1] and Cohorte Coris[12]

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AIDS, non-AIDS events and death according to early MCI

Event type	No early MCI		Early MCI		IRR (95%CI)	
	Number	IR × 1,000 py (95%CI)	Number	IR × 1,000 py (95%CI)	Crude (95%CI)	Adjusted (95%CI)
AIDS event	425	4.56 (4.14, 5.01)	122	19.91 (16.67, 23.77)	4.37 (2.97, 6.42)	3.58 (2.47, 5.18)
Non-AIDS event	714	7.74 (7.19, 8.32)	56	8.52 (6.55, 11.07)	1.10 (0.87, 1.39)	0.93 (0.67, 1.30)
Death	513	5.38 (4.93, 5.87)	98	14.50 (11.89, 7.67)	2.69 (2.08, 3.50)	1.53 (1.13, 2.06)

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Objectives: We assessed the association between having an early HIV medical care interruption (MCI) and the development of AIDS, non-AIDS events and death among people living with HIV (PLWH) from the CoRIS cohort.
Methods: We included antiretroviral-naïve individuals aged ≥ 18 years at enrolment, recruited between January 1, 2004, and August 30, 2021, and followed-up until November 30, 2022. Individuals with a time interval > 15 months between two visits, where the first of these visits occurred within the first 15 months of enrolment were classified as having an early MCI. We calculated the incidence rate (IR) of AIDS, non-AIDS events and death according to having an early MCI. Follow-up of individuals started 15 months after enrolment and ended at the date of occurrence of the outcome of interest, date of last visit, date of death, or November 30, 2022, whichever arose first. Multivariable Poisson regression models were used to estimate adjusted incidence rate ratios (IRR) of the association between early MCI and the rate of AIDS, non-AIDS events and death.
Results: Of 15,342 individuals included (85% men and median age 36 [IQR: 30-44] years), 1,067 (7.0%) had an early MCI. Individuals with an early MCI showed a higher rate of developing an AIDS event (3.58; 2.47, 5.18) and death (aIRR: 1.53; 95%CI: 1.13, 2.06) than those who did not (Table). The most frequent AIDS events among individuals with an early MCI were *Pneumocystis jirovecii* pneumonia (20.5%), candidiasis (13.9%), pulmonary tuberculosis (13.1%) and cerebral toxoplasmosis (7.4%); corresponding percentages among individuals without an early MCI were 12.5%, 7.1%, 6.4% and 6.8%, respectively. AIDS-related deaths accounted for 21.4% and 14.0% of deaths among individuals with and without an early MCI, respectively.
Conclusions: Early MCI was associated with an increased risk of developing AIDS events and death, highlighting the need of designing and implementing public health strategies to strengthen retention in care among PLWH.

CO-15. VIGILANCIA EPIDEMIOLÓGICA MOLECULAR POS-PREP PARA IDENTIFICAR CLÚSTERES DE TRANSMISIÓN DEL VIH-1 EN EXPANSIÓN EN ESPAÑA

