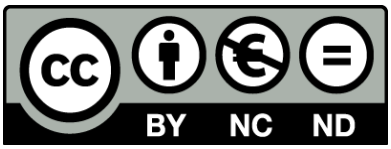
UNIVERSITAT DE BARCELONA

Simplificación del tratamiento antiretroviral con biterapias e impacto de la pandemia de COVID

Elisa De Lazzari



SIMPLIFICACIÓN DEL TRATAMIENTO ANTIRRETROVIRAL CON BITERAPIAS E IMPACTO DE LA PANDEMIA DE COVID

Memoria de tesis doctoral presentada por
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para optar al grado de doctora por la Universidad de Barcelona

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Índex

Abreviaturas y Acrónimos

2DR	biterapia (del inglés: 2 drugs regimen)
3DR	terapia triple (del inglés: 3 drugs regimen)
AEMPS	Agencia Española de medicamentos y productos sanitarios
ARN	Ácido ribonucleico
aRR	Riesgo relativo ajustado (equivalente a risk ratio ajustado)
BIC/TAF/FTC	bictegravir/tenofovir alafenamida/emtricitabina
COVID-19	Enfermedad por coronavirus 2019
CRDe	Cuaderno de recogida de datos electrónico
CV	Carga viral
CVRS	Calidad de vida relacionada con la salud
DMO	Densidad mineral ósea
DXA	Densitometría
EE. UU.	Estados Unidos
FDA	Food and drug administration
FGe	Filtrdo Glomerular estimado
GRT	Genotipado de resistencias
HDL	High-density lipoprotein
HSH	Hombres que tienen sexo con hombres
IC	Intervalo de confianza
IE	Inhibidores de la entrada
IF	Inhibidores de la fusión
IgM	Inmunoglobulina M
INI	Inhibidores de la integrasa
IP	Inhibidores de la proteasa
ITIAN	Inhibidores de la transcriptasa inversa análogos de nucleósidos
ITINN	Inhibidores de la transcriptasa inversa no análogos de nucleósidos
ITT	Intención de tratar (Intent-to-treat)
LDL	Low-density lipoprotein

MERS-CoV	Coronavirus del síndrome respiratorio de Oriente Medio
mITT	Intención de tratar (Intent-to-treat) modificado
NPS	Net-promoter score
OMS	Organización Mundial de la salud
OT	En tratamiento (On-treatment)
PCR	Reacción en cadena de la polimerasa
PREM	Experiencia reportada por el paciente
PrEP	Profilaxis pre-exposición al VIH
PSQI	Pittsburg sleep quality index
PVVIH	Personas que viven con una infección por VIH
RIC	Rango intercuartil
RR	Riesgo relativo (equivalente a risk ratio)
SARS-CoV-2	Coronavirus de tipo 2 causante del síndrome respiratorio agudo severo
SIDA	Síndrome de inmunodeficiencia adquirida
SNC	Sistema nervioso central
SUS	System usability scale
TAR	Tratamiento antirretroviral
TAT	Tejido adiposo total
TAV	Tejido adiposo visceral
TE	Experimentado al tratamiento
TG	Triglicéridos
TN	Naïve al tratamiento
VDRL	Venereal Disease Research Laboratory
VHB	Virus de la hepatitis B
VIH	Virus de la inmunodeficiencia humana

Enumeración de los artículos de la tesis

Tesis en formato de compendio de publicaciones.

La tesis consta de 7 objetivos y 8 artículos.

1. **Elisa de Lazzari**, Ana Gonzalez-Cordon, Alexy Inciarte, Ainoa Ugarte, Lorena de la Mora, Maria Martinez-Rebollar, Montserrat Laguno, Juan Ambrosioni, Berta Torres, Josep Mallolas, Jose L. Blanco, Jose M. Miro and Esteban Martinez. *Factors associated with the use and composition of two-drug regimens in a large single-centre HIV cohort*. J Antimicrob Chemother. 2021; 76: 2988–2992.
   [Factor de impacto: 5.758; Quartil: Q1]

2. Adrián Martínez-Serra*, **Elisa De Lazzari***, Leire Berrocal, Alberto Foncillas, Lorena De La Mora, Alexy Inciarte, Iván Chivite, Ana González-Cordón, Maria Martínez-Rebollar, Berta Torres, Montserrat Laguno, José Luis Blanco, Esteban Martinez, Josep Mallolas†, Juan Ambrosioni†. *Clinical use and effectiveness of Dolutegravir and lamivudine: a long-term, real-world, retrospective study.*
   * Contributed equally as first authors
   † Contributed equally as senior authors
   J Antimicrob Chemother. 2023; 78(8): 1955-1962
   [Factor de impacto: 5.2; Quartil: Q1]

3. **Elisa de Lazzari**, Montserrat Lonca, Jhon Rojas, Ana Gonzalez-Cordon, Jordi Blanch, Alexy Inciarte, Amparo Tricas, Ana Rodriguez, Maria Martinez-Rebollar, Montserrat Laguno, Josep Mallolas, Sonsoles Sanchez-Palomino, Montserrat Plana, Jose L. Blanco and Esteban Martinez. *A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine. AIDS* 2019, 33: 1891–1896.
   [Factor de impacto: 4.511; Quartil: Q1]

4. Jhon Rojas*, **Elisa de Lazzari***, Eugenia Negredo, Pere Domingo, Juan Tiraboschi, Esteve Ribera, Nadia Abdulghani, Jordi Puig, Maria G Mateo, Daniel Podzamczer, Maria M Gutierrez, Roger Paredes, Bonaventura Clotet, Jose M Gatell, Jose L Blanco†, Esteban Martínez†, en nombre del grupo de studio del DOLAM. *Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial.*
   * Contributed equally as first authors
   † Contributed equally as senior authors
   Lancet HIV 2021; 8: e463–73.
   [Factor de impacto: 16.07; Quartil: Q1]

5. **Elisa De Lazzari**, Eugenia B. Negredo, Pere Domingo, Juan M. Tiraboschi, Esteve Ribera, Nadia Abdulghani, Verònica Alba, Salvado Fernández-Arroyo, Consuelo Viladés, Joaquim Peraire, Jose M. Gatell, Jose L. Blanco, Francesc Vidal, Anna Rull*, Esteban Martínez*, en nombre del grupo de studio del DOLAM. *Multiomics plasma effects of switching from triple antiretroviral regimens to dolutegravir plus lamivudine.*

   * Contributed equally as senior authors

   J Antimicrob Chemother. 2024; 79(5):1133-114
   [Factor de impacto: 5.2; Quartil: Q1]

6. **Elisa de Lazzari***, Alejandra Martínez-Mimbrero*, Iván Chivite, Ana González-Cordón, Maria M. Mosquera, Montserrat Laguno, Josep Costa, Jordi Bosch, Jose L. Blanco, Miriam Álvarez-Martínez, Ainoa Ugarte, Alexy Inciarte, Lorena de la Mora, Berta Torres, Maria Martínez-Rebollar, Juan Ambrosioni, Emma Fernández, Juan Carlos Hurtado, Josep Mallolas, José M. Miró, María A. Marcos† and Esteban Martínez†. *Impact of coronavirus disease 2019 epidemics on prevention and care for HIV and other sexually transmitted infections.*

   * Contributed equally as first authors
   † Contributed equally as senior authors

   AIDS 2022;36(6):829-838.
   [Factor de impacto: 3.8; Quartil: Q1]

7. **Elisa de Lazzari**, Leire Berrocal, Emma Fernández, Montserrat Laguno, Iván Chivite, Berta Torres, Ana González-Cordón, Lorena de la Mora, Juan Ambrosioni, Alexy Iniciarte, José Luis Blanco, José María Miró, Esteban Martínez, María Martínez-Rebollar, Josep Mallolas. *Perception of quality of care using patient reported experience measures (PREMs) in a cohort of adults with HIV: A cross-sectional study.* Medicine 2023. 102(14), e33442.
   [Factor de impacto: 1.6; Quartil: Q3]

8. **Elisa de Lazzari**, Montserrat Laguno, Josep Mallolas, Esteban Martínez. *Usability and user's satisfaction of an eCRF implemented in the REDCap system in the HIV clinical research context: the use case of DOLAM clinical trial.*

   En fase de redacción para enviar a una revista científica.

Introducción

Hipatia de Alejandría *(Filósofa y matemática, entre 355 y 370 - 415). Se puede considerar la primera mujer científica. Se dedicó a la investigación en astronomía y en matemáticas, además de enseñar matemáticas, astronomía, filosofía y mecánica a personas sin exclusión por género, religión, raza y procedencia.*

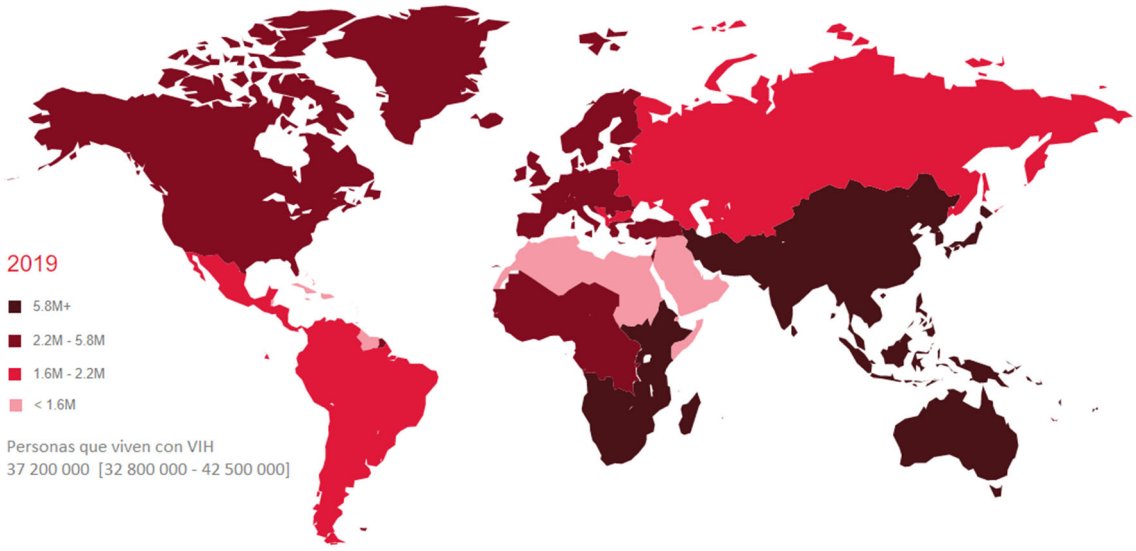
"La ciencia nos enseña a no descuidar nada, a no despreciar los comienzos modestos, porque en lo pequeño están siempre presentes los principios de lo grande, como en lo grande está lo pequeño." *Michael Faraday (Científico, 1791-1867)*

"Nada en este mundo debe ser temido… solo entendido. Ahora es el momento de comprender más, para que podamos temer menos." *Maria Skłodowska-Curie (Física y química, 1867-1934)*

1.1 Epidemiología del VIH

El programa Conjunto de las Naciones Unidas sobre el VIH/SIDA (ONUSIDA) se comprometió en 2016 a alcanzar "cero nuevas infecciones por el VIH, cero muertes relacionadas con el sida y cero discriminación" en el año 2030 (1). Como objetivo intermedio fijó para el año 2020 el "90-90-90": que el 90% de las personas con infección por el VIH conocieran su estado serológico respecto al VIH, que el 90% de las personas diagnosticadas con el VIH recibieran tratamiento antirretroviral y que el 90% de las personas con el VIH en tratamiento estuvieran en supresión viral. Además, se comprometió en alcanzar la reducción del 75% de las nuevas infecciones por el VIH con respecto al año 2010 y llegar al 0% de discriminación. Según el informe ONUSIDA de 2018 con datos hasta 2017 (2), globalmente se consiguió llegar al 75% [55-92%] de PVVIH que conocen su estado serológico (primer 90), al 79% [59-95%] de PVVIH en tratamiento (segundo 90) y al 81% [60-95%] de PVVIH en supresión viral (tercer 90). Se estima que en 2019 había más de 37 millones de personas en todo el mundo viviendo con una infección por VIH, con una distribución por áreas geográficas muy dispar (3) (Figura 1).

Figura 1: Distribución por zonas geográficas del número de personas que viven con una infección por VIH.



Fuente: ONUSIDA (3).

Las estimaciones obtenidas a partir de las métricas de transición epidémica del VIH demuestran que la tendencia es favorable a nivel global pero existe mucha heterogeneidad a

nivel geográfico, por edad, sexo y poblaciones de riesgo (4). En la tabla 1 se reportan los datos del 2019 en cuanto a la ratio incidencia:prevalencia, que representa la proporción de nuevas infecciones que ocurren por año en una población dividido por el número de personas que viven con el VIH en esa misma población; la ratio incidencia:mortalidad, que se define como la relación entre el número de personas que se infectan con el VIH al año y el número de personas ya infectadas que mueren (por cualquier causa) al año; el número de muertes por causas relacionadas con SIDA y de nuevas infecciones por VIH.

