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Sesión de Comunicaciones Orales 1 - 25 de noviembre - 09:45-11:45h

CO-01. NON-INFERIOR EFFICACY AND LESS WEIGHT GAIN WHEN SWITCHING TO DTG/3TC THAN WHEN SWITCHING TO BIC/FTC/TAF IN VIROLOGICALLY SUPPRESSED PEOPLE WITH HIV: PASODOBLE (GESIDA_11720) RANDOMIZED CLINICAL-TRIAL

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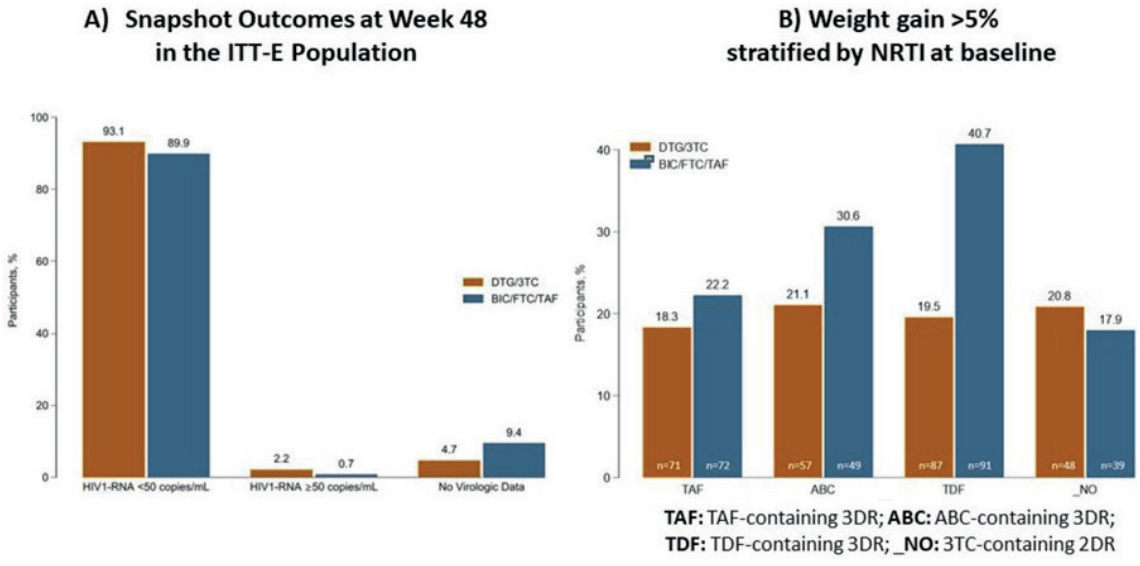
Introduction: DTG/3TC and BIC/FTC/TAF are preferred regimens in major guidelines, but there are no fully powered trials comparing between them.
Methods: PASO-DOBLE (ClinicalTrials.gov NCT04884139) is a randomized, open-label trial conducted at 30 sites throughout Spain. Virologically suppressed PWH on regimens containing ≥ 1 pill/day,



boosters, or drugs with cummulative toxicity such as efavirenz or TDF were eligible. Participants were randomized (1:1) to switch stratifying by TAF in the regimen discontinued and sex. Primary endpoint was the proportion of PWH with RNA ≥ 50 copies/mL at 48 weeks (FDA snapshot, 4% non-inferiority margin) in the exposed intention-to-treat population. Weight changes were also evaluated.

Results: Between 14-July-2021 and 24-March-2023, 553 PWH initiated DTG/3TC (n = 277) or BIC/FTC/TAF (n = 276), including 155 (28%) with TAF in the regimen discontinued and 147 (27%) women. At 48 weeks, DTG/3TC was non-inferior to BIC/FTC/TAF [risk difference between DTG/3TC (2.2%) minus BIC/FTC/TAF (0.7%) 1.4%, 95%CI -0.5 to 3.4] (Fig. A). HIV RNA levels were low (≤ 282 copies/mL) in those showing detectable viral load. Mean adjusted weight increased significantly more with BIC/FTC/TAF (1.81 kg, 95%CI 1.28-2.34) than with DTG/3TC (0.89 kg, 95%CI 0.37-1.41) [difference 0.92 kg, 95%CI 0.17-1.66]. The proportion of participants with weight gain > 5% at 48 weeks was 29.9% for BIC/FTC/TAF vs. 20% for DTG/3TC (adjusted OR 1.81, 95%CI 1.19-2.76). While proportions of PWH experiencing > 5% weight gain with DTG/3TC were similar irrespective of the nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone discontinued, proportions of PWH experiencing > 5% weight gain with BIC/FTC/TAF were 50% or 100% higher than those with DTG/3TC when switching from abacavir or TDF (Figure B). Weight change in women (OR 1.131, 95%CI: 0.700-1.826) didn't differ from that in men. There were few discontinuations (DTG/3TC=1, 0.4%; BIC/FTC/TAF = 2, 0.7%) due to adverse events.

Conclusions: Switching to DTG/3TC demonstrated non-inferior efficacy and resulted in less weight gain than switching to BIC/FTC/TAF at 48 weeks.

CO-02. LONG-TERM EFFICACY AND SAFETY OF DOLUTEGRAVIR/LAMIVUDINE IN VIROLOGICALLY SUPPRESSED PERSONS WITH HIV AND HISTORY OF RESISTANCE TO LAMIVUDINE: WEEK-96 RESULTS OF VOLVER TRIAL-GESIDA 11820

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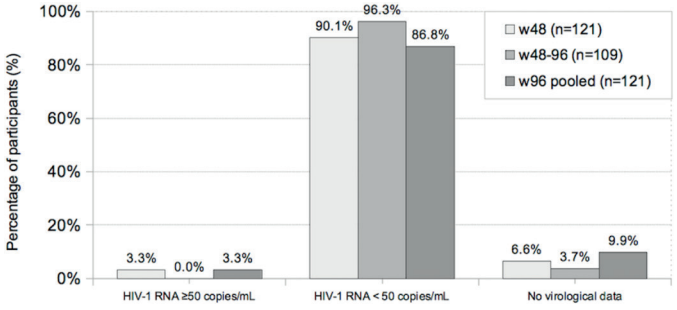
Introduction: VOLVER trial demonstrated at 48 weeks that dolutegravir/lamivudine maintained virological suppression in people with HIV and historical confirmed or suspected lamivudine resistance after excluding lamivudine mutations in proviral-DNA by population sequencing. No treatment-emergent resistance was observed. We present week-96 results.

Methods: Single-arm, multicentric trial. Participants were virologically suppressed at baseline and proviral-DNA Sanger sequencing at screening did not detect lamivudine-resistance mutations. Proviral-DNA next-generation-sequencing (NGS) was retrospectively performed in baseline samples. The efficacy endpoint was the proportion of participants with HIV-1 RNA viral load [VL] ≥ 50 copies/mL at 96-weeks in the intention-to-treat exposed (ITT-e) population using the US Food and Drug Administration (FDA) snapshot algorithm. Safety and tolerability outcomes were treatment-emergent resistance, incidence of adverse events and treatment discontinuations. NCT04880785.

Results: 121 participants, 114 with a prior plasma genotype with M184V/I and 23 (19%) with M184V/I in baseline proviral-DNA NGS (> 5% threshold). At 48 weeks, 4/121 participants had VL ≥ 50 copies/mL, with no evidence of integrase mutations nor re-emergence of M184V/I or K65R; 8 (6.6%) participants discontinued the study for other reasons. Between week 48 and 96, there were no new virological failures among the 109 remaining participants including 21 with M184V/I (> 5%) in baseline proviral-DNA NGS. Overall, the proportion of participants with HIV-1 RNA VL ≥ 50 copies/mL through 96 weeks was 4/121 (3.3%, 95%CI: 0.9-8.2%) (Fig.). No new resistance genotyping tests were performed per-protocol. Between 48w and 96w there were 4 (3.7%) additional discontinuations: 1 treatment-unrelated death (progression of baseline condition COPD), 1 protocol deviation (HBsAg+ although HBV-DNA undetectable), 1 consent withdrawal and 1 loss of follow-up. There were no new discontinuations related to adverse events. At 96 weeks, the proportion of participants with VL < 50 copies/mL was 86.8% (105/121; 95%CI: 79.4-92.2).