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Introducción y objetivos: Desde 1999, hemos analizado filogenéticamente 15482 infecciones por VIH-1 en pacientes de 11 CC. AA., identificando clústeres de transmisión (CTs). Tras la implementación de la profilaxis preexposición (PrEP) en España, hemos observado una reducción de los grandes CTs (LBPEA01, IAS 2023), pero otros continúan expandiéndose. El objetivo de este estudio es identificar CTs del VIH-1 en expansión en España tras la implementación de la PrEP.
Métodos: Analizamos filogenéticamente secuencias de proteasa-retrotranscriptasa de pacientes infectados por VIH-1 con FastTree2. Designamos CTs a los clados con ≥ 4 individuos, ≥ 50% de origen español, apoyados por valores SH-like ≥ 0,95. Comparamos los periodos pre-PrEP (pacientes diagnosticados en 2016-2019) y post-PrEP (en 2020-2023) por CC.AA. Estimamos la dinámica de crecimiento poblacional de CTs mediante un método bayesiano, utilizando el modelo *Bayesian skyline plot* (BSP).
Resultados: El 42% de 4.055 infecciones por VIH-1 diagnosticadas en 2016-2023 en 11 CC. AA. agrupaban en CTs. Identificamos 39 CTs con ≥ 10 infecciones, que comprendían el 21% de los diagnósticos de este período. Comparando los periodos pre- y post-PrEP, observamos una disminución generalizada de nuevos diagnósticos en estos CTs, aunque en 16 CTs registramos ≥ 5 diagnósticos post-PrEP en una sola C.A. En otros 3 CTs observamos un fuerte crecimiento post-PrEP: B328, que aumentó de 1 a 17 diagnósticos en Castilla y León (CyL), 15 de ellos en Valladolid, de los que 9 se diagnosticaron en 2022 (45% de las infecciones analizadas diagnosticadas en Valladolid en 2022); B261, que forma un subclúster de 15 diagnósticos post-PrEP, incluyendo 10 de Burgos; y B289, con 20 diagnósticos post-PrEP, de los que 13 forman un subclúster, 8 de ellos diagnosticados en Burgos. B261 y B289 comprenden el 42% de las infecciones analizadas diagnosticadas en Burgos desde 2021. B328 y B261 se asocian a hombres que tienen sexo con hombres (HSH). En B289 registramos un 95% de varones y transmisión HSH (60%) y heterosexual (40%). Los individuos pertenecientes a estos CTs son 70% de origen español y 28% latinoamericano. Los análisis mediante BSP estimaron un crecimiento exponencial en periodo post-PrEP de B289 y B328.
Conclusiones: Identificamos 19 CTs del VIH-1 que siguen expandiéndose en diferentes CC.AA. tras la implementación de la PrEP, de los que 3 experimentaron una gran expansión en CyL, mostrando los análisis filodinámicos un crecimiento post-PrEP en 2 de ellos. La vigilancia epidemiológica molecular y la filodinámica permiten detectan variantes virales en expansión, de utilidad para monitorizar y optimizar la eficacia de la PrEP.

CO-16. TAMING THE VIRAL RESERVOIR OVER THREE DECADES OF ADVANCEMENTS IN HIV TREATMENT

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Introduction: Since the advent of combination antiretroviral therapy (ART), the clinical management of HIV infection has steadily improved, not only because of the availability of more potent and safer drugs, but also because of recommendations for universal treatment at diagnosis, regardless of disease stage and CD4 count, and efforts to increase HIV diagnose at its earliest stage after HIV acquisition. However, little is known about the effects of such improvements on the establishment of the latent HIV reservoir. Here, we characterize a large group of people with HIV (PWH) on ART to determine the influence of multiple factors on the evolution of the HIV reservoir.
Methods: We analyzed the reservoir of 893 PWH treated and virologically suppressed for > 3 years by measuring total HIV-DNA in PB-

MCs by ddPCR. Those with < 50 HIV-DNA copies/10^6 PBMCs were classified as LoViReT. 40 demographic, clinical, virologic, and immunologic variables were collected to explore their association with the LoViReT status using the Random Forest machine learning algorithm, and additional methods such as LOESS and logistic regression, or PCA.

Results: 180 (20%) of the 893 PWH were classified as LoViReTs. Minimum CD4 counts and maximum viremia during clinical follow-up, as well as shorter time from ART initiation to viral suppression and longer time on an integrase strand transfer inhibitor (INSTI)-based regimen predicted LoViReT status (classification error - 30%). The multiple logistic regression model estimation of the effect of these parameters was: minimum CD4 counts OR = 1.52 (per 100 cells/μL), maximum viremia OR = 0.73 ($\log_{10}$ plasma HIV-1-RNA copies/mL), and time to achieve suppression OR = 0.59 (years). We further analyzed how those factors fluctuate based on ART start date. We observed a decrease in total HIV-DNA and a greater percentage of LoViReTs when ART was started after 2007. Indeed, time from treatment to suppression changed from 1.7 years in 1998 to < 4 months in 2020. Since INSTIs were introduced in 2007, we performed a sub-analysis of the effect of INSTI-based regimens on HIV proviral levels, noting that individuals initiating ART with INSTIs had lower reservoir levels ($p = 0.001$) and shorter times to undetectable viremia ($p = 2.2 \times 10^{-16}$).

Conclusions: The constant improvement in ART guidelines and the introduction of new generation drugs are related to the establishment of lower levels of the HIV reservoir in PWH and, therefore, to the increase in the LoViReT phenotype among the individuals examined, which could facilitate the future success of medical strategies aimed at achieving a functional cure.