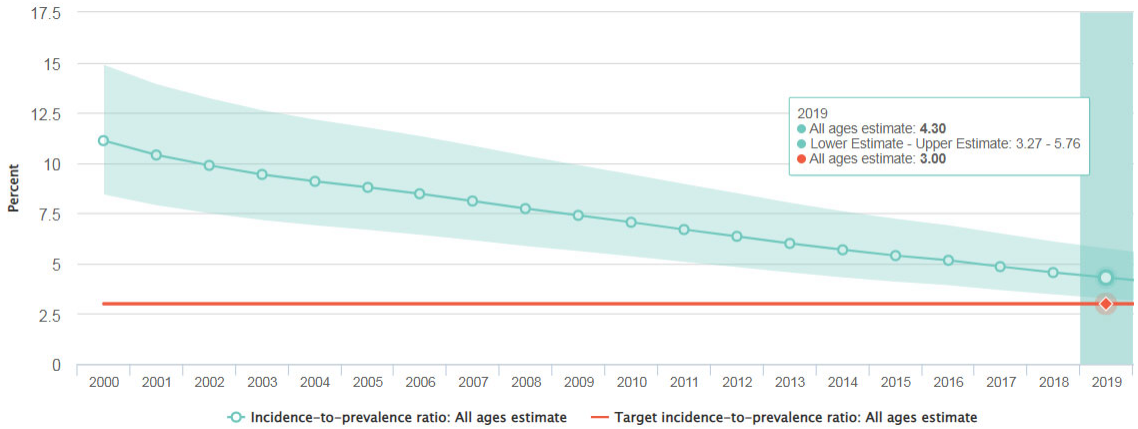
Tabla 1: Métricas de transición epidémica del VIH, estimaciones para el año 2019.

Region	**Ratio Incidencia: Prevalencia (%)**	**Ratio Incidencia: Mortalidad (%)**	**Muertes por causas relacionadas con SIDA**	**Nuevas infecciones por VIH**
Asia and the Pacific	4.50 [3.28 - 6.26]	1.45 [1.06 - 2.01]	150 000 [110 000 - 220 000]	260 000 [190 000 - 360 000]
Caribbean	4.54 [3.20 - 6.15]	1.75 [1.23 - 2.37]	6 600 [4 900 - 8700]	15 000 [10 000 - 20 000]
East and Southern Africa	3.70 [2.90 - 4.96]	1.67 [1.31 - 2.24]	310 000 [250 000 - 400 000]	740 000 [580 000 - 1 000 000]
Eastern Europe and Central Asia	9.06 [7.52 - 10.47]	3.05 [2.53 - 3.53]	41 000 [34 000 - 50 000]	150 000 [120 000 - 170 000]
Latin America	5.27	2.52	34 000 [21 000 - 48 000]	110 000 [67 000 - 150 000]
Middle East and North Africa	7.88 [6.35 - 10.13]	2.18 [1.76 - 2.81]	5200 [3900 - 7000]	13 000 [10 000 - 16 000]
West and Central Africa	4.97 [3.55 - 7.15]	1.14 [0.82 - 1.64]	170 000 [140 000 - 210 000]	240 000 [180 000 - 350 000]
Western & Central Europe and North America	3.01 [2.44 - 3.65]	2.70 [2.18 - 3.27]	13 000 [9700 - 17 000]	66 000 [53 000 - 80 000]
Global	**4.30 [3.27 - 5.76]**	**1.65 [1.25 - 2.20]**	**730 000 [570 000 - 950 000]**	**1 600 000 [1 200 000 - 2 100 000]**

Fuente: Datos extraídos de ONUSIDA (3).

En la figura 2 se puede observar la evolución favorable de la ratio incidencia:prevalencia global hacia el valor de referencia 3.00 (5).

Figura 2: Tendencia temporal en la ratio incidencia:prevalencia global.



Fuente: ONUSIDA (5).

A pesar de los grandes avances para reducir los indicadores epidemiológicos, queda mucho camino por recorrer para cumplir con los objetivos del 2030, especialmente cuando nos focalizamos en los resultados estratificados por áreas geográficas, edad, sexo y poblaciones de riesgo.

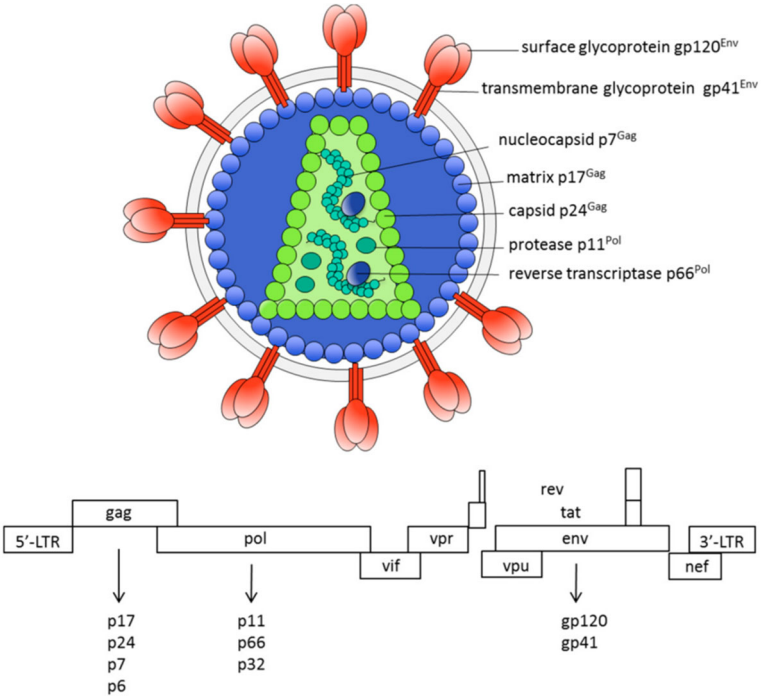
1.2 Estructura molecular del VIH

El VIH pertenece a la subfamilia de los lentivirus, que son retrovirus exógenos no oncogénicos que producen infecciones persistentes y enfermedades con largos periodos de latencia. Existen dos serotipos: el VIH-1, que es el responsable principal de la epidemia mundial de sida, y el VIH-2, menos patogénico y transmisible, restringido principalmente en África Occidental y de forma esporádica en migrantes con VIH de esa zona.

Siendo un retrovirus, tiene la capacidad de sintetizar el ADN a partir del ARN vírico gracias a la enzima transcriptasa inversa. En su estructura esférica se pueden identificar tres capas: la envoltura (capa externa) constituida por una membrana lipídica donde se encuentran las glucoproteínas gp120 y gp41 y receptores celulares y, más al interior, la proteína matriz p17 que se une a la gp41; la segunda, cápside icosaédrica, está constituida por la proteína p24; la tercera, la más interna, es el nucleoide, donde se encuentra el ARN viral, la proteína p7, las enzimas proteasa, integrasa y transcriptasa interna.

El genoma viral consta de dos copias de un ARN monocatenario. Gag, Pol y Env son los tres genes estructurales típicos de los retrovirus, pero el VIH además codifica proteínas reguladoras, Tat y Rev, y accesorias, NVpu, Vpr, Vif y Nef, imprescindibles para la replicación viral (Figura 3) (6).

Figura 3: Genoma y virión del VIH-1.



Fuente: Trovato M. Int J Mol Sci. 19 de abril de 2018;19(4):1241.(6).

1.3 Fármacos y familias antirretrovirales

En el año 1981 aparecieron los primeros casos de sida y solo seis años después la *Food and Drug Administration* (FDA) aprobó el primer fármaco antirretroviral, la zidovudina, de la familia de los inhibidores de la transcriptasa reversa análogos de nucleósidos y nucleótidos (ITIAN). A éste le siguieron otros fármacos de la misma familia, que constituyeron el tratamiento antirretroviral de esos primeros diez años de infección. Eran pautas constituidas por un único fármaco o una combinación doble que no consiguieron alcanzar el éxito terapéutico debido a la potencia subóptima y al desarrollo de mutaciones de resistencia (7). Fue con la aprobación de los inhibidores de la proteasa (IP) y de la transcriptasa inversa no-análogos de nucleósidos (ITINN) a mediados de los años 90, que el tratamiento

antirretroviral pudo basarse en combinaciones triples de dos ITIAN más un IP y de dos ITIAN más un ITINN, suficientemente potentes para controlar la replicación del virus de forma sostenida (8) (9) (10). Empezó la época del tratamiento antirretroviral de gran eficacia (TARGA). Posteriormente, más fármacos, también de nuevas familias, se añadieron al arsenal terapéutico disponible. En particular en 2007 se aprobó el primer inhibidor de la integrasa (INI), el raltegravir, luego el elvitegravir y finalmente el dolutegravir. La terapia triple por tanto se amplió a combinaciones de dos ITIAN más un INI, pautas con altas tasas de control virológico y mejor toleradas que las basadas en inhibidores de la proteasa (11). En la Tabla 2 se enseñan los fármacos antirretrovirales por familias y ordenados por año de aprobación por la FDA.

Tabla 2: Fármacos antirretrovirales contra el VIH y año de aprobación por la FDA.

	FAMILIAS ANTIRRETROVIRALES					
Año	**ITIAN**	**ITINN**	**IP**	**IF**	**IE**	**INI**
1987	Zidovudina					
1991	Didanosina					
1992	Zalcitabina*					
1994	Estavudina					
1995	Lamivudina		Saquinavir			
1996		Nevirapina	Indinavir Ritornavir			
1997		Delavirdine*	Nelfinavir			
1998	Abacavir	Efavirenz				
1999			Amprenavir*			
2000			Lopinavir/ritonavir			
2001	Tenofovir disoproxil fumarato					
2003	Emtricitabina		Atazanavir Fosamprenavir	Enfuvirtida		
2005			Tipranavir			
2006			Darunavir			
2007					Maraviroc	Raltegravir
2008		Etravirina				
2011		Rilpivirina				
2012						Elvitegravir
2013						Dolutegravir
2015	Tenofovir alafenamida					
2018		Doravirina				Bictegravir

*: fármacos actualmente no disponibles o no recomendados
ITIAN: inhibidores de la transcriptasa inversa análogos de nucleósidos y nucleótidos
ITINN: inhibidores de la transcriptasa inversa no-análogos de nucleósidos
IP: inhibidores de la integrasa
IF: inhibidores de la fusión
IE: inhibidores de la entrada
INI: inhibidores de la integrasa

Con el tiempo, se ha podido disponer de tratamientos más sencillos en los que los fármacos juntos van como combinaciones a dosis fijas y la dosificación se ha ido espaciando hasta

hacerse una vez al día (tabla 3), lo cual representa un avance muy importante en la simplificación del tratamiento antirretroviral.

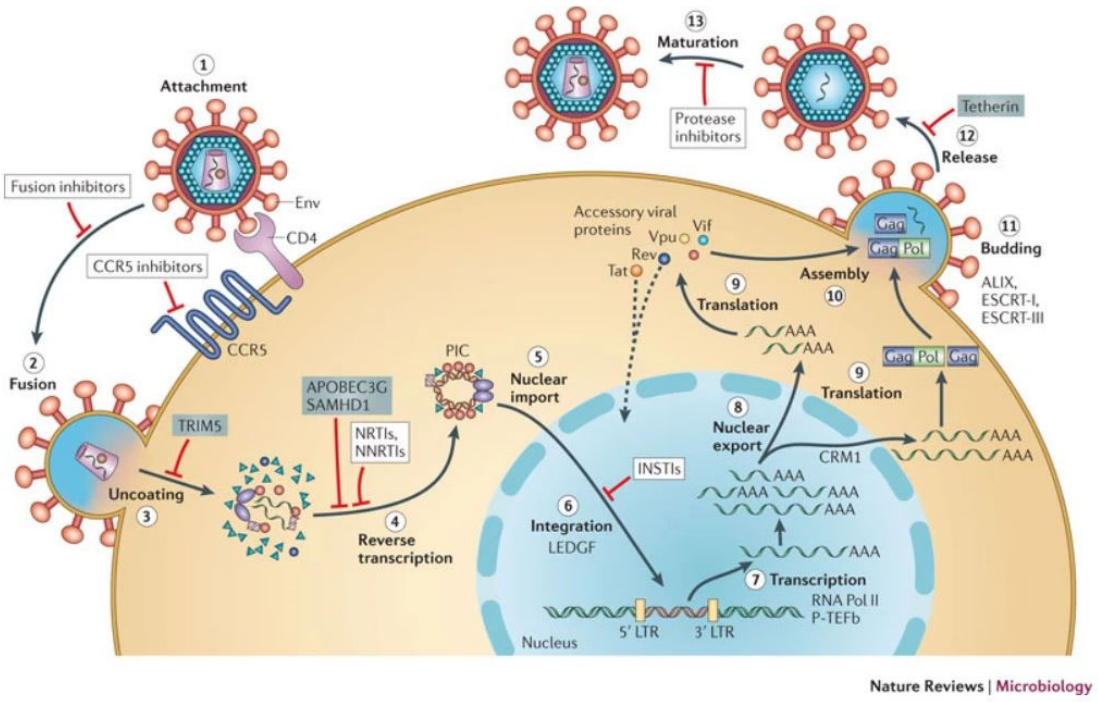
Tabla 3: Combinaciones de fármacos antirretrovirales orales a dosis fijas y año de aprobación por la FDA.