	All (n = 121)
HIV-1 RNA < 50 copies/mL	**105 (86.8%)**
HIV-1 RNA ≥ 50 copies/mL	**4 (3.3%)**
HIV-1 RNA ≥ 50 copies/mL in week 96 window	0 (0%)
Discontinuation due to lack of efficacy1	2 (1.7%)
Discontinuation for other reasons and last available HIV-1 RNA ≥ 50 copies/mL[2]	2 (1.7%)
No virologic data at week 96	**12 (9.9%)**
Discontinuation due to an adverse event	3 (2.5%)
Discontinuation for other reasons and last available HIV-1 RNA < 50 copies/mL3	9 (7.4%)



Conclusions: After excluding lamivudine mutations in proviral-DNA by population sequencing, dolutegravir/lamivudine effectively maintained virological suppression after two years of follow-up in participants with history of lamivudine resistance. Notably, no treatment-emergent resistance was observed. Virological efficacy was not affected by detection of M184V/I in proviral-DNA using NGS.

CO-03. CHANGES IN IMMUNOLOGICAL AND INFLAMMATORY PARAMETERS THROUGH 24 MONTHS IN TREATMENT-NAÏVE PEOPLE WITH HIV-1 AFTER STARTING DOLUTEGRAVIR PLUS LAMIVUDINE VS. DOLUTEGRAVIR PLUS TENOFOVIR AF/EMTRICITABINE

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CO-03. Tabla 1

		Basal	Month 6	Month 12	Month 24	p
CD4⁺ CD38⁺HLA-DR⁺	**2DR**	4.1 (2.7-7.8)	2.6 (1.8-4.0)	2.1 (1.3-3.0)	2.3 (1.7-3.0)	0.207
	3DR	3.6 (2.7-8.5)	2.4 (1.4-3.0)	1.9 (1.3-2.9)	1.9 (1.4-2.9)	
CD8⁺ CD38⁺HLA-DR⁺	**2DR**	26.6 (15.9-34.6)	11.1 (4.8-17.8)	8.9 (4.8-10.8)	6.6 (4.0-9.4)	0.719
	3DR	21.6 (15.4-37.0)	7.7 (5.6-14.0)	8.7 (3.4-16.6)	5.1 (3.7-8.9)	
IL-6 (pg/mL)	**2DR**	0.9 (0.4-1.7)	1.2 (0.6-2.6)	1.3 (0.5-2.6)	0.8 (0.3-1.3)	0.513
	3DR	1.0 (0.5-2.6)	1.2 (0.2-3.4)	1.5 (0.3-2.6)	0.6 (0.3-1.2)	
D-Dimer (mL/L)	**2DR**	230 (190-370)	250 (160-325)	175 (100-240)	182 (131-316)	0.486
	3DR	270 (200-410)	205 (150-303)	190 (138-313)	240 (107-398)	
sCD14 (pg/mL)	**2DR**	2.2 (1.5-2.5)	2.0 (1.5-2.4)	1.8 (1.4-2.3)	1.7 (1.1-2.0)	0.580
	3DR	2.1 (1.3-2.9)	1.9 (1.2-2.5)	2.1 (1.6-2.4)	1.5 (1.2-2.1)	
IP-10 (pg/mL)	**2DR**	517.5 (339.7-1075.7)	325.3 (221.5-593.9)	265.5 (201.5-486.7)	153.0 (106.4-227.8)	0.187
	3DR	542.8 (406.7-1216.3)	342.9 (244.0-501.7)	306.0 (201.9-486.1)	161.2 (103.4-220.1)	

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Introduction: In pivotal clinical trials, two-drug regimen (2DR) DTG/3TC has demonstrated similar virological efficacy and immune reconstitution to three-drug regimen (3DR) in treatment-naïve people with HIV-1 (PWH). However, whether there are differences in the inflammatory and immunological parameters compared with DTG+TAF/FTC remains to be elucidated.

Methods: The TRIDUNA (TRIple versus DUal therapy in treatment-NAïve patients) is a randomized, open-label, multicenter, phase IV clinical trial enrolling adult treatment-naïve PWH (Nº EudraCT: 2019-000800-14) in which participants started treatment with 2DR or 3DR. Through 24 months we evaluated CD4⁺ and CD8⁺ activation (CD38⁺/HLA-DR⁺), apoptosis (Annexin V), proliferation (Ki67), senescence (CD57), and exhaustion (PD-1/TIGIT/TIM-3/LAG-3) by FACS; monocyte activation (sCD14/sCD16), β2-microglobulin, inflammatory plasma markers: hsCRP, D-dimer, IL-1β, IL-6, IL-8, TNF-α, IFN-γ, and IP-10 by different immunoassays. Statistical analysis: χ^2, Mann-Whitney U test, and general linear model for repeated measures adjusted for possible confounders. Results were expressed as medians, interquartile ranges, and p-values.

Results: Seventy-four treatment-naïve PWH were enrolled. Sixty-six PWH were evaluable at month 24, of whom 50% were randomly assigned to each treatment arm.

Baseline characteristics without differences. 97% were male in each group. 2DR vs. 3DR: CD4⁺, 394 cells/mL (281-533) vs. 421 (334-545); CD4⁺/CD8⁺, 0.57 (0.31-0.82) vs. 0.47 (0.40-0.63); and viral load 57300 copies/mL (17309-202500) vs. 53900 (15850-148777). The evolution of some of the determined parameters is presented in the Table.

Conclusions: After 24 months of follow-up, irrespective of whether the antiretroviral treatment was started with 2DR or 3DR, the changes in CD4⁺ and CD8⁺ phenotype and in plasma inflammatory markers were similar among participants.

Main funder: ViiV Healthcare without role in the clinical trial.

CO-04. ACUTE/RECENT INFECTIONS AND REINFECTIONS BY HCV IN MSM WITH AND WITHOUT HIV IN THE REGION OF MADRID (ATHENS STUDY)

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Introduction and objectives: High-risk transmission behavior among MSM challenges HCV elimination goals. We examined the epidemiology of acute/recent HCV infections and reinfections in MSM with and without HIV in the Madrid region.

Methods: This prospective study (2021-2023) enrolled MSM with HIV from CoRIS at multiple centers and those with prior HCV treated with DAA from Madrid-CoRE. HIV-negative MSM on PrEP were re-