Año	Combinaciones a dosis fijas
1997	Zidovudina/lamivudina
2000	Lopinavir/ritonavir
2000	Zidovudina/abacavir/lamivudina
2004	Emtricitabina/tenofovir disoproxil
2004	Abacavir/lamivudina
2006	Efavirenz/emtricitabina/tenofovir disoproxil
2011	Emtricitabina/rilpivirina/tenofovir disoproxil
2012	Elvitegravir/cobicistat/emtricitabina/tenofovir disoproxil
2014	Dolutegravir/abacavir/lamivudina
2015	Atazanavir/cobicistat
2015	Darunavir/cobicistat
2015	Elvitegravir/cobicistat/emtricitabina/tenofovir alafenamida
2016	Emtricitabina/tenofovir alafenamida
2017	Dolutegravir/rilpivirina
2019	Dolutegravir/lamivudina

Recientemente, se ha aprobado un tratamiento inyectable consistente en cabotegravir y rilpivirina que se puede administrar cada dos meses. La disminución del número de tomas a sólo seis al año puede ser apreciada por personas con VIH que así no necesitan llevar el tratamiento a casa o acordarse de tomarlo cada día. No obstante, la administración exige dos inyecciones intramusculares profundas cada vez (que pueden no ser aceptables para una proporción de personas) y exige que sea administrado desde un centro hospitalario, lo cual puede verse como una restricción de la libertad para algunas personas.

Las familias de antirretrovirales se distinguen entre sí por sus dianas virales de inhibición del VIH. Con respecto a las fases del ciclo de vida del VIH (Figura 4) (12), cada etapa es susceptible a ser una diana terapéutica.

Figura 4: Ciclo de vida del VIH y acción inhibidora de las familias de fármacos antirretrovirales



Fuente: Deeks, S. Nat Rev Dis Primer. 2015;1(1):15035. (12)

A continuación, se resume brevemente las dianas sobre las que ejercen su acción, los efectos adversos principales y las recomendaciones de uso según GeSIDA 2020 (13) de las familias de antirretrovirales resumidas en la tabla 2.

Inhibidores de la transcriptasa inversa análogos de nucleósidos y nucleótidos (ITIAN)

Inhiben de forma competitiva la enzima transcriptasa inversa, que es la encargada de convertir el ARN del virus en ADN. Bloquean la elongación de la cadena viral insertándose en su ADN y como consecuencia interrumpen la replicación viral. Para activarse, los fármacos pertenecientes a esta familia necesitan una triple fosforilación en el interior de la célula, excepto para el tenofovir que es doble.

Los efectos adversos más relevantes de esta familia son la toxicidad mitocondrial a largo plazo (lipoatrofia, pancreatitis, neuropatía periférica), en particular debido al uso de didanosina y estavudina (fármacos que ya fueron retirados de la comercialización) e hipersensibilidad grave (erupción cutánea) debida al uso de abacavir, cuya probabilidad de

aparición se incrementa en caso de tener el alelo HLA-B*5701. Para evitar la potencial toxicidad renal del tenofovir y ósea de la formulación inicial del tenofovir disoproxil fumarato (TDF) (14), se desarrolló la formulación de tenofovir alafenamida (TAF) que es la que se utiliza mayoritariamente en la actualidad. Los fármacos de esta familia se administran en combinación para evitar el desarrollo de mutaciones de resistencias, siendo emtricitabina/tenofovir alafenamida y abacavir/lamivudina las recomendadas, a su vez en combinación con un tercer fármaco de una familia con mecanismo distinto. En cuanto a las dos formulaciones existentes del tenofovir, TDF o TAF, se prefiere TAF en terapia triple por su mayor eficacia a dosis inferiores con respecto a TDF.

Inhibidores de la transcriptasa inversa de no-análogos de nucleósidos (ITINN)

Los fármacos de esta familia impiden la síntesis de ADN viral gracias a un mecanismo no competitivo que los une a la transcriptasa inversa induciendo un cambio irreversible en su conformación. Nevirapina, efavirenz y delavirdina, los ITINN de primera generación, presentan una barrera genética muy baja que favorece la selección de mutaciones de resistencias, en particular la K103N. Los de segunda generación, etravirina, rilpivirina y doravirina, en cambio se caracterizan por su más alta barrera genética activa frente a diversas variantes con mutaciones de resistencia a los ITINN de primera generación.

Los efectos adversos más relevantes son de tipo dermatológico (exantema cutáneo) y hepatotoxicidad, relacionados al uso de nevirapina, y del sistema nervioso central, en el caso de efavirenz. Los ITINN de segunda generación son mejor tolerados que los de la primera y apenas plantean toxicidades graves.

Los fármacos de esta familia no están incluidos en los esquemas recomendados de tratamiento en la actualidad. Por tanto, se utilizan en personas que iniciaron su tratamiento hace años o bien en la actualidad como alternativas cuando no se pueden utilizar los fármacos de preferencia.

Inhibidores de la proteasa (IP)

Impiden la replicación viral actuando en la fase final de la maduración del virus. La proteasa viral fragmenta las poliproteínas Gag-Pol y Gag no funcionales para convertirlas en proteínas más pequeñas que, juntamente con el material genético, constituyen los viriones maduros

que pasan al plasma para infectar más células. Estos fármacos inhiben la fragmentación de las poliproteínas impidiendo la maduración de los viriones.

Ritonavir se comercializó en 1996 como IP, pero con el tiempo os efectos adversos digestivos llevaron a utilizar este fármaco a dosis más bajas como potenciador. Los fármacos de esta familia se deben administrar potenciados con ritonavir o cobicistat, excepto atazanavir que puede administrarse solo (en pautas de inicio). Cobicistat en concreto está aprobado como potenciador de atazanavir y darunavir.

Los efectos adversos más relevantes afectan al perfil metabólico (dislipemia, resistencia a la insulina, hiperglucemia, lipodistrofia).

La ventaja de esta familia es la alta barrera genética y los inconvenientes, el alto riesgo de interacciones farmacológicas y la corta vida media.

Inhibidores de la integrasa (INI)

Cuando el virus llega al núcleo de la célula, la enzima integrasa se encarga de integrar el ADN proviral formado por la transcriptasa inversa con el ADN del linfocito. La acción de esta familia es la de inhibir esta integración, impidiendo la replicación viral. Raltegravir y elvitegravir son INI de primera generación, más sujetos a resistencias que dolutegravir y bictegravir, los dos INI de segunda generación con más alta barrera genética. Elvitegravir debe ir potenciado y por esto se comercializa en pastillas únicas con cobicistat y TDF o bien TAF. Más recientemente, se dispone de cabotegravir que se administra por vía intramuscular cada dos meses.

Es una clase de fármacos bien tolerados siendo los efectos adversos más frecuentes náuseas, cefalea y diarrea.

Inhibidores de la entrada (IE)

Inhiben la entrada del virus a la célula T CD4+. El único fármaco perteneciente a esta familia es el maraviroc que, de forma selectiva, se une al correceptor CCR5 del linfocito para impedir la interacción con la proteína gp120 del virus. Su eficacia no es válida en caso virus que utilizan el correceptor CXR4 o tropismo dual o mixto. Esta clase terapéutica se denomina antagonistas de los correceptores CCR5. No es un fármaco recomendado y su uso es anecdótico.

Los efectos adversos más reportados son astenia, cefalea, náuseas y rinitis.

Desde la introducción del tratamiento antirretroviral de gran actividad, la terapia triple se ha convertido en la pauta de referencia y hoy en día el *gold standard* del tratamiento antirretroviral, además de la combinación de inicio recomendada (13) (15) (16). Dos fármacos de la familia ITIAN constituyen la base de la pauta, el tercer fármaco puede ser un ITINN, un IP potenciado o un INI. Actualmente la recomendación para el binomio de ITIAN es abacavir/lamivudina o tenofovir alafenamida/emtricitabina y para el tercer fármaco un INI, dando lugar a las combinaciones preferentes:

Bictegravir/emtricitabina/TAF

Raltegravir/emtricitabina/TAF

Dolutegravir/emtricitabina/TAF

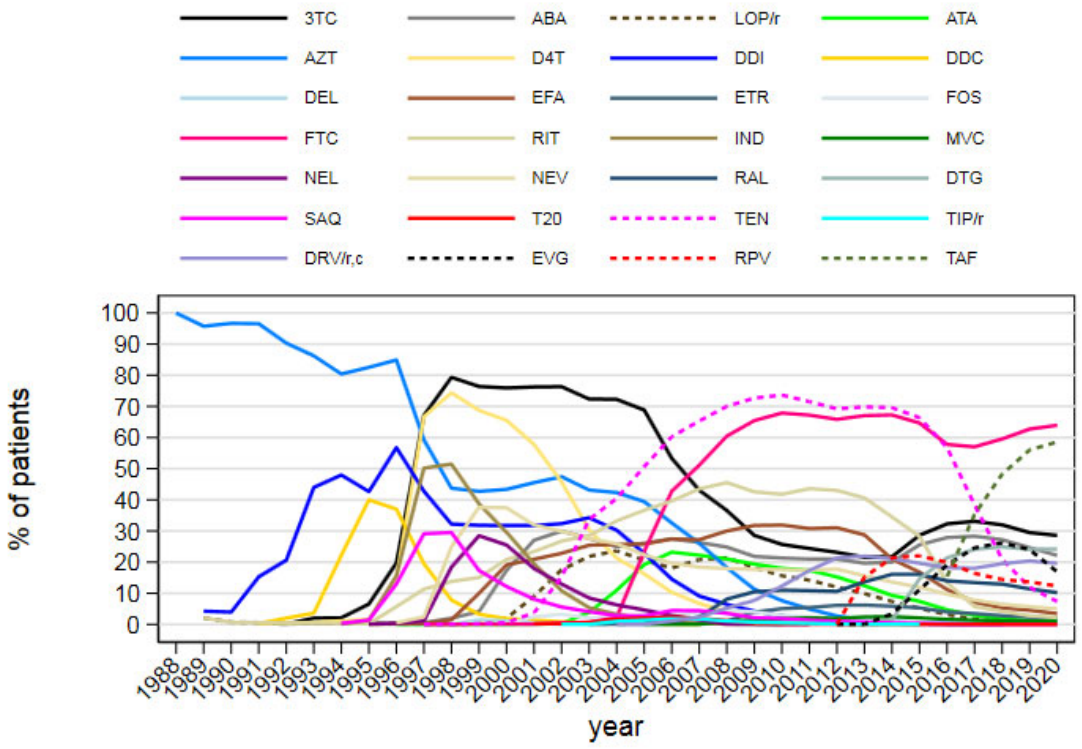
Dolutegravir/lamivudina/abacavir (en caso de HLA-B*5701 negativa)

La potencia y la alta barrera a la resistencia de los inhibidores de proteasa potenciados y de los inhibidores de integrasa de segunda generación ha permitido poner en evidencia la factibilidad de tratamientos dobles, en ocasiones coformulados, en la que uno de los fármacos es uno de los previos y el otro es un nucleósido (generalmente, lamivudina o 3TC) o un no nucleósido.

La evolución de la terapia antirretroviral está marcada por la evolución científica, la aprobación por las autoridades sanitarias, la evidencia de su eficacia y tolerabilidad que queda recogida en las guías internacionales y nacionales, el coste-beneficio, y las particularidades específicas de cada persona que vive con el VIH.