CO-04. Tabla 1

Active HCV prevalence at baseline and HCV incidence during follow-up

Participants	Nº	Nº with prevalent HCV	HCV prevalence % (95%CI)	Years FU	N. with incident HCV	HCV incidence per 100 py (95%CI)
All MSM	1,372	23	1.68 (1.07-2.20)	1240.4	18	1.45 (0.91-2.30)
HIV+	733	17	2.32 (1.36-3.69)	705.3	13	1.84 (1.07-3.17)
HIV-	639	6	0.94 (0.35-2.03)	535.1	5	0.93 (0.39-2.24)
No prior HCV	1,106	8	0.72 (0.31-1.42)	886.4	7	0.79 (0.38-1.66)
Prior HCV	266	15	5.64 (3.19-9.13)	252.5	11	4.35 (2.41-7.87)

cruited at Centro Sanitario Sandoval. Participants were assessed at baseline and 6 and 12 months, with evaluations including liver enzymes, HCV serology, and HCV-RNA. The primary outcomes were the prevalence of active HCV infection at baseline and the incidence of new infections during follow-up.
Results: 1,372 MSM (733 HIV-positive and 639 HIV-negative) were enrolled. At baseline, both HIV-positive and negative participants reported high rates of condomless anal intercourse (66 vs. 98%) and previous STIs (75 vs. 68%). Chemsex use was 33% in HIV-positives and 27% in HIV-negatives. The Table shows the prevalence of active HCV at baseline and incidence rate of new HCV infections during follow-up. The prevalence ratio for prior HCV vs. no prior HCV was 7.80 (95%CI: 3.34-18.20), and for HIV-positive vs. negative was 2.47 (95%CI: 0.98-6.23). The incidence rate ratio for prior HCV vs. no prior HCV was 5.52 (95%CI: 2.14-14.20), and for HIV-positive vs. negative was 1.97 (95%CI: 0.70 - 5.53). Two reinfections were detected in 39 MSM with confirmed active HCV during the study for a reinfection incidence of 8.7 per 100 py (95%CI: 1.05-31.4).
Conclusions: Low HCV prevalence and incidence were found among MSM without prior HCV. However, figures were significantly higher in MSM with previous HCV, regardless of HIV. Targeted interventions for HCV screening, rapid treatment initiation, and harm reduction strategies are crucial for MSM with prior HCV to achieve HCV elimination goals.

CO-05. ¿CUÁL ES EL TIEMPO DE DEMORA AL INICIAR EL TRATAMIENTO ANTIRRETROVIRAL UNA VEZ CONFIRMADO EL DIAGNÓSTICO DE INFECCIÓN POR VIH?

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Introducción y objetivos: Nuestro objetivo es analizar el tiempo de demora entre el diagnóstico de infección por VIH y el inicio del tratamiento antirretroviral e identificar los factores asociados en su reducción.
Métodos: Diseño: estudio de cohortes retrospectivo multicéntrico (7 hospitales de Madrid y Castilla la Mancha) Se analizaron todos los nuevos diagnósticos de infección por VIH realizados en los últimos 9 años (2015-2023). Se estudió el tiempo de demora (desde el diagnóstico hasta el inicio de TAR).
Resultados: Se estudiaron 610 sujetos diagnosticados entre 2015-2023. El 75,9% fueron hombres con una mediana de edad de 35,8 años (RIC 28,1-43,5). El 19% habían presentado SIDA. Se inició tratamiento con Inhibidores de la integrasa (I.int), con NNRTI o con IP/p en un 86,4, 4,8% o 8,7% respectivamente. La mediana de tiempo entre el diagnóstico y la primera consulta fue de 14 días (IIC 6-31) y entre la consulta y el inicio de tratamiento de 0 días (RIC 0-15). La mediana del tiempo de demora (desde el diagnóstico al inicio del TAR) fue de 25 días (RIC 8,5-53). El 51,9% de los pacientes iniciaron el tratamiento el mismo día de la consulta (inicio rápido) y el 74,5% en los primeros 14 días tras la consulta. La mediana de tiempo hasta lograr una CV indetectable fue de 133 días (IIC 78-210). Los factores asociados en la demora de inicio del TAR fueron: presentar < 200 linfocitos, (diferencia de medias de 14,3 días (IC95% 9,9-18,6 días; p < 0,001), presentar SIDA al diagnóstico (-13,5 días IC95%: -7,6 a -19,2 días; p < 0,001), el uso de I.Int frente a IP o NNRTI (p < 0,001) y por cada año (2015-2023) se redujo un promedio de 4, días (IC95% 3,1-4,8; p < 0,001) el tiempo de demora. El tiempo promedio desde que el paciente fue visto en consulta hasta el inicio del TAR con BIC/FTC/TAF vs. DTG/3TC fue de 2,9 días vs. 5,7 días (p = 0,073).
Conclusiones: Existe un importante margen de mejora en la reducción en el tiempo de demora para iniciar el TAR una vez realizado el diagnóstico de VIH. Las variables asociadas a una disminución en la demora fueron presentar SIDA, una reducción en los linfocitos CD4 e iniciar el TAR en años más recientes.

CO-06. INCIDENCE AND OUTCOMES OF PREGNANCIES AMONG WOMEN WITH HIV INFECTION: A MULTICENTER COHORT IN SPAIN

Belén Alejos[1], Inés Suarez-García[2], Cristina Moreno Prieto[3], Otilia Bisbal[4], María Jesús Pérez Elías[5], Francisco Arnaiz de Las Revillas[6], María José Ríos-Villegas[7], Sara Gutiérrez[8], Marta Montero Alonso[9], María de La Villa López Sánchez[10], Dácil García Rosado[11], Juan Francisco Delgado[12], Cristina Hernández Gutiérrez[13], Inma Jarrín[3] and Cohorte CoRIS[3]

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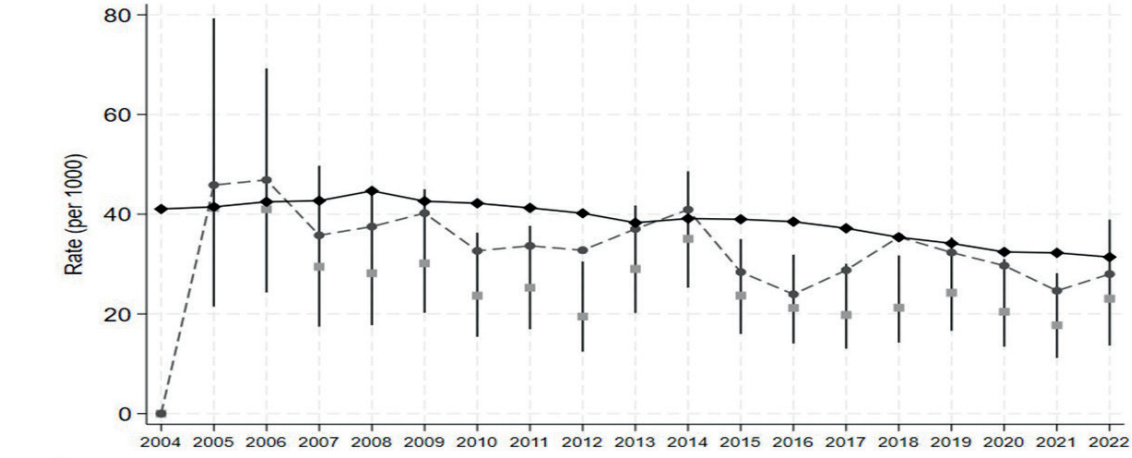
Introduction: We aimed to describe the incidence, temporal trends, and outcomes of pregnancies, as well as antiretroviral treatment (ART) among HIV-positive women who became pregnant during follow-up in the CoRIS cohort.
Methods: We included HIV-positive women aged 18-50 years enrolled in CoRIS between 2004 and 2022. The incidence of pregnancies and fertility rates were calculated as the number of pregnancies (both first and recurrent) and live births, respectively, divided by the total number of woman-years (wy) of follow-up.
Results: Among 2,102 women included, 358 (17%) reported 509 pregnancies (incidence rate: 32.6 per 1,000 wy, 95%CI: 29.9;35.6) and 383 live births (fertility rate: 24.6 per 1,000wy, 95%CI: 22.3;27.2). Pregnancy incidence and fertility rates by year are shown in figure 1. Among 509 pregnancies, 384 (75.4%) resulted in delivery, 63 (12.4%) resulted in miscarriage, 53 (10.4%) were voluntarily terminated and 4 (0.8%) were ectopic pregnancies. Among the deliveries, 51.8% were vaginal and 48.2% caesarean (57.3% elective). There were 17 instrumented deliveries (8.5%) and labor was induced in 131 women (37.5%). There was one neonatal death, and one infant was born HIV-positive. Among 384 pregnancies that resulted in delivery, in 300 (78.1%) women were on ART at Last Menstruation Period, 39 (10.2%) initiated ART during pregnancy, 37 (9.6%) were treatment-experienced but not on ART at conception and 8 (2.1%) did not report ART initiation during pregnancy. Among 39 women who started ART during pregnancy, 31 (79.5%) had been diagnosed with HIV before 2011, with 79.5% (n = 31) receiving a regimen of 2 NRTIs+ 1 IP. Among the 300 pregnancies where women were on ART at conception, the most common regimens included 1 NNRTI+ 2 NRTIs (n = 105, 35%), and 1 PI+ 2 NRTIs (n = 85, 28.3%). 54% (n = 162) of the women were using a regimen containing TDF+FTC (n = 162, 54%) and 35% (n = 105)

CO-06. Figura 1. *Temporal trends in the incidence and fertility rates of pregnancies in 2004-2022.*



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
General Population Fertility Rate	41.04	41.47	42.49	42.71	44.68	42.61	42.19	41.26	40.19	38.29	39.13	38.98	38.5	37.18	35.37	34.15	32.42	32.25	31.4
CoRIS Fertility Rate		41.3 (21.5;79.3)	41.0 (24.3;69.2)	29.5 (17.4; 49.7)	28.1 (17.7;44.7)	30.2 (20.2;45.0)	23.6 (15.4;36.3)	25.2 (16.9;37.7)	19.5 (12.4; 30.5)	29.0 (20.2;41.8)	35.1 (25.3;48.6)	23.7 (16.0;35.0)	21.2 (14.1;31.9)	19.8 (13.0;30.0)	21.3 (14.2;31.7)	24.2 (16.6;35.3)	20.4 (13.4;31.0)	17.7 (11.2;28.2)	23.1 (13.7;38.9)
CoRIS Pregnancy rate		45.8 (24.7;85.2)	46.9 (28.7;76.5)	35.8 (22.2; 57.5)	37.5 (25.1;56.0)	40.2 (28.4;56.9)	32.7 (22.7;47.0)	33.7 (23.8;47.6)	32.8 (23.2; 46.3)	37.0 (26.8;51.1)	40.9 (30.2;55.3)	28.4 (19.9;40.6)	23.9 (16.3;35.2)	28.8 (20.3;40.7)	35.4 (26.0;48.3)	32.3 (23.3;44.8)	29.7 (21.0;42.0)	24.6 (16.7;36.5)	28.0 (17.4;45.0)

were receiving a non-recommended ART regimen at conception. The proportion of women with undetectable viral Load (VL) at week 36 of pregnancy was 90.9%. The proportion of cesareans in women with VL≤ 50 copies/ml and VL≤ 1000 copies/ml at week 36 of pregnancy were 45.5% (136/299) and 47.0% (151/321), respectively.

Conclusions: Seventeen percent of women became pregnant at least once after HIV diagnosis, with favourable outcomes associated with effective ART and high rates of viral suppression. There was a high proportion of elective caesareans, even among women with undetectable viral load.

CO-07. COMBINATION OF ANTIRETROVIRAL TREATMENT WITH BLOCKADE OF TIGIT AND/OR KLRG1 DIFFERENTIALLY ASSOCIATES WITH MEMORY NK AND CD8+ T CELLS PROTECTION IN HIV-1 INFECTED HUMANIZED MICE

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Introduction: Combination of antiretroviral therapy (ART) and checkpoint receptor blockade may be an attractive strategy and to enhance immune responses, reduce persistent reservoirs and promote control of viral replication in people living with HIV-1 (PWH). Expression of inhibitory receptors TIGIT and KLRG1 has been linked to dysfunctional natural killer (NK) and CD8+ T cell, limited capacity to eliminate HIV-infected CD4+ T cells from PWH *in vitro*. However, potential benefits of individual or combined strategies targeting these receptors during HIV-1 infection have not been evaluated *in vivo*.

Methods: Out of n = 25 humanized Bone, Marrow, Liver and Thymus (hBLT) mice, n = 20 reconstituted animals were intravenously infected with 5,000 $TCID_{50}$ HIV-1_{JRCSF} and n = 5 mice were kept uninfected as controls. Oral ART was administered to all HIV+ animals at two weeks post-infection in combination with a weekly intraperitoneal injection of either human IgG1 isotypic control or aTIGIT or aKLRG1 or bispecific mAbs (n = 5 mice per group). Upon ART interruption (ATI), immunotherapy was maintained weekly until 3 days before sacrifice. HIV-1 plasma viral load (pVL) was quantified at 3, 6, 10 and 13 days after ATI. FACS characterization of memory NK cells and CD8+T cell subsets was analyzed longitudinally in blood and in the spleen.

Results: Co-administration of ART with aTIGIT (p = 0.04), aKLRG1 (p = 0.0079) and bispecific (p = 0.0079) Abs significantly reduced HIV-1 pVL more efficiently than combination with Isotype Ab (p = 0.324) after 2 weeks. Further, mice treated with aTIGIT and aKLRG1 mAbs showed decreased viremia compared to mice receiving Isotypic control at 6 days post-ATI (p < 0.0001 for both cases). In contrast, animals receiving the bispecific mAb displayed increased pVL (p = 0.0020). In addition, BLT mice treated with aTIGIT were characterized by a higher proportion of splenic IFNg+TNFa+CD107a- CD8+ T cells (40% Isotype vs. 80% aTIGIT, p < 0.0001) and CD107a+ NKG2C+ CD57- memory NK cell precursors (p = 0.05) that correlated with lower VL (p = 0.012) compared to the control group. On the other hand, aKLRG1 treatment was associated with increased Granzyme B+ CD8+ T cells in spleen (p = 0.0083) whose expression of CD107a negatively correlated with pVL (p = 0.0211) and higher CD107a+ TNFa+ NK cells (p = 0.04). Last, bispecific Ab treatment was associated with lower proportions of memory NK cells (p = 0.0411) and higher percentages of TRAIL+CD57+ CD8+ T cells in tissue (p = 0.05).

Conclusions: Combination of ART with individual TIGIT or KLRG1 blockade leads to differential NK and CD8+ T cell modulation mechanisms associated with viral control potentially relevant for future immunotherapies against HIV-1.

CO-08. DISTINCT CD4 TISSUE-RESIDENT MEMORY CELL (TRM) DEPLETION AND CD8 TRM FUNCTION BETWEEN THE SMALL AND LARGE INTESTINE INDICATE REGION-SPECIFIC MECHANISMS FOR GUT PATHOLOGY IN PWH

Miguel Marín[1], Osaretin Asowata[1], Sarah Nyquist[2], Heeva Baharlou[3], Kevin Hu[3], Precious Mthabela[1], Lindiwe Madziwa[1], Kevyna Chetty[1], Farina Karim[1], V. Manzini[4], S. Kader[5], F. Madela[4], Andrew Harman[3], Al Leslie[1], Alex K. Shalek[2] and Henrik Kløverpris[6]

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HIV infection impairs gut homeostasis and resident T-cells in people with HIV (PWH) and is associated with immunopathology and co-morbidities. However, the differential impact between the small and large intestine remains unknown. We recruited 151 participants from high HIV-endemic areas in South Africa for small and large intestinal mucosal and matched blood sampling and applied an array of assays, including flow—and mass cytometry (CyTOF), population and single-cell RNAseq, and spatial mucosal profiling, to study differential impacts between the small and large intestines from PWH. Tissue-resident memory (TRM) like ($CD69^+CD103^+$) and HIV susceptible ($CCR5^+$) CD4 T-cells were enriched in the duodenum compared to the colon with selective depletion of TRM CD4 T-cells in the lamina propria duodenum but not in the colon. Transcriptional profiles, unique to the remaining duodenal TRM CD4 T-cells, show downregulation of genes involved in pro-inflammatory signalling (IL-2/6/8 and GM-CSF), integrin (TFGbeta) signalling, consistent with loss of integrin ($CD103^+$) T-cells, and upregulation of IL-17 and Th2 pathways in PWH. Limited gene alterations were observed in the colon. In contrast, TRM-like CD8 T-cells were enriched in both the duodenum and colon. TRM-like CD8 T cells in the duodenum express T cell activation (CCL5, CD3D/E/G, CD8B/A) and exhaustion markers (TIGIT, CD160, CD39 and LAG3) compared to blood with strong cytolytic (GZMA/B/K), pro-inflammatory, interferon signalling and immune checkpoint (TIGIT) regulation in PWH compared to uninfected controls. Our study shows distinct and selective depletion and dysfunction of integrin-expressing CD4 TRM cells coinciding with increased cytolytic CD8 TRM activity unique to the small but not large intestine. This suggests differential gut immunopathogenesis during HIV persistence in these compartments with implications for the development of novel treatment strategies to restore gut homeostasis in PWH.