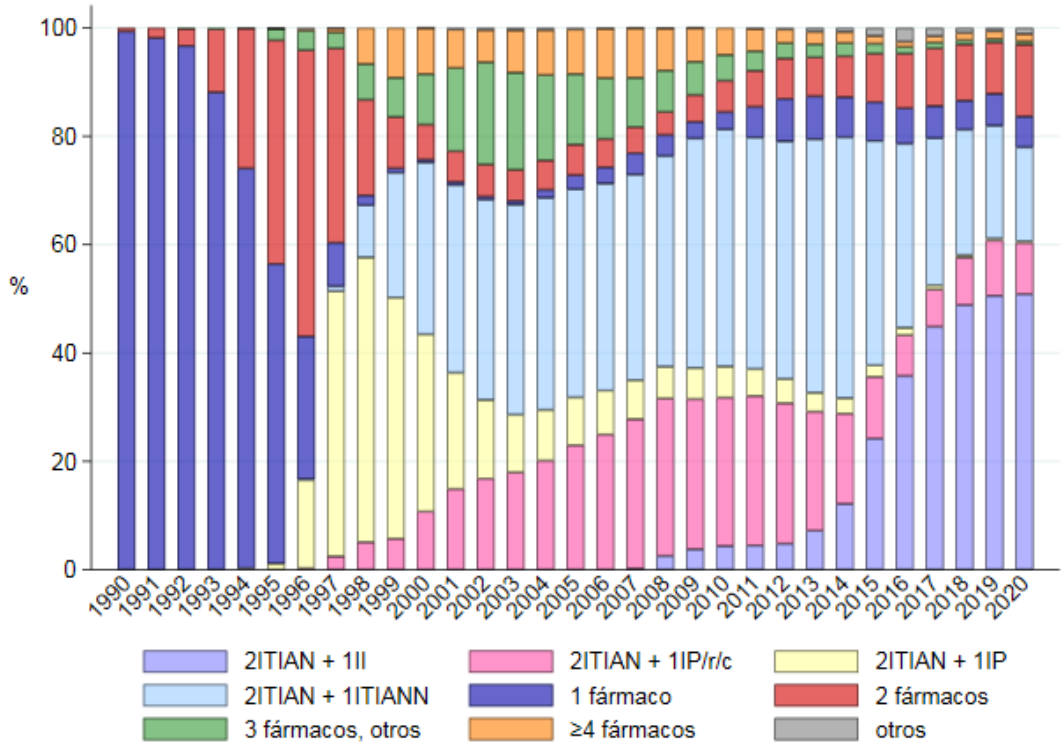
Este hecho se ve muy bien reflejado en la evolución del uso de fármacos antirretrovirales y combinación de ellos en pautas antirretrovirales en la cohorte de personas que viven con una infección por el VIH (PVVIH) atendidas en la Unidad de VIH del Hospital Clínic durante los últimos 30 años (Figura 5 y 6).

Figura 5: Evolución del uso de fármacos antirretrovirales en las personas que viven con una infección por el VIH atendidas en la Unidad de VIH del Hospital Clínic.



Fuente: Datos y gráfica originales (Elisa De Lazzari y Unidad de VIH, Hospital Clínic de Barcelona)

Figura 6: Evolución de las pautas antirretroviral en las personas que viven con una infección por el VIH atendidas en la Unidad de VIH del Hospital Clínic.



Fuente: Datos y gráfica originales (Elisa De Lazzari y Unidad de VIH, Hospital Clínic de Barcelona)

En nuestra cohorte podemos apreciar que la proporción de uso de bi-terapias ha ido aumentando en la última década, reflejando la necesidad de un enfoque terapéutico individualizado con menor carga de medicación, respaldado por la disponibilidad de fármacos cada vez más efectivos, simples y mejor tolerados. La optimización del tratamiento es una de las estrategias para la mejora de la calidad de vida de los pacientes que atienden la Unidad de VIH de nuestro hospital y la simplificación a dos fármacos es sin duda un ámbito de investigación fundamental en este sentido.

1.4 Simplificación del tratamiento antirretroviral

1.4.1 Introducción

La terapia antirretroviral ha mejorado mucho en la última década y ha transformado la infección por VIH en una enfermedad crónica con una larga supervivencia y una excelente calidad de vida para los pacientes que reciben TAR (8) (17) (18). Los regímenes

antirretrovirales actuales son muy eficaces y logran la supresión viral en más del 90% de los casos, según análisis por intención de tratar de grandes ensayos clínicos aleatorios. Además, estos regímenes muestran buena tolerabilidad, y sólo un pequeño porcentaje de pacientes necesita suspender el tratamiento debido a efectos adversos relacionados con el fármaco. Los regímenes son fáciles de tomar y convenientes, con varias formulaciones que proporcionan una sola pastilla para administrar una vez al día. A pesar de todas estas ventajas, se pueden obtener algunos beneficios en pacientes virológicamente suprimidos cambiando uno o más fármacos del régimen en lo que se conoce como "estrategia de cambio". Esta estrategia se implementó por primera vez hace más de 20 años, cuando se cambiaron los inhibidores de proteasa (IP) de primera generación y los análogos de timidina para disminuir la toxicidad o reducir la carga de píldoras. Aunque el arsenal antirretroviral actual ha mejorado mucho, esta útil estrategia todavía tiene una utilidad, que puede proporcionar beneficios individuales y al sistema de salud. Algunos pacientes pueden experimentar efectos adversos y todavía seguimos prescribiendo medicamentos con ciertas limitaciones, como la necesidad de administrar con alimentos o la presencia de potenciadores con el riesgo de interacciones medicamentosas no deseadas. Además, las diferencias de precios, especialmente con los compuestos genéricos, pueden ayudar al sistema de salud a respaldar el uso ampliado de ART. A continuación resumo el uso actual de estrategias de cambio y las opciones disponibles (19).

1.4.2 Razones para la simplificación de la terapia antirretroviral

a) Disminuir la complejidad

Aunque los regímenes antirretrovirales son muy eficaces, el cumplimiento del paciente sigue siendo esencial para lograr y mantener la supresión viral (20) (21). Una mejor adherencia reduce el riesgo de rebote viral y el desarrollo de resistencia a los medicamentos (22–25) y ayuda a evitar el fracaso del tratamiento, minimizando así las limitaciones de futuras opciones de tratamiento. En la actualidad, una elevada proporción de pacientes infectados por el VIH reciben un régimen sencillo de una o dos pastillas al día. Sin embargo, aquellos con varios fracasos virológicos (FV) previos pueden necesitar seguir regímenes complejos con varias pastillas o dosis al día. Muchos de estos pacientes fracasaron anteriormente debido a problemas de cumplimiento, y el cumplimiento deficiente puede deberse a una o

más razones, por ejemplo, problemas psicológicos, comorbilidades que requieren tratamientos farmacológicos adicionales, etc. El problema es ciertamente complejo, pero los regímenes simples pueden ayudar a los pacientes a mantener un buen cumplimiento. Aunque los datos actuales son escasos, la disponibilidad de nuevos fármacos parece permitir la prescripción de regímenes simples de dos comprimidos en terapias de simplificación o incluso de rescate.

b) Aumento de la barrera genética de los medicamentos antirretrovirales

En pacientes con adherencia irregular, picos virales o supresión viral, una estrategia de cambio preventivo a regímenes que incluyan medicamentos con una barrera genética alta puede evitar el desarrollo de rebote viral y la selección de mutaciones resistentes. A continuación, se analizan las opciones con una barrera genética alta dentro de las diferentes familias de medicamentos antirretrovirales.

Inhibidores de la integrasa: raltegravir y elvitegravir son inhibidores potentes de la integrasa de primera generación que generalmente son bien tolerados en adultos con VIH que no han recibido tratamiento previo y en adultos con VIH (26) (27). Sin embargo, estos fármacos tienen una barrera genética relativamente baja. En consecuencia, los pacientes con tratamiento previo que fracasan en los regímenes basados en raltegravir o elvitegravir pueden optar por mutaciones resistentes a los inhibidores de la integrasa, y se ha informado de resistencia cruzada entre los dos fármacos (27–29). Dolutegravir y el recientemente aprobado bictegravir tienen una barrera genética más alta. Ninguno de los fármacos ha mostrado mutaciones resistentes en ensayos clínicos aleatorios realizados con cientos de pacientes sin tratamiento previo, lo que demuestra la sólida barrera genética de estos agentes. Incluso en pacientes con fracasos previos en otras familias, dolutegravir fue superior a raltegravir en un gran estudio aleatorizado. Sin embargo, los estudios de monoterapia con dolutegravir han demostrado que los sujetos con fracaso virológico desarrollaron resistencia con esta estrategia, lo que sugiere que la barrera genética del fármaco no es tan alta como la de los inhibidores de proteasa potenciados utilizados actualmente.

Inhibidores de proteasa potenciados: Aunque los inhibidores de la integrasa son los regímenes preferidos en la mayoría de las guías internacionales, en pacientes con resistencias previas a la integrada, los regímenes de inhibidores de proteasa potenciados pueden resultar necesarios debido a que tienen una barrera genética tan alta a la resistencia viral que es muy improbable que desarrollen resistencias. Darunavir se ha utilizado para tratar personas con VIH durante más de una década, tanto en sujetos que no habían recibido antirretrovirales como en sujetos experimentados (30). La afinidad de unión del darunavir a la proteasa del VIH-1 de tipo salvaje es de más de 100 veces que otros inhibidores de proteasa potenciados, con una tasa de disociación muy lenta, lo que explica su potente actividad antiviral y su alta barrera genética (31). La disponibilidad por primera vez de una única pastilla administrada una vez al día de un régimen de IP potenciados con darunavir + cobicistat + emtricitabina + TAF hace que este régimen sea adecuado en un escenario de cambio, especialmente para pacientes en quienes el cumplimiento puede representar una limitación que supone riesgo de resistencias o que experimentan eventos adversos con regímenes que contienen inhibidores de la integrasa.

No nucleósidos: Los no nucleósidos de primera generación, como efavirenz y nevirapina, así como la rilpivirina de segunda generación, tienen una barrera genética baja, y el fracaso virológico debido a una mala adherencia se asocia con la selección de mutaciones resistentes en un alto grado. proporción de pacientes. La etravirina tiene una barrera genética más alta, pero se administra en dos pastillas al día que no son fáciles de tragar, lo que la convierte en un mal candidato para la simplificación. Por el contrario, el medicamento recientemente aprobado conocido como doravirina se prescribe en una pastilla al día, puede administrarse en un régimen de dosis fija triple combinado con TDF y lamivudina o solo para asociarse con otros fármacos *backbone*s. Estudios recientes han demostrado que doravirina es eficaz y bien tolerado en pacientes que nunca han recibido tratamiento antirretroviral, y el fármaco se está investigando actualmente en pacientes con experiencia en tratamiento y en aquellos con resistencia transmitida a fármacos inhibidores no nucleósidos de la transcriptasa inversa.

Análogos de nucleósidos: La combinación de TAF y emtricitabina es probablemente la mejor estructura de nucleósidos desarrollada hasta la fecha. Esta nueva formulación de un profármaco de tenofovir tiene muy buena tolerabilidad y no está asociada con las

toxicidades renales y óseas de la antigua formulación de tenofovir disoproxil fumarato. En la actualidad, la mayoría de los regímenes de triple fármaco administrados en una pastilla al día contienen TAF + FTC. Además, TAF + TFC también se ha comercializado solo para asociarlo con otros "terceros" medicamentos. Estos hechos hacen de tenofovir alafenamida + emtricitabina un buen fármaco básico en regímenes de tres fármacos que se administran en escenarios de cambio.

c) Prevención de las toxicidades asociadas al tratamiento antirretroviral

Aunque los regímenes antirretrovirales actuales tienen muy buena tolerabilidad, algunos pacientes todavía experimentan efectos adversos relacionados con los medicamentos. Las tablas 4a y 4b resumen el motivo y necesidad del cambio de TAR y la nueva pauta (13).

Tabla 4a: Necesidad de cambio de TAR

TAR actual	Motivo del cambio	Necesidad del cambio
TDF	Osteopenia/osteoporosis. Disminución del FGe o disfunción tubular.	Obligado Variable, dependiendo de la magnitud de descenso del FGe. Obligado si se desarrolla insuficiencia renal o parámetros de disfunción tubular.
EFV o DTG	Sintomatología del SNC: mareo, trastornos del sueño. Toxicidad del SNC subclínica.	Obligado. No se ha demostrado beneficio.
IP/r	Diarrea u otros síntomas gastrointestinales asociados a ritonavir. Dislipidemia, alto riesgo cardiovascular.	Obligado. Variable. No se ha demostrado que el cambio sea mejor que el uso de hipolipemiantes ni el impacto sobre el riesgo cardiovascular.
Múltiples comprimidos	Comprimido único.	No se ha demostrado que el cambio sea necesario en la mayoría de los pacientes.
DTG, BIC, COBI, TAF	Teratogenicidad peri concepción. Sin datos de seguridad en embarazo.	Obligado en mujeres que deciden quedarse embarazadas.