Sesión de Comunicaciones Orales 2 - 26 de noviembre - 09:45-11:45h

CO-09. ANÁLISIS DE 16 AÑOS DE RESISTENCIA A ARV EN NUEVOS DIAGNÓSTICOS (2007-2023): ACTUALIZACIÓN 2023 E IMPACTO DE LA PREP EN DETECCIÓN DE M184V

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Introducción: La evaluación de la resistencia en los nuevos diagnósticos de VIH en España se realiza en CoRIS desde 2007, con actualizaciones anuales hasta 2023. En este estudio, presentamos la tendencia interanual 2007-2023 de la TDR en nuevos diagnósticos de VIH, así como las resistencias primarias a los fármacos de primera línea.
Métodos: Se incluyeron nuevos diagnósticos de los centros CoRIS. Tras el control de calidad de las secuencias, se investigaron las mutaciones en RT/Pro/INI asociadas a TDR utilizando CPR-Stanford. Además, evaluamos las resistencias clínicamente relevantes a los fármacos recomendados como tratamiento de primera línea en las guías de GESIDA en los diferentes periodos analizados. Para el subtipado, se utilizó la herramienta de Stanford y análisis filogenético (Mega).
Resultados: En el periodo 2007-2023, se analizaron 9.027 personas con VIH (PVIH) nuevos diagnósticos. La TDR muestra una tendencia estable en este periodo, con máximos niveles para los NNRTIs. La resistencia primaria a los ARV de primera línea presenta un notable descenso en 2014, cuando los NNRTI dejan de ser recomendados como pautas preferentes de inicio. En 2023, se analizaron 562 PVIH, con datos disponibles en RT, Pro e INI de 532, 549 y 341 PVIH, respectivamente. La prevalencia global de TDR fue del 12,5%, y por clases fue del 4,1% para NRTI (M184V, 1,13%), 8,6% para NNRTI, 1,1% para IP y 0,3% para INI. Es relevante que M184V se detectó en 5/6 personas en PREP y se encontraron RAMS a rilpivirina en el 7,5% de los pacientes. Para los fármacos de primera línea, las resistencias fueron: 0,6% tenofovir, 1,7% abacavir, 1,3% lamivudina/emtricitabina, 9,4% efavirenz, 7,7% rilpivirina, 2,1% doravirina, 1,5% raltegravir, y 0,3% a bictegravir y dolutegravir. La mayoría de las PVIH presentaron subtipos B (77,4%); entre los subtipos no-B, los CRFs fueron los más prevalentes (11,2%), con una representación del 1,9% de A6 y 2,5% de A1.
Conclusiones: Se confirma la mayor prevalencia de resistencias transmitidas para los NNRTI, siendo en 2023 doravirina el fármaco de esta familia con menores niveles de TDR. La resistencia transmitida a los IPs, INIs y 3TC/FTC sigue en niveles muy bajos, con solo una PVIH presentando resistencia completa a los inhibidores de la integrasa de segunda generación. En 2023, la mutación M184V se detectó mayoritariamente en personas que hacían o habían tomado PREP. Nuestros resultados reflejan la situación epidemiológica de las TDR y el nivel de resistencias primarias a ARV de primera línea en España.

CO-10. TENDENCIAS TEMPORALES EN LA APARICIÓN DE COMORBILIDADES ASOCIADAS A LA EDAD EN PERSONAS CON VIH: ESTUDIO LONGITUDINAL DE UNA COHORTE NACIONAL, 2006-2023

Alejandro García García[1], Matilde Sánchez-Conde[1], Jorge Díaz Álvarez[1], Marta Rosas Cancio-Suárez[1], Antoni Abdon Campins Rosselló[2], Joaquim Peraire[3], Juan Macías[4], Adrián Curián[5], Xabier Camino Ortiz de Barrón[6], María Saumoy[7], Marta Herrero Romero[8], María Jesús Pérez-Elías[1], Santiago Moreno Moreno-Guillén[1] y Javier Martínez-Sanz[1] en nombre de CoRIS

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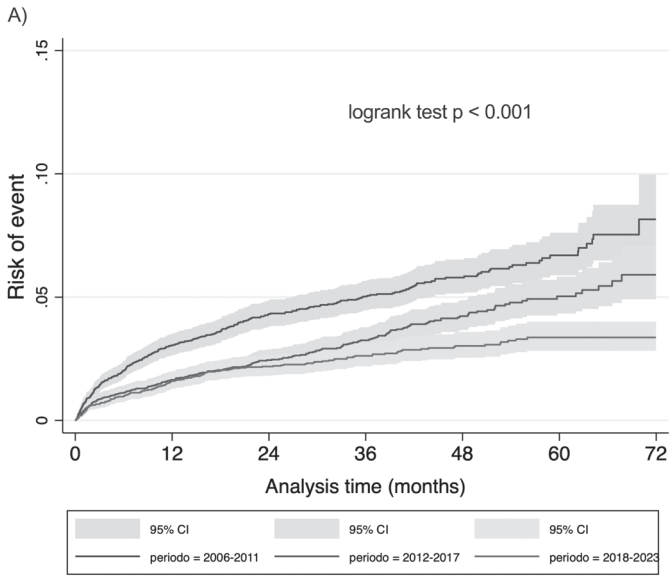
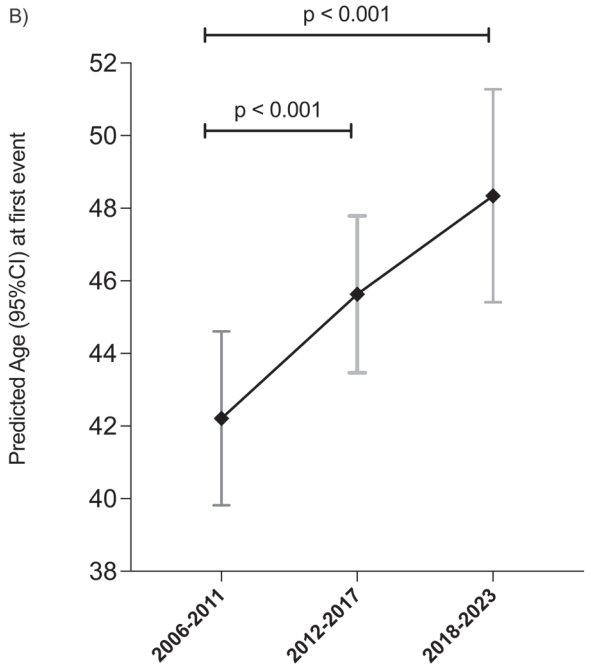
Introducción: Gracias a la gran efectividad del tratamiento antirretroviral (TAR), la infección por el VIH ha pasado a ser una enfermedad crónica, dando lugar a un aumento de la esperanza de vida de las personas que viven con VIH (PVVIH) y por tanto a un envejecimiento de dicha población. Nuestro objetivo fue evaluar la tendencia en la aparición de comorbilidades relacionadas con la edad en la cohorte CoRIS a lo largo del tiempo.
Métodos: Utilizando la cohorte CoRIS, definimos tres periodos de seis años: 2006-2011, 2012-2017 y 2018-2023. El desenlace primario fue el diagnóstico de un evento grave no relacionado con SIDA (ENOS) durante el seguimiento. Definimos ENOS como un evento compuesto que incluyó eventos adversos cardiovasculares mayores (MACE), neoplasias malignas no definitorias de SIDA y muertes no accidentales. Los MACE incluyeron infarto agudo de miocardio no mortal, ictus no mortal y muerte cardiovascular. Utilizamos curvas de Kaplan-Meier para trazar las probabilidades acumuladas de eventos para cada uno de los periodos. Se utilizaron modelos de riesgos proporcionales de Cox para evaluar las *hazard ratios* (HR) de evento en cada periodo, ajustados por edad, sexo, nivel educativo, práctica de riesgo, origen geográfico, nadir de CD4, cociente CD4/CD8 basal y carga viral basal. Utilizamos regresión lineal ajustada para predecir la edad media al momento del primer evento en cada periodo.
Resultados: Un total de 18.659 pacientes *naïve* para TAR entraron en la cohorte entre 2006 y 2023. La incidencia de ENOS en cada periodo fue 1,44 (IC95% 1,29-1,61), 0,95 (IC95% 0,83-1,08), y 0,67 (IC95% 0,57-0,79) eventos por 1000 personas-año, respectivamente, ($p < 0,001$; fig. 1A). El HR de aparición de un ENOS comparado con el periodo 1 fue de 0,81 (IC95% 0,66-0,99) en el periodo 2 y de 0,58 (IC95% 0,45-0,73) en el periodo 3. Por periodo, la edad ajustada predicha para la aparición del primer evento fue de 42,2 (IC95% 39,8-44,6), 45,6 (IC95% 43,5-47,8), y 48,3 (IC95% 45,4-51,3) años, respectivamente.
Conclusiones: Pese al envejecimiento de la población, la incidencia de ENOS en PVVIH ha disminuido de manera significativa a lo largo del tiempo. Existe un retraso notable en la edad de aparición de estos eventos. Esto podría indicar que las mejoras en el TAR y la atención del VIH contribuyen a un envejecimiento más saludable en esta población.