Fuente: Panel de Expertos de GeSIDA y Plan Nacional sobre el SIDA. (13)

Tabla 4b: Cambios entre fármacos antirretrovirales, con el motivo de cambio y la evidencia sobre la eficacia del cambio

TAR actual	Motivos del cambio	TAR nuevo
Cambio a regímenes que siguen incluyendo 3 fármacos		
TDF TDF/FTC	Evitar los efectos de TDF sobre riñón y/o hueso.	ABC TAF/FTC
ABC/3TC	Decisión clínica.	TAF/FTC
ITINN + 2 ITIAN	Evitar los efectos de TDF sobre riñón y/o hueso; Decisión clínica; Evitar toxicidad de los ITINN (especialmente de EFV sobre SNC); Disminución del número de comprimidos; Evitar interacciones.	BIC/FTC/TAF EVG/c/FTC/TAF DTG/ABC/3TC RAL + 2 ITIAN DOR/3TC/TDF RPV/FTC/TAF
ATV/r DRV/r 800/100 mg	Disminución del número de comprimidos.	ATV/c DRV/c
IP/p + 2 ITIAN	Evitar los efectos de TDF sobre riñón y/o hueso; Decisión clínica; Dislipemia o síntomas gastrointestinales por IP/p; Disminución del número de comprimidos; Evitar interacciones.	BIC/FTC/TAF EVG/c/TAF/FTC DTG/ABC/3TC DTG + 2 ITIAN RAL + 2 ITIAN DOR/3TC/TDF RPV/FTC/TAF DRV/c/FTC/TAF
INI + 2 ITIAN	Decisión clínica; Disminución del número e comprimidos.	DTG/ABC/3TC BIC/FTC/TAF
Cambio a regímenes con menos de 3 fármacos		
IP/p + 2 ITIAN	Evitar efectos adversos del régimen actual; Simplificación.	DRV/p o ATV/p + 3TC
IP/p o ITINN o INI + 2 ITIAN	Evitar efectos adversos del régimen actual; Simplificación; Evitar interacciones.	DTG/3TC DTG/RPV
IP/p + 2 ITIAN; regímenes varios	Evitar efectos adversos del régimen actual; Simplificación.	DTG + DRV/p

Fuente: Panel de Expertos de GeSIDA y Plan Nacional sobre el SIDA. (13)

d) Reducción de costes

Cambiar los medicamentos antirretrovirales por otros menos costosos con el mismo perfil de eficacia y seguridad puede ser una estrategia útil para limitar el gasto en salud pública en países actualmente en recesión económica o con recursos limitados de atención médica.

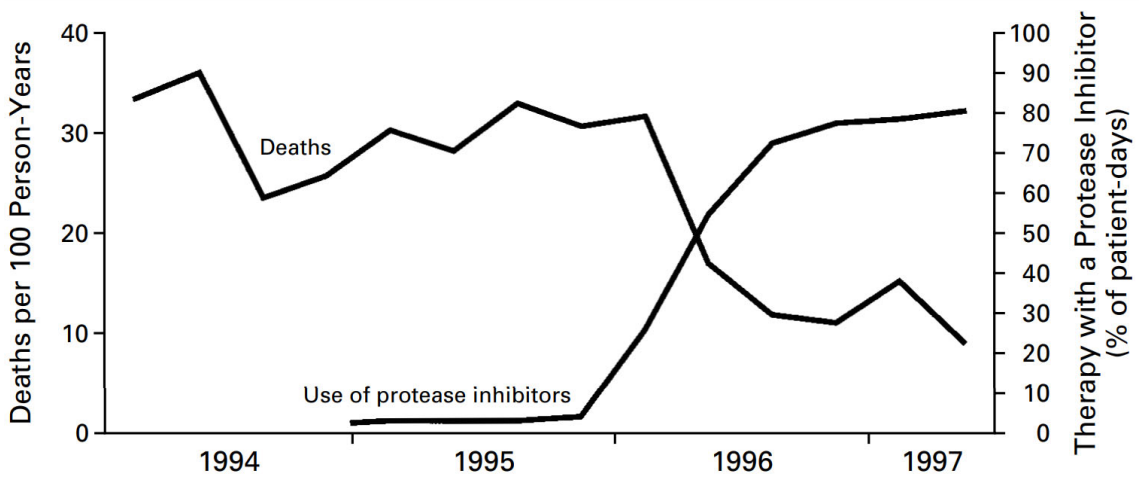
Varios estudios financieros han evaluado el impacto de cambiar las estrategias de un régimen de múltiples tabletas (MTR) basado en una combinación de dosis fija a un régimen de una sola tableta (STR) en el uso de recursos de salud (32). Cohen et al. informaron menos servicios para pacientes hospitalizados y ambulatorios, un menor número de recetas y menos consultas de atención médica por mes para los pacientes que recibían STR en comparación con los pacientes que recibían dos o más píldoras por día (33). Beck et al. (34) encontraron resultados similares, quienes informaron un servicio de hospitalización sustancialmente menor para pacientes con SIDA y sin SIDA en STR en comparación con aquellos en MTR y otros regímenes, al mismo tiempo que encontraron costos comparables por paciente/año a los 6 y 12 meses. Dos estudios (35) (36) informaron costos de uso de recursos de salud totales por mes más bajos estadísticamente significativos ($p<0.0001$) y un costo anual medio más bajo ($p<0.0001$) en pacientes con STR en comparación con MTR. Estos resultados llevan a la conclusión de que cambiar a la simplificación del tratamiento antirretroviral podría generar importantes ahorros de costos. A pesar de estos datos, en los países desarrollados, la mayoría de los médicos prefieren administrar regímenes de dosis fija no genéricos administrados en una pastilla por día para mejorar la conveniencia del tratamiento y la calidad de vida y mejorar la adherencia, particularmente en pacientes con comorbilidades que deben tomar una serie de medicamentos basados en otras pastillas.

1.4.3 Evidencia acumulada de la simplificación de la terapia antirretroviral

Los avances conseguidos en el tratamiento antirretroviral permiten evitar la progresión de la infección, favoreciendo la recuperación inmunológica, y mantener la carga viral por debajo de la detectabilidad. Sin tratamiento la replicación viral se vuelve a activar llegando a niveles detectables e incluso muy elevados. La dificultad para encontrar una cura para el VIH debida a los distintos reservorios virales (moleculares, celulares y anatómicos) implica que las personas que viven con una infección por VIH deban recibir tratamiento de por vida. Además, con el paso de los tiempos y la evidencia científica, el inicio del TARGA ha pasado a ser inmediato (*test&treat*) independientemente del nivel de CD4. Tal como se ha mencionado anteriormente, la terapia triple ha cambiado la historia natural de la infección. Palella et al. (1998) (37) describe cómo la morbi-mortalidad disminuyó con la introducción de la terapia triple: la mortalidad bajó de un 29.4 por 100 persona-años en 1995 a un 8.8 por 100 persona-año a finales del 1997 (independientemente de edad, sexo, raza y modo de

transmisión del VIH) (figura 7) y la incidencia de Pneumocystis carinii pneumonia, Mycobacterium avium complex y retinitis por citomegalovirus del 21.9 por 100 persona-años en 1994 al 3.7 por 100 persona-años a mediados del 1997.

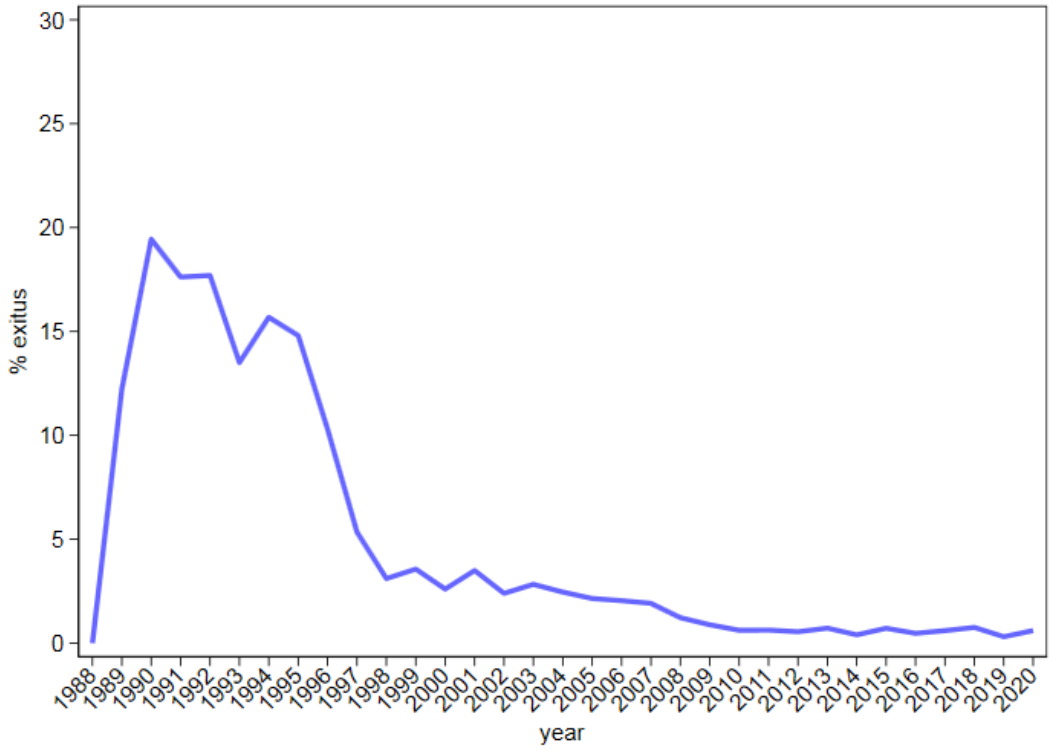
Figura 7: mortalidad y frecuencia de uso de pautas combinadas con IPs en pacientes con T CD4+ <100 células/mL, entre 1994 y 1997



Fuente: Palella FJ. N Engl J Med. 1998;338(13):853-60 (37).

El impacto en nuestra cohorte también es evidente con una disminución de la mortalidad desde el 18% en 1898 hasta el 4% en 1998 (figura 8).

Figura 8: Mortalidad (%) en la cohorte de PVVIH de la Unidad de VIH del HCB entre 1986 y 2020



Fuente: datos y gráfica originales (Elisa De Lazzari y Unidad de VIH, Hospital Clínic)

Sin embargo, las pautas triples de la primera época, basadas en un IP más dos ITIAN o dos ITINN, podían llegar a incluir muchas pastillas al día con posologías distintas; eran pautas complejas difíciles de mantener en el tiempo y con asociados problemas de adherencia. En los más de 25 años de vida de los inhibidores de la proteasa, se ha acumulado evidencia de distintos efectos adversos asociados a su uso. La Organización Mundial de la Salud (OMS) emitió una alerta a mediados del 1997 (38) sobre el riesgo de hiperglicemia y diabetes mellitus en personas con VIH en tratamiento con IP, recomendando su estricta monitorización. La exposición a indinavir se demostró asociada a la acumulación de grasa visceral abdominal en un estudio comparativo entre tres grupos de participantes de 10 sujetos cada uno, todos ellos con infección por VIH (39): el primer grupo de participantes estaban recibiendo indinavir y presentaban síntomas abdominales; el segundo, con indinavir pero sin síntomas; y el tercero, sin exposición al fármaco. Los resultados demostraron que la exposición a indinavir aumentaba significativamente el valor medio de ratio entre el tejido adiposo visceral y el tejido adiposo total (TAV:TAT) y del área del tejido adiposo visceral,

siendo de 0.40 (DE 0.15) y 106 cm^2 (DE 72), respectivamente, en los no expuestos; 0.59 (DE 0.18) y 141 cm^2 (DE 65) en los expuestos asintomáticos; 0.70 (DE 0.20) y 202 cm^2 (DE 93) en los expuestos sintomáticos (p-valor 0.004 y 0.03, respectivamente). Además, se detectó una correlación positiva entre la ratio TAV:TAT y la duración de exposición a indinavir (r=0.47, p-valor=0.01). Sin embargo, no hubo diferencias entre grupos en cuanto al índice de masa corporal. Un estudio realizado en Francia entre 1996 y 1999 con datos de hombres con VIH (40) demostró que la exposición a los IP se asociaba a un mayor riesgo de infarto de miocardio (Hazard Ratio 2.56; IC 95% 1.03; 6.34) y además que la incidencia esperada por 10'000 personas/año tenía una relación con la duración de la exposición (con respecto a una exposición <18 meses, la incidencia esperada fue de 1.9 (IC 95% 1.0; 3.1) con exposición entre 18 y 29 meses y de 3.6 (IC 95% 1.8; 6.2) con exposición ≥30 meses.

Otro efecto adverso reportado es la diarrea crónica (41), cuya incidencia es mayor en la fase inicial del tratamiento y posteriormente disminuye gracias a la tolerancia que las personas consiguen al cabo de varias semanas. La disfunción sexual también se ha reportado como efectos adverso asociado al uso de IP (42), en particular el tiempo de exposición (por incremento de 1 año: OR 1.6, IC 95% 1.12; 2.4, p-valor=0.01) juntamente con la edad (por incremento de 10 años: OR 2.2, IC 95% 1.04; 4.5, p-valor=0.04), mientras que el uso y la duración de exposición a ITIAN e ITINN no presentaron asociación significativa con la disfunción sexual. Los efectos adversos comprometen la adherencia al tratamiento y la calidad de vida de las personas. La diarrea puede afectar también a la efectividad del tratamiento antirretroviral. Además, hay que tener en cuenta que los tratamientos concomitantes para los efectos adversos pueden interaccionar con el antirretroviral.

Hasta la comercialización de los inhibidores de la integrasa, las opciones de simplificación del tratamiento por sustitución de los IP eran limitadas. En el ensayo clínico randomizado NEFA (43) demostramos que la sustitución por un ITINN (nevirapina, efavirenz) o por un ITIAN (abacavir) no era óptima. En el grupo de nevirapina y de efavirenz hubieron significativamente más discontinuaciones por efectos adversos que en el de abacavir (17% vs. 17% vs. 6%, respectivamente, p-valor=0.01) (figura 9). Pero en el grupo de abacavir detectamos más fracasos virológicos (todos ellos durante el tratamiento) y más fallos terapéuticos en el análisis por protocolo (figura 10).

Figura 9: Distribución de pacientes que tuvieron al menos un efecto adverso (estudio NEFA).

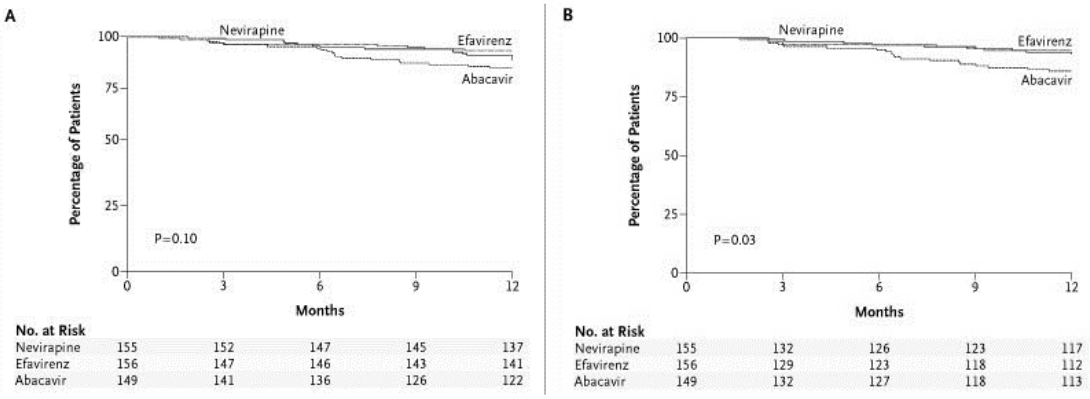
Table 3. Number of Patients Who Had One or More Adverse Events.*

Adverse Event	Nevirapine (N=155)			Efavirenz (N=156)			Abacavir (N=149)		
	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation	Any Adverse Event	Grade 3 or 4 Adverse Event	Adverse Event Leading to Discontinuation
	number of patients (percent)								
Clinical									
Neuropsychiatric	11	6	6	48	22	19	14	1	0
Cutaneous	20	13	12	11	3	3	7	0	0
Gastrointestinal	6	2	0	8	4	4	12	2	1
Systemic†	7	1	1	5	2	0	10	8	8
Other	25	8	1	11	5	1	12	3	0
Laboratory									
Increased aminotransferase levels	12	6	4	4	1	0	5	1	0
Hyperglycemia	2	2	2	2	2	0	1	1	0
Total	83 (54)‡	38	26 (17)§	89 (57)‡	39	27 (17)§	61 (41)‡	16	9 (6)§

* A grade 3 event was defined as severe, and a grade 4 event as life-threatening.
† Systemic adverse events included hypersensitivity reactions.
‡ P=0.03 by the chi-square test.
§ P=0.01 by the chi-square test.

Fuente: Martínez, E. N Engl J Med. 2003;349(11):1036-46 (43)

Figura 10: Proporción de pacientes con fracaso virológico (A) y con fallo terapéutico (B), análisis por protocolo (estudio NEFA).

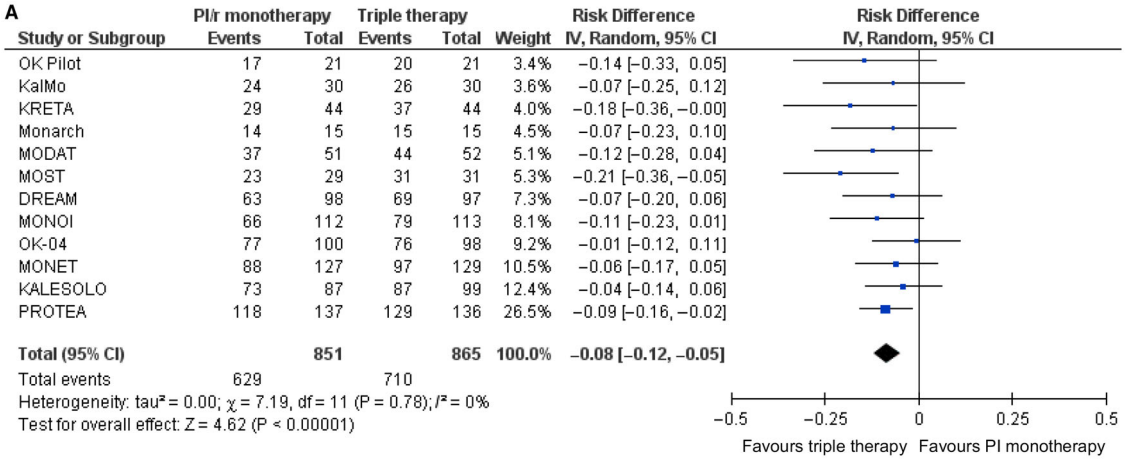


Fuente: Martínez, E. N Engl J Med. 2003;349(11):1036-46 (43)

El primer intento de simplificación reduciendo el número de fármacos de tres a dos tampoco llevó a resultados satisfactorios (44). La biterapia con efavirenz e indinavir no consiguió niveles de éxito virológico superiores a la triple terapia con indinavir, zidovudina y lamivudina y se veía afectada por efectos adversos asociados con el IP. Con el tiempo ha mejorado mucho también la simplificación a nivel de posología y dosis. Si en la segunda mitad de los años 90 el TARGA estaba caracterizado por pautas con entre 12 y 28 pastillas de 2-3 tomas diarias, a mediados del año 2000 las pautas se basaban en 3-4 pastillas de toma

única diaria y, posteriormente, se simplificaron aún más con la co-formulación en pastilla única a partir del 2008. Sin embargo, las pautas estándares eran y siguen siendo las triples, manteniendo el problema de las múltiples toxicidades a largo plazo que promueven comorbilidades, en particular el uso de ITIAN que se asocia a riesgo cardiovascular, lipodistrofia, osteoporosis, enfermedad crónica renal y del hígado, depresión y alteraciones cognitivas. Los resultados de un meta-análisis de 12 ensayos clínicos que reunía un total de 2303 pacientes indicaron que la simplificación a monoterapia basada en IP potenciados era inferior a la terapia triple (45) en cuanto a la eficacia virológica evaluada por intención de tratar (ITT) considerando fracaso el cambio de tratamiento (figura 11).

Figura 11: Resultados del meta-análisis de 12 ensayos clínicos de no-inferioridad de monoterapia con IP respecto a la triple terapia. Eficacia por intención de tratar (cambio TARV=fracaso).



Fuente:

Arribas, JR. HIV Med 2016. (45)

En el contexto de una enfermedad crónica como es el VIH que requiere un tratamiento de por vida, es de fundamental importancia que ese tratamiento no contribuya con toxicidades, ya que pueden disminuir su eficacia y afectar a la calidad de vida de las personas. Las toxicidades promueven comorbilidades y aumentan la morbi-mortalidad. Todo ello se refleja también en un aumento de los gastos sanitarios. Las toxicidades a corto plazo pueden ser (o parecer) tolerables, pero conllevan el riesgo de ser subclínicas y desenlazar, a medio/largo plazo, en situaciones más complejas y graves. Además, pueden afectar al cumplimiento del tratamiento con el riesgo de provocar un descontrol virémico y/o selección de mutaciones. La discontinuación del fármaco puede llevar a una resolución completa, pero es importante

tener en cuenta que a veces es solo aparente. Las toxicidades a largo plazo contribuyen a las comorbilidades y la resolución que podemos obtener con la discontinuación es incompleta o, incluso, inexistente.

A pesar que la esperanza de vida de la población que vive con VIH es similar a la general, si se tienen en cuenta las comorbilidades los resultados son más dispares. A los 21 años de edad, por ejemplo, la esperanza de años de vida libres de comorbilidades es de unos 15 años superior en las personas VIH negativas con respecto a las positivas (46). Evidentemente las comorbilidades aumentan con la edad, pero son más prevalentes en las personas con VIH, colectivo donde se ha estimado sistemáticamente una mayor prevalencia de comorbilidades en todas las franjas de edad (47).

En todo este contexto, es evidente que la optimización del tratamiento antirretroviral constituye una herramienta fundamental para reducir las toxicidades, mejorar el cumplimiento del tratamiento y la calidad de vida de las personas.

En la familia de los ITIAN, la zidovudina y la estavudina son los dos análogos de la timidina que demostraron producir lipoatrofia, una alteración de la distribución de la grasa corporal casi inexistente fuera del contexto de infección por VIH. Desde la activación del mecanismo patogénico hasta la manifestación clínica pasando por la fase intermedia de enfermedad subclínica, pueden pasar hasta 40 meses. La progresión es lenta (48). Abacavir contribuye al riesgo de enfermedad cardiovascular y tenofovir disoproxil fumarato puede producir nefrotoxicidad (49) y tiene un impacto negativo en la densidad mineral ósea (50). Tenofovir alafenamida en cambio contribuye a una mayor ganancia de peso (51), así como los inhibidores de la integrase de segunda generación (elvitegravir, dolutegravir y bictegravir). La lamivudina es el único ITIAN no obligatoriamente co-formulado con otros fármacos de la misma familia que no tiene toxicidades reconocidas (52). A la luz de los resultados de simplificación de terapia triple a doble basada en IP, actualmente la alternativa más atractiva se basa raltegravir y dolutegravir. Además hemos demostrado que la monoterapia con dolutegravir no es aconsejable (53).

A partir de estos resultados, dimos comienzo a la investigación incluida en la presente tesis doctoral. Pero, de forma totalmente inesperada otro virus apareció en nuestras vidas creando verdaderos desafíos a todos los niveles: el coronavirus SARS-CoV-2, causante la

enfermedad denominada COVID-19. No sólo afectó nuestra vida como ciudadanos, sino que afectó al desarrollo y los objetivos de esta tesis doctoral.

1.5 COVID-19 y VIH

En las últimas décadas ha habido dos infecciones zoonóticas de coronavirus que afectan de forma aguda el sistema respiratorio humano y que se han propagado más allá de las fronteras locales: el síndrome respiratorio agudo severo (SARS-CoV) en 2003 y el síndrome respiratorio del Medio Oriente (MERS-CoV) en 2012 (54). En diciembre de 2019 en Wuhan (China) se originó la reciente pandemia causada por el coronavirus SARS-CoV-2, a partir de un clúster de individuos afectados por neumonía de etiología desconocida en aquel entonces. El contagio entre humanos de la COVID-19 fue extremadamente rápida y el 11 de marzo de 2020 la Organización Mundial de la Salud la declaró una pandemia (55). En España, debido a la excepcionalidad de la situación, el Gobierno español aprobó el 14 de marzo de 2020 un primer estado de alarma e impuso un estricto confinamiento domiciliario para todos los ciudadanos a excepción de los trabajadores esenciales. En junio del mismo año finalizó el primer estado de alarma pero en octubre se impuso el segundo, debido al incremento de los casos detectados durante el verano, y a finales de diciembre de 2020 empezó la vacunación masiva contra la COVID-19 (56).

La pandemia afectó gravemente el acceso y la calidad de la atención médica a nivel mundial. Resultados preliminares sobre el impacto de la pandemia de COVID-19 en Europa (57) reportan una disminución del 95% en el volumen de test realizados de VIH, hepatitis virales y otras infecciones de trasmisión sexual entre marzo y mayo de 2020 y del 58% entre junio y agosto de 2020, con respecto a los mismos periodos del año anterior. Conocer la afectación del primer año de pandemia de COVID-19 en nuestro hospital en cuanto a la prevención y cuidado clínico del VIH y al cribado y diagnóstico del VIH y otras infecciones de trasmisión sexual era sin duda de mucho interés para poder hacer frente a siguientes olas y seguir trabajando en la mejora de la calidad de vida de las personas que atienden nuestro centro.