CO-11. PRIORITIZING ANAL CANCER SCREENING IN PWH: NOT ALL ARE AT THE SAME RISK

Boris Revollo[1], Raquel Martín-Iguacel[2], Jordi Aceiton[2], Pere Domingo[3], Georgia Escaramis[2], Joaquín Burgos[4], Patricia Sorni[5], María Saumoy[6], Hernando Knobel[7], Marta Navarro[8], Elena León[9], Amat Orti[10], Josep María Miró[11], Jordi Casabona[2] and Josep María Llibre[1]

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Introduction: People with HIV (PWH) are up to 100 times more likely to develop anal cancer (AC) compared to the general population, where overall incidence is 1.6/100,000 person-years (PY). Screening programs are efficient in preventing AC but are not accessible to all PWH. Identifying individuals at higher risk is crucial to implement effective and targeted screening strategies.
Methods: In this cohort study, we included all treatment naïve PWH ≥ 16 years from 16 hospitals in Catalonia and Balearic Islands, included in the PISCIS HIV cohort (1998-2022). The primary outcome was the incidence rate (IR) of confirmed AC. We used Poisson regression to identify AC risk factors, including age at AC, risk group, nadir CD4+ count, and period of HIV diagnosis.
Results: Among 14,238 people with HIV, 107 (0·8%) developed AC, with an overall IR of 72.5 cases per 100,000 person-years (95%CI 59.4-87.6) and median follow-up of 9.5 years (IQR 4.4-15.7). Of these patients with AC, 37 (34.6%) died, of which 24 (64.9%) deaths were related to AC. Incidence was highest among people with HIV with historical nadir CD4 counts of less than 200 cells per μL (IR 105.0 person-years, 95%CI 82.0-132.5) and lowest among those with counts of more than 350 cells per μL (2·9 person-years, 0·1-16·0). Among men who have sex with men (MSM), the IR was 211.5 person-years (95%CI 151.1-211.7) among those with a CD4 count of less than 200

cells per μL, 37.6 person-years (16.2-74.1) among those with a count of 200-350 cells per μL, and 4.8 person-years (0.1-26.9) among those with a count of more than 350 cells per μL. Among people with HIV younger than 30 years, there were no cases of AC among women or men who do not have sex with men, and one case among MSM with a nadir CD4 count of more than 350 cells per μL (IR 4.8 person-years, 95%CI 0.1-26.9). In the multivariable analysis, people with HIV with nadir CD4 counts of more than 350 cells per μL had the lowest risk of developing anal cancer, compared with people with HIV with counts of less than 200 cells per μL (adjusted IR ratio 0.03, 95%CI 0.00-0.25; p = 0.0010) or 200-350 cells per μL (0.30, 0.17-0.55; p < 0.0001).
Conclusion: A nadir CD4 count threshold below 350, particularly less than 200 cells per μL, has the potential to identify people with HIV at heightened risk of developing anal cancer.

CO-12. PROFILAXIS POST-EXPOSICIÓN CON DOXICICLINA (DOXIPEP) EN HOMBRES QUE TIENEN SEXO CON HOMBRES (HSH) CON ALTO RIESGO DE INFECCIONES DE TRANSMISIÓN SEXUAL (ITS). ESTUDIO PRIDOX

Rosario Palacios Muñoz, Cristina Gómez Ayerbe, María López Jódar, Salvador Martín Cortés, Isabel Ascensión Pérez Hernández, Andrea Prolo Acosta, Marina Villalobos Hernández, Victoria García López y Jesús Santos González

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Introducción: La profilaxis posexposición de ITS con doxiciclina (DoxiPEP) ha demostrado alta eficacia en ensayos clínicos, pero los datos en vida real son limitados.
Objetivos: Analizar el impacto de la DoxiPEP en la incidencia de *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) y sífilis (SFL) en HSH de alto riesgo.
Métodos: A los usuarios de PrEP en seguimiento en nuestra consulta, con criterios de alto riesgo de ITS de los ensayos IPERGAY y DoxiPEP, se les ofreció DoxiPEP; se incluyen en este análisis los que la iniciaron en marzo/23-junio/24. El periodo pre-DoxiPEP comprende desde la fecha de inicio de PrEP hasta la de inicio de DoxiPEP y el periodo pos-DoxiPEP desde el inicio de DoxiPEP hasta el 30/junio/24 o su suspensión. Se realizó PCR de NG y CT en faringe, recto y orina y serología de SFL basalmente, en cada visita y si presentaban síntomas; también se hizo cultivo de NG. Se realizaron cultivos para bacterias multirresistentes en exudados nasal y rectal al inicio de la DoxiPEP y a las 48 semanas. Las incidencias del primer episodio de cada ITS fueron calculadas y se compararon entre ambos periodos mediante modelos de riesgo proporcional de Cox.
Resultados: De los 846 usuarios de PrEP, 189 (22,3%) recibieron DoxiPEP; todos HSH con edad media 39 ± 8,9 años. La mediana de seguimiento fue 464 ± 346 y 257 ± 142 días para los periodos pre- y pos-DoxiPEP. Las tasas de incidencia por 100 PA del primer episodio de cada ITS en los periodos pre- y pos-DoxiPEP fueron 31,8 y 8,53 (p = 0,0001) para CT, 41,7 y 26,6 (p = 0,0228) para NG y 21,6 y 2,52 (p = 0,0001) para SFL. El cultivo de NG fue positivo en 33% de las PCR positivas; 25% eran resistentes a tetraciclinas, similar a los sujetos sin DoxiPEP (42%; p = 0,2). La DoxiPEP se discontinuó en 5 (2,6%) participantes (2 efectos adversos, 2 reducción del riesgo de ITS, 1 indicación facultativa). Los cultivos de bacterias multirresistentes estaban disponibles en 150 (79,8%) sujetos: 16 (10,6%) positivos al inicio de DoxiPEP y 13 (8,6%) a las 48 semanas.
Conclusiones: La DoxiPEP fue muy bien aceptada, reduciendo de forma significativa la incidencia de ITS con buena tolerancia. Nuestros resultados demuestran la eficacia y seguridad de esta estrategia en vida real. No hay evidencia del impacto de la DoxiPEP en la emergencia de gérmenes multirresistentes o de NG resistente; su impacto en las resistencias bacterianas y en la microbiota requiere evaluación adicional.