1.6 Medidas de experiencias reportadas por los pacientes

La "calidad de vida relacionada con la salud" (CVRS) (58) se define como la percepción que tiene el paciente de los efectos de una enfermedad o de la aplicación de cierto tratamiento en diversos ámbitos de su vida, especialmente de las consecuencias que provoca sobre su bienestar físico, emocional y social. En el ámbito de una enfermedad crónica como actualmente se considera el VIH, la CVRS se ha convertido en una importante medida del impacto de los cuidados médicos y para ello es imprescindible conocer la percepción del paciente, que es quien recibe el servicio. Además, al anteriormente mencionado objetivo de la OMS 90-90-90, se propuso añadir un cuarto 90 relacionado con la obtención de una adecuada CVRS de las personas que viven con VIH (59). Las medidas de la experiencia reportada por los pacientes (PREM, por su sigla en inglés *Patient Reported Experience Measurements*) permiten medir la evaluación que hacen los pacientes de su experiencia respecto a la interacción con el sistema de salud. En un contexto de pandemia como la causada por la COVID-19 estas medidas son muy relevantes y se suman a las bien establecidas basadas en las variables médicas de resultados como la eficacia clínica, la seguridad, los síntomas clínicos, etc.

1.7 Usabilidad de la tecnología en investigación y satisfacción de los profesionales

La investigación biomédica desarrollada en las últimas dos décadas se ha visto particularmente beneficiada por los avances tecnológicos que, paulatinamente, se han introducido en ámbito médico y de la salud en general. En la Unidad de VIH introducimos el uso de una aplicación web de captura de datos mediante cuadernos electrónicos de datos y encuestas on-line, el REDCap (60), con el objetivo de mejorar la recogida y gestión de datos de investigación. Al fin y al cabo, la calidad de los ensayos depende de la calidad de sus datos (61). Este sistema se ha utilizado en los ensayos clínicos incluidos en la presente tesis. Cuando se introduce un sistema tecnológico nuevo es importante medir la usabilidad por parte de los usuarios y su satisfacción. Según la Organización Internacional para la Estandarización y Comisión Electrotécnica Internacional (ISO/IEC) la usabilidad "es la eficacia, eficiencia y satisfacción con la que un producto permite alcanzar objetivos específicos a usuarios específicos en un contexto de uso específico" (62). Esta definición se centra en la calidad en el uso del sistema, en la efectividad con que el usuario realiza sus

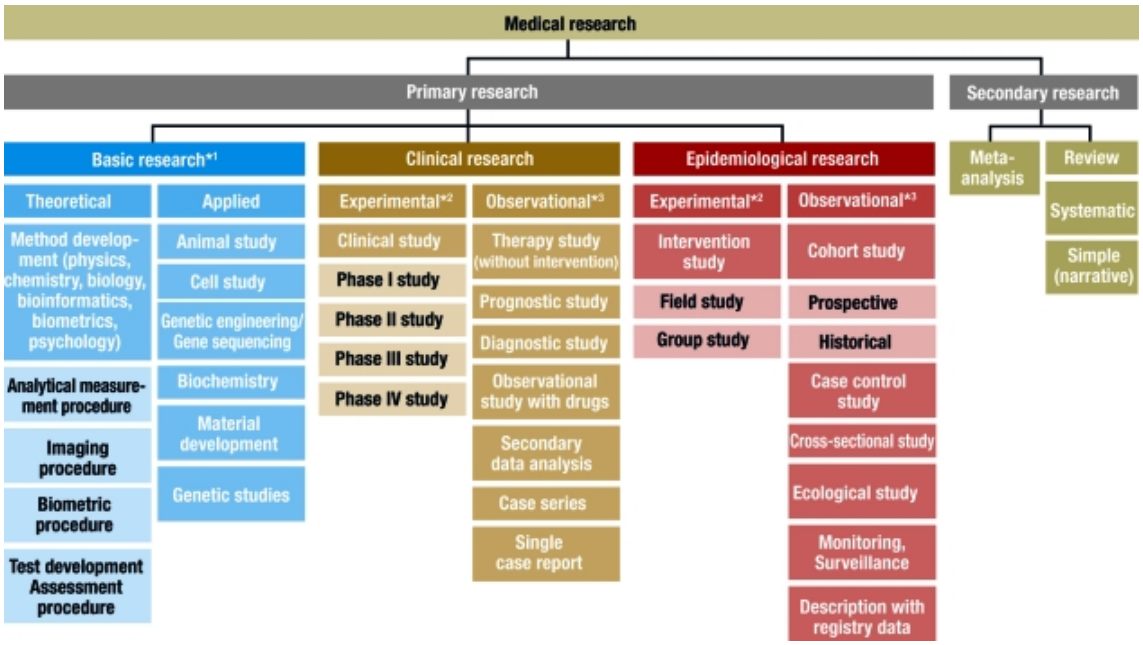
tareas específicas en su contexto específico. Consideramos importante evaluar la usabilidad percibida por parte de los profesionales que utilizan el nuevo sistema, así como su satisfacción ya que una interacción usuario-sistema satisfactoria revierte directamente en la calidad de la investigación.

1.8 Diseños de estudios en investigación biomédica

En la investigación biomédica el diseño del estudio es de fundamental importancia ya que define los métodos y técnicas para seleccionar las unidades de análisis, recoger la información, analizar los resultados e interpretarlos. En la planificación de un proyecto de investigación, una vez definidos los objetivos primarios y secundarios, hay que elegir el diseño de estudio más adecuado con respecto a cada uno de los objetivos. Es posible que distintos objetivos requieran diseños de estudios diferentes, aumentando la complejidad del proyecto.

La figura 12 (63) resume los principales tipos de estudios clasificándolos en dos grandes áreas: investigación primaria, en la cual encontramos los estudios en investigación básica, clínica y epidemiológica; y secundaria, que incluye estudios basados en resultados de la investigación primaria.

Figura 12: Esquema de clasificación de diseños de estudios en investigación médica.



*1, conocida también como investigación experimental;
*2, término análogo: intervencional;
*3, término análogo: no-intervencional o no-experimental

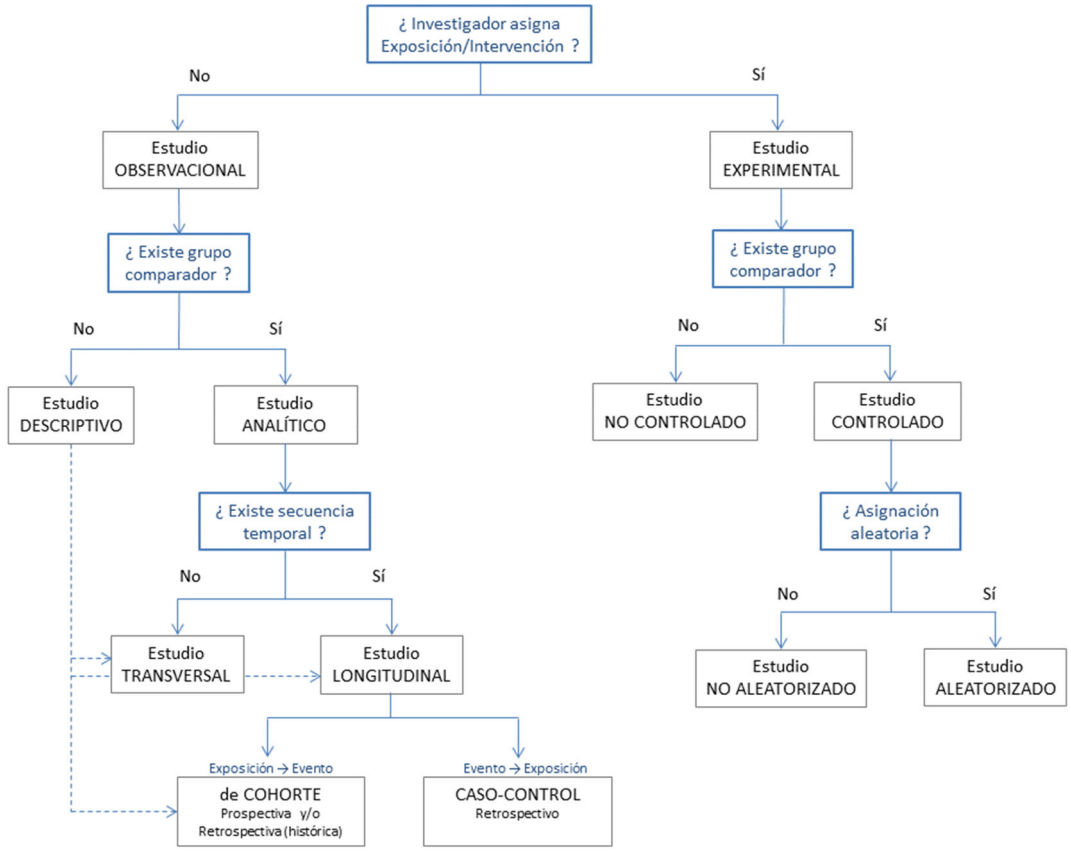
Fuente: Röhrig, B. Dtsch Arztebl Int. 2009;106(15):262-8. (63)

Centrándonos en la investigación primaria clínica y epidemiológica con datos individuales de pacientes, para poder elegir el tipo de estudio más adecuado hay cuatro aspectos que debemos tener en cuenta:

- La finalidad del estudio: analítica (hay grupo comparador) o descriptiva (no se comparan grupos);
- Si existe asignación por parte del equipo investigador de una (o más) exposición o intervención: en caso afirmativo el estudio es experimental, en caso negativo es observacional;
- Si existe una secuencia temporal entre exposición y evento de interés: en caso afirmativo es un estudio longitudinal, en caso negativo es transversal;
- Qué relación cronológica existe entre el inicio del estudio y el desarrollo del evento de interés y exposición: el estudio es retrospectivo si el evento de interés y la exposición ya han ocurrido cuando empieza el estudio; en caso contrario es prospectivo. Los estudios que, con respecto su inicio, se basan en datos prospectivos y también retrospectivos se definen ambispectivos.

En base a mi experiencia, para simplificar el proceso de selección es de mucha ayuda preguntarse primero si los investigadores estamos asignando una exposición o intervención o bien si observamos la práctica clínica habitual, luego si tenemos un grupo comparador, posteriormente la secuencia temporal entre desenlace y exposición y por último la relación cronológica con respecto al inicio del estudio. En el diagrama que he desarrollado (figura 13) para la elección de los diseños de estudio más frecuentes en la investigación que realizamos en la Unidad de VIH, las preguntas aparecen en azul y las características de los estudios en negro.

Figura 13: diagrama de clasificación de los estudios más frecuentes en la investigación que realizamos en la Unidad de VIH con datos individuales de pacientes.



Fuente: gráfica original (Elisa De Lazzari)

Los estudios observacionales descriptivos tradicionalmente son estudios de reporte de caso y de series de casos. En la literatura la tendencia es dejar estos estudios en una caja terminal (64). Sin embargo, en el diagrama los he enlazado (línea discontinua) con la secuencia temporal, ya que pueden ser también estudios transversales o longitudinales, y en

este segundo caso serían únicamente de cohortes. La falta de un grupo comparador no impide realizar estudios observacionales descriptivos de cohorte para estimar, por ejemplo, la incidencia de algún evento de interés, o bien estudios transversales de prevalencia.

En la tabla 3 he resumido las características de los estudios transversales (*cross-sectional*), de cohorte, caso-control y de intervención randomizados.

Tabla 3: resumen de las características de los principales diseños de estudio.

	Diseños de estudio			
	Transversal	Cohorte	Caso-Control	Estudio clínico randomizado
Características principales	Fotografía instantánea de la población en un momento dado. Se pueden estudiar múltiples desenlaces. Permite estimar prevalencia.	Selección individuos en base a la exposición. Adecuado para estudiar exposiciones raras. Permite estimar incidencia, historia natural de una enfermedad. Se pueden estudiar múltiples desenlaces.	Selección individuos en base al desenlace. Adecuado para estudiar desenlaces raros o de latencia larga. Selección de los casos incidentes o prevalentes.	Asignación aleatoria de la exposición/intervención. Se puede aplicar enmascaramiento. Miden la eficacia de una intervención. Prospectivos.
Ventajas	Recolección rápida de datos. Económico en tiempo y dinero (no hay seguimiento). Útil para generar hipótesis.	Se controla la secuencia temporal (exposición anterior al desenlace). Puede ser prospectivo, retrospectivo, ambispectivo. Se pueden estudiar múltiples exposiciones y desenlaces. Se puede controlar por variables confusoras.	Se pueden estudiar múltiples exposiciones. Duración relativamente corta. Menos costoso en tiempo y dinero que el de cohorte.	Asignación aleatoria. Buena validez interna. Estimación de la eficacia de la intervención. Permiten comprobar equivalencia, no-inferioridad.
Desventajas	Si existe exposición, difícil asegurar si es anterior al desenlace. No apto para desenlaces poco recuentes (raros). Dificultoso si desenlace con duración corta.	Pérdidas de seguimiento. No apto para desenlaces poco frecuentes (raros). Poco eficientes si latencia larga del desenlace. Costoso, sobre todo si seguimiento largo. Exposición puede cambiar durante seguimiento.	Exposiciones pueden ser difíciles de identificar. Desenlace único. No apto para exposiciones poco frecuentes (raras). No permite estimar prevalencia.	Criterios de inclusión y exclusión que pueden rebajar la validez externa. Costosos en tiempo y dinero. Pérdida de adherencia. Pérdidas de seguimiento.
Medida de frecuencia	Prevalencia.	Incidencia acumulada. Tasa de incidencia. Riesgo. Odds*.	Odds*.	Proporciones. Riesgo. Odds*.
Medida de asociación	Ratio de prevalencias. Diferencia de prevalencias. Odds Ratio*.	Ratio de riesgos (Risk Ratio, Relative Risk). Riesgo atribuible. Número necesario para tratar. Ratio de tasas de incidencia. Hazard Ratio. Odds Ratio*.	Odds Ratio*.	Diferencia de proporciones e intervalo confianza (a comparar con el margen de equivalencia, no-inferioridad). Ratio de riesgos. Odds Ratio*.