CO-13. ROBUSTA RESPUESTA INMUNE FRENTE A MPOX EN PERSONAS CON VIH Y USUARIOS DE PREP DESPUÉS DE INFECCIÓN NATURAL, PERO NO EN RESPUESTA A LA VACUNACIÓN

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Introducción y objetivos: En 2022, la OMS consideró el brote de mpox una emergencia de salud pública de importancia internacional (ESPII) y recomendó la vacunación a personas con VIH (PCV) y usuarios de profilaxis preexposición (PrEP). Un brote reciente ha renovado la necesidad de vacunar a estas poblaciones en riesgo, aunque aún se desconoce la eficacia de la vacuna. En este estudio analizamos la respuesta inmune generada en estas poblaciones tras la infección en comparación con la vacunación.
Métodos: Se reclutaron PCV y usuarios de PrEP con diagnóstico de infección por mpox (mpox+) (n = 31), fueron vacunados con Imvanex® (n = 13 una dosis; n = 11 dos dosis) o no estuvieron en contacto con mpox o viruela (*non-exposed*) (n = 38). La activación y producción de citoquinas de linfocitos CD8+ y CD4+ estimulados con pooles de péptidos de mpox MHC-I y MHC-II restringidos, respectivamente, fueron analizados mediante citometría de flujo.
Resultados: 1) Personas mpox+ se infectaron hace una mediana de 279 (IQR 256-299) días; los vacunados recibieron una dosis hace una mediana de 339 días (IQR 288-349) o dos dosis hace 126 (IQR 72-169) días. La mediana de edad fue 38 (IQR 34-46), 34 (IQR 32-40), 38 (IQR 35-42) y 34 (IQR 27-46) años, respectivamente. Todos los participantes eran hombres. Dentro de los grupos, 18 mpox+ (58,1%), 4 vacunados (16,7%) y 11 *non-exposed* (28,9%) eran PCV. 2) Los niveles de CD4 eran 1,5 (p = 0,0128) y 1,3 (p = 0,0486) veces menores en el grupo mpox+, en comparación con vacunados con una dosis y *non-exposed*. 3) Los linfocitos CD4 de personas mpox+ producían niveles 1,8 (p = 0,0439) veces mayores de IL-2 respecto a vacunados con dos dosis. 4) Los linfocitos CD4 *naïve* del grupo mpox+ expresaban mayores niveles de CD25 (1,5 veces; p = 0,0155), comparados con *non-exposed;* y de IFNγ (2,5 veces; p = 0,0265) comparados con vacunados con dos dosis. 5) Las células CD4 de memoria central aumentaron 3,1 (p = 0,0118) y 2 (p = 0,0183) veces más en personas mpox+ en comparación con vacunados con dos dosis y *non-exposed*, respectivamente. 6) Las células CD8 expresaban 1,6 (p = 0,0321) y 2,1 (p = 0,0084) veces más IFNγ y TNFα, respectivamente, que los vacunados con una dosis. 7) No había diferencias entre la respuesta de PCV y usuarios de PrEP dentro de cada grupo.
Conclusiones: La infección por mpox en PCV y usuarios de PrEP produjo una respuesta inmune de tipo celular más robusta que la vacunación con una o dos dosis. Más estudios son necesarios para valorar el nivel de protección ejercido por la vacuna en poblaciones de riesgo ante la eventualidad de nuevos brotes.

CO-14. CHARACTERISTICS, CLINICAL OUTCOMES AND QUALITY OF CARE AMONG TRANSGENDER WOMEN WITH HIV THE CORIS COHORT

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Baseline characteristics and clinical outcomes in TWH and CWH (CoRIS 2004-2021)

	TWH (N 158)	CWH (N 2315)	
Baseline characteristics			p
Age Median (IQR)-yr.	32.4 (26.5-37.9)	35.0 (28.1-43.5)	*< 0.001*
Region of birth-N (%)			
Europe	22 (13.9)	1318 (56.9)	*< 0.001*
Latin America	135 (85.4)	549 (23.7)	*< 0.001*
Africa	1 (0.6)	426 (18.4)	*< 0.001*
HIV acquired by sex-N (%)	154 (97.4)	1977 (85.4)	*< 0.001*
Prior AIDS at diagnosis -N (%)	21 (13.3)	283 (12.2)	*0.700*
Baseline CD4+ T-cell count Median (IQR)	360 (183-490)	338 (155-548)	*0.040*
Incidence rate per 100 py (95%CI)			**IRR (TWH vs. CWH)**
Loss to follow-up	5.7 (4.1-7.8)	2.1 (1.9-2.4)	2.7 (1.9- 3.7)
Virological failure	6.5 (4.4-9.7)	5.6 (5.1-6.1)	1.2 (0.8-1.8)
New AIDS defining conditions	2.0 (1.07-3.69)	1.1 (0.9-1.3)	1.8 (1.0-3.4)
Mortality	0.5 (0.1-1.4)	0.8 (0.7- 1.0)	0.5 (0.2-1.7)

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Introduction: Little is known about the characteristics and clinical outcomes of transgender women with HIV (TWH) in Spain. Our study aims to describe the clinical and epidemiological characteristics, outcomes, and quality of care (QoC) among TWH and compare them with cisgender women with HIV (CWH).
Methods: Longitudinal study based on CoRIS from 2004-2021. We calculated the frequency and incidence rate of events (lost to follow-up [FU], virological failure [VF], new AIDS-defining conditions, and mortality) per 100 person-years (100-py) of FU for TWH and CWH. Poisson regression was used to calculate incidence rate ratios (IRR) in TWH vs. CWH. We assessed QoC indicators: linkage to care within 1 month after HIV diagnosis (LC-1Mo) and viral suppression (VS, < 50 copies/mL) within 3 months after diagnosis (VS-3Mo) in two periods (2004-2013, 2014-2021). Multivariable logistic regression models estimated adjusted odds ratios (aOR) of QoC outcomes. Independent variables were age, gender, region of birth, and AIDS at diagnosis.
Results: A total of 158 TWH and 2315 CWH were enrolled. Baseline characteristics and incidence rates of outcomes are summarized in the Table. LC-1Mo increased from 38.1% (95%CI 30.8-45.4) in 2004 to 69.9% (95%CI 59.3-80.4) in 2021, with lower figures in TWH vs. CWH in 2004-2013 (aOR 1.9; 95%CI 1.1-3.3) but not in 2014-2021. Overall, VS-3Mo increased from 9.5% (95%CI 5.1-14.0) in 2004 to 32.9% (95%CI 22.1-42.7) in 2021 without significant differences between groups in any period.
Conclusions: TWH were younger, more frequently non-European, acquired HIV more often sexually, and had higher baseline CD4 counts. Outcomes were not significantly different between groups except for higher loss to FU in TWH vs. CWH. QoC indicators in the last study period showed no significant group differences.

CO-15. NEXT-GENERATION MRNA-ENCODED ENV-SPECIFIC T CELL ENGAGERS FOR HIV CURE STRATEGIES

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Objectives: Antiretroviral treatment (ART) has been vital in controlling HIV-1. However, the virus persists in the individuals for life in a latent reservoir. Developing a cure for HIV-1 is a global priority. Bispecific antibodies (bsAbs) promise to target and eliminate this reservoir. Here, we present a next-generation, small-sized bsAb codified in mRNA format, designed to engage T-cells by targeting the TCR/CD3 complex and the HIV-1 Envelope (Env) on the surface of infected cells. Here, we evaluate the specificity and activity of an mRNA "light T-cell engager", mRNA Env-LiTE, in terms of binding specificity, activation and killing of HIV-1 latently infected cells.
Methods: We designed Env-LiTE prototypes and produced them via transfection in Expi-293F cells using nucleoside-modified mRNA. We evaluated mRNA Env-LiTE binding capacity and specificity by ELISA with immobilized CD3 and Env and flow cytometry in Jurkat and K562 Env-expressing (K562-Env) cells. We study on-target T-cell activation in Jurkat and PBMCs. Additionally, we tested the ability of mRNA Env-LiTE to activate PBMCs by killing by co-culture of PBMCs with the ACH-2 cell line (HIV+ latently infected) or the A3.01 parental cell line. We used Anti-CD3 (OKT-3) as a positive control. We monitored T-cell activation by CD25 and CD69 expression and the killing of ACH-2 cell lines by flow cytometry.
Results: We demonstrate the specific binding of mRNA Env-LiTE to CD3 and Env by ELISA. In addition, CD3 and Env antigen-specific binding to the cellular membrane was validated in Jurkat and K562-Env cells. Functional assays demonstrate the ability of mRNA Env-LiTE to promote on-target CD3-mediated activation, dependent on Env recognition, with a significant increase in CD69 ($p < 0.001$) in Jurkat. We observe a similar activation pattern in total PBMCs, CD4+ and CD8+ T-cells, marked by a significant increase of CD69 and CD25/CD69 expression ($p < 0.001$). Coculture of PBMCs with ACH-2 cells showed increased CD69 in CD8+ T-cells, alongside the killing of HIV-1 latently infected ACH-2 cells by mRNA Env-LiTE.
Conclusions: We demonstrate that mRNA Env-LiTE specifically binds to CD3 and Env-targeted antigens and activates T cells without off-target effects. These data support the specific activation of CD8+ T-cells and killing of HIV-1 latently infected cells in the ACH-2 coculture model by mRNA Env-LiTE. Overall, these results support the continued preclinical development of our prototype. Additional *in vitro* and *in vivo* data are needed to fully address the potential of mRNA Env-LiTE as a next-generation cure strategy.

CO-16. FUNCTIONAL, METABOLIC AND TRANSCRIPTIONAL PROFILES OF DISTINCT MEMORY NK CELL SUBPOPULATIONS IN PEOPLE WITH HIV

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Introduction: Memory NKG2C+ Natural Killer (NK) are a novel key immune cell subset associated with control of viral infections and may represent a valuable tool for the development of immunotherapies to reduce persistent viral reservoirs in People with HIV (PWH). However, the relationships of different memory NK cell subpopulations with the expression of checkpoint receptors such as TIGIT and

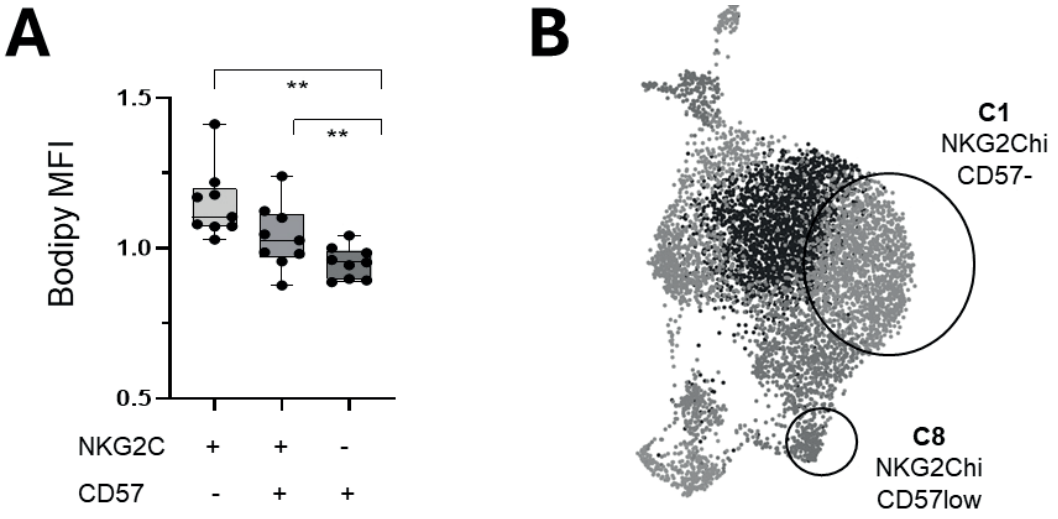

Figure 1 Metabolic and transcriptional characterization of memory NK cells from PWH. A) Mean of fluorescence intensity of Bodipy 500/510 C12 in gated memory NK subsets defined by NKG2C and CD57 expression within CD56dim CD16+ NK from n=8 PWH. B) t-SNE representation of sc-RNAseq analysis of NK subsets from a representaive PWH defining two clusters of NKG2Chi memory cell precursors differing on CD57 expression.

TIM3, their functional and metabolic properties and the transcriptional programs regulating them have not been studied.

Methods: PBMC samples from n = 17 PWH (94% males, 6% females), median age of 45 (min-max = 27-63) on ART (median = 5 years, min-max = 2-31) with undetectable plasma viremia, and with > 500 CD4+T cell counts/μl (median = 920, min-max = 301-1,617), CMV serology (67% IgG+) were recruited at Hospital la Princesa for the study. Functional and metabolic characterization of memory NK was performed by FACS analysis of degranulation and cytokine markers (IFNg, CD107a and GranzymeB) and the incorporation of Mitotracker, MitoSox, Bodipy and 2NBDG after a co-culture with autologous dendritic cells activated with nanoparticles loaded with Poly I:C. Finally, combined multiplex-antibody labelling and single-cell RNA-seq analysis of memory NK cell subsets from PWH enriched in memory NK was performed.

Results: Significantly higher expression of TIM3 but not TIGIT was found in NKG2C+CD57- memory precursors compared to NKG2C+CD57+ mature memory cells (p = 0.0156). Moreover, memory NK precursors expressed significantly higher levels of CD107a (p = 0.0078), IFNγ (p = 0.0078) and increased proportions of polyfunctional IFNγ+CD107a+ (p = 0.0078) and CD107a+ GranzymeB+ (p = 0.0078) cells compared to NKG2C+CD57+ and/or NKG2C-CD57+ NK. In contrast, a higher proportion of Mitosox+Mitotracker+ cells associated to mitochondrial stress were observed in NKG2C+CD57+ mature memory NK compared to memory precursors (p = 0.0078). While no differences were observed in the glucose uptake in these subsets, a higher lipid content was observed in the NKG2C+CD57- and NKG2C+CD57+ memory NK populations compared to the NKG2C-CD57+ cells (p = 0.0039 and 0.0078 respectively) (Fig. 1A). Finally, sc-RNAseq analysis of DC-primed-NK from PWH identified 2 clusters of transcriptional distinct NKG2Chi memory precursor populations: C1 CD57-, characterized by the absence of checkpoint receptors and TRAIL, transcription of higher levels of CD94 as well as IFN stimulated genes, perforin and CCL5 and C8 CD57lo defined by selective expression of TRAIL, NKG2A, SLAMF7 and transcripts associated with OXPHOS, NADPH complex and hypoxia (Fig. 1B).

Conclusions: Together, these data indicate sequential functional and metabolic plasticity in different populations of memory NK cell precursors during maturation, potentially relevant for the modulation of NK and development of new immunotherapies against HIV-1.