*: En los diseños de cohorte y estudios clínicos randomizados la medida de asociación apropiada es la ratio de riesgos, que puede ser aproximada por el Odds Ratio si el desenlace es poco frecuente. En la mayoría de estudios caso-control el Odds Ratio de la exposición aproxima bien la ratio de riesgos. (65) (66)

Fuente: tabla original (Elisa De Lazzari)

Las principales fuentes de sesgo en los estudios son:

- El sesgo de selección, que puede afectar tanto a la validez interna como externa del estudio. Puede tener su origen en la fase de selección de los participantes si se incluyen participantes sistemáticamente distintos de los de la población objetivo (por ejemplo, por auto-selección). En este caso la validez externa del estudio se ve afectada por falta de representatividad. O bien, puede existir una diferencia sistemática entre los grupos a comparar, en este caso se vería afectada la validez interna. El sesgo puede que se origine en la fase misma de selección de los participantes o bien, en estudios donde hay un período de seguimiento, por altas proporciones de pérdidas de seguimiento que además pueden ser distintas entre los grupos a comparación. Las pérdidas de seguimiento no representan fuente de sesgo si son independientes de la exposición y desenlace.

  En los estudios caso-control, la técnica de selección de los casos debe minimizar el sesgo de supervivencia (falacia de Neyman) (67) que puede ser evitado, por ejemplo, escogiendo los casos incidentes en vez de los prevalentes. La elección de los controles también se debe realizar de forma cuidadosa para no introducir sesgos: los controles deben provenir de la misma población de los casos y deben ser lo más parecidos a los casos excepto que en la exposición. Una técnica para maximizar la homogeneidad entre casos y controles es el emparejamiento (*matching*) según ciertas características que, en caso de asociarse al desenlace, hubiesen podido actuar como confusoras.

  El diseño de estudios aleatorizados, donde la exposición o intervención se asigna de forma aleatoria, minimiza este tipo de sesgo.

- Sesgo de información. Ocurre cuando existen errores sistemáticos en la recopilación y obtención de los datos. En particular, en caso de existir grupos a comparar, la información se obtiene de forma sistemáticamente diferente entre grupos. Se puede

originar a nivel de observador, es decir quien mide los datos (sesgo del observador), o a nivel de los mismos participantes del estudio (sesgo del respondedor), o a nivel de herramientas de medición como pueden ser cuestionarios, balanzas, técnicas de laboratorio, etc (sesgo de medición). Este último sesgo puede ser controlado utilizando herramientas validadas o validándolas previamente al comienzo del estudio. El sesgo del observador puede ocurrir en las cohortes prospectivas si el hecho de conocer el estado de exposición afecta la clasificación del estado del desenlace; en las cohortes retrospectivas, cuando el conocimiento del desenlace afecta la clasificación de la exposición, hecho que puede llevar a un sesgo sistemático de clasificación errónea.

La clasificación errónea de la exposición o del estado del desenlace puede ser aleatoria o no aleatoria. En caso de ser aleatoria las estimaciones no serán sesgadas, pero podrían subestimar la intensidad real de la asociación entre exposición y desenlace (riesgo relativo, odds ratio, hazard ratio, …) acercándolas al valor nulo. En el caso de no ser aleatorias, la clasificación de la exposición depende del conocimiento del desenlace o, al revés, la clasificación del desenlace depende del conocimiento de la exposición, y es debida generalmente al mismo observador o al respondedor. Plantear un estudio ciego es una técnica para reducir este tipo de sesgo.

Hipótesis

Elena Cornaro Piscopia *(Filósofa, 1646-1684) y* ***Juliana Morell*** *(Teóloga y traductora, 1594-1653). Fueron las primeras mujeres en obtener un doctorado universitario. Elena, de Vencia, obtuvo el doctorado en filosofía por la Universidad de Padua (Italia) y Juliana, de Barcelona, en Derecho por la Universidad de Aviñón.*

"No hay viento favorable para el que no sabe dónde va." *Lucio Anneo Séneca (Filósofo, 4 a. C. - 65 d. C.)*

"Si un hombre comienza con certezas, terminará en dudas; pero si se contenta con comenzar con dudas, terminará en certezas." *Francis Bacon (Filósofo, 1561-1626)*

1. La documentación sobre las características poblacionales asociadas a las pautas antirretrovirales dobles (2DR) en la vida real ayudará a conocer el perfil necesidades no cubiertas por las pautas antirretrovirales triples (3DR) actuales y qué antirretrovirales pueden cubrirlas mejor en las personas con VIH.

2. En las personas con VIH con supresión viral sostenida en terapia antirretroviral combinada, la terapia dual con raltegravir más lamivudina puede ser una opción de simplificación factible, capaz de mantener la supresión viral y bien tolerada.

3. En las personas con VIH en TARV triple y con supresión viral, el régimen dual con dolutegravir/lamivudina puede ser una opción de cambio antirretroviral conveniente y eficaz. La alta barrera genética a la resistencia de dolutegravir se combina con las ventajas de seguridad y coste de la lamivudina.

4. En la población diana del punto 3, consideramos que el uso de ciencias ómicas es una herramienta que puede permitir una mejor comprensión de la fisiopatología inmunometabólica asociada al cambio del tratamiento antirretroviral triple en una pauta 2DR con dolutegravir más lamivudina.

5. La epidemia de COVID-19 probablemente ha tenido un impacto en la atención a las personas con VIH y en la prevención de la infección por VIH y otras enfermedades de transmisión sexual. El conocimiento del impacto puede ayudar a estar mejor preparados para responder a los efectos de nuevas olas epidémicas y a diseñar estrategias de mitigación.

6. Conocer la experiencia de las personas con VIH con respecto a la atención sanitaria recibida puede ayudar a mejorar el abordaje y atención a los pacientes.

7. El cuaderno electrónico de recogida de datos es una herramienta utilizada por distintos profesionales en el ámbito de la investigación. La evaluación de la interacción entre el sistema y el usuario que lo utiliza puede ayudar a mejorar el trabajo del usuario y tener un efecto positivo en la calidad de los datos y, por ende, en la investigación.

Objetivos

Rosalind Franklin *(Química, 1920-1958). Fue la primera persona en desvelar la estructura molecular a doble hélice del ADN y ARN.*

"Toda la vida es un experimento. Cuantos más experimentos hagas, mejor." *Ralph Waldo Emerson (Escritor y filósofo, 1803-1882)*

"No me importa caminar. No hay distancias cuando se tiene un motivo." *Jane Austen (Escritora, 1775-1817)*

Objetivo general

Abordaré la optimización de la atención a las personas que viven con una infección por VIH, mediante:

- el estudio de nuevas estrategias para la simplificación del tratamiento antirretroviral oral,
- la evaluación de la inesperada epidemia de COVID-19 en la prevención y atención del VIH y otras infecciones de transmisión sexual,
- la medición de la experiencia de las personas que viven con VIH con respecto a la atención sanitaria recibida como estrategias de mejora de su calidad de vida relacionada con la salud, y
- la satisfacción de los profesionales de la salud involucrados en investigación que utilizan un nuevo sistema informatizado para recopilar y manejar datos de salud

Objetivos relacionados con la simplificación del tratamiento antirretroviral:

1) En una gran cohorte de personas que viven con el VIH: evaluaré las características clínicas asociadas con el uso de regímenes basados en dos fármacos (2DR) y los factores asociados con antirretrovirales específicos en 2DR; también, evaluaré la efectividad y seguridad del tratamiento 2DR con dolutegravir/lamivudina y la tasa de discontinuación.

2) En un ensayo clínico piloto, valoraré la factibilidad, la eficacia virológica y tolerabilidad de la terapia dual con raltegravir/lamivudina en personas que viven con VIH con supresión viral sostenida en terapia antirretroviral combinada.

3) En un ensayo clínico con personas que viven con VIH virológicamente suprimidas, evaluaré la no-inferioridad de la terapia dual con dolutegravir/lamivudina con respecto a la terapia triple en cuanto a la eficacia virológica y seguridad.

4) En el ensayo clínico mencionado en el punto 3), realizaré una aproximación multi-ómica, que incluya proteómica, metabolómica y lipidómica, para tener una mejor comprensión de las vías metabólicas que podrían verse afectadas en la simplificación terapéutica a dolutegravir más lamivudina.

Objetivos relacionados con la atención a las personas que viven con VIH y prevención del VIH y otras infecciones de trasmisión sexual:

5) Evaluaré el impacto de las epidemias de COVID-19 en la prevención y atención clínica de las personas que viven con VIH y el diagnóstico de la infección por el VIH y otras enfermedades de transmisión sexual, en el ámbito del Hospital Clínic de Barcelona.

6) Investigaré la calidad percibida de la atención recibida por las personas que viven con VIH en la Unidad de VIH del Hospital Clínic, para conocer el grado de satisfacción de los usuarios con el cuidado que se les presta e identificar posibles áreas de mejora.

Objetivos relacionados con el uso de la tecnología y la satisfacción de los profesionales de la investigación en VIH:

7) Evaluaré la usabilidad del cuaderno electrónico de recogida de datos (CRDe) que se implementará en el sistema REDCap y la satisfacción de los profesionales usuarios e identificar posibles áreas de mejora.

Material, Métodos y Resultados

Florence Nightingale *(Enfermera y estadística, 1820 -1910). Pionera de la enfermería moderna. Aplicó sus conocimientos de estadística a la epidemiología y a la estadística sanitaria. Fue la primera mujer admitida en la Royal Statistical Society británica, y miembro honorario de la American Statistical Association.*

"Mide lo que puedas medir, y lo que no puedas medir, hazlo medible." *Galileo Galilei* *(Astrónomo, 1564-1642)*

"Solo puedes analizar los datos que tienes. Sé estratégico sobre qué reunir y cómo almacenarlo." *Maria Skłodowska-Curie* *(Física y química, 1867-1934)*

"La estadística es la gramática de la ciencia." *Karl Pearson* *(Matemático, 1857-1936)*

Trabajo 1

Factors associated with the use and composition of two-drug regimens in a large single-centre HIV cohort.

Elisa de Lazzari, Ana Gonzalez-Cordon, Alexy Inciarte, Ainoa Ugarte, Lorena de la Mora, Maria Martinez-Rebollar, Montserrat Laguno, Juan Ambrosioni, Berta Torres, Josep Mallolas, Jose L. Blanco, Jose M. Miro and Esteban Martinez.
J Antimicrob Chemother. 2021; 76: 2988–2992.

Resumen

Objetivos: Se evaluaron las características clínicas asociadas al uso de regímenes de dos fármacos (2DRs) y los factores asociados con antirretrovirales específicos en 2DRs en una gran cohorte de VIH de un solo centro.

Métodos: Análisis retrospectivo de las características demográficas, del VIH y eventos SIDA, prescripción de antirretrovirales, fallo virológico y pruebas de resistencia genotípica, y resultados de laboratorio de todas las personas adultas con VIH seguidos prospectivamente en el Hospital Clínico de Barcelona que recibían una pauta de tres fármacos (3DR) o de dos (2DR) en enero de 2020. Se evaluaron los factores asociados a la probabilidad de recibir 2DR en relación con 3DR mediante un modelo de regresión logística, ajustado por edad, sexo y año de diagnóstico del VIH. Se aplicó la misma metodología para identificar los factores asociados a la prescripción de regímenes basados en inhibidores de la integrasa o en inhibidores de la proteasa en las personas que recibieron 2DR.

Resultados: Hubo 3432 (88%) PVH que recibieron 3DR y 463 (12%) que recibieron 2DR. En el modelo final ajustado, ≥2 fracasos virológicos previos, mutaciones de resistencia previas, diagnóstico previo de SIDA, mayor tiempo en el régimen actual, mayor colesterol total y triglicéridos y menor hemoglobina basal fueron factores independientes asociados con 2DR. La mayoría de los 2DR incluían un inhibidor de la integrasa y/o un IP. En las personas que recibieron 2DR, identificamos factores independientes asociados a la inclusión de

inhibidores de la integrasa (colesterol HDL inferior) o IP (SIDA anterior, mutaciones de resistencia genotípica anteriores y menor ratio CD4/CD8).

Conclusiones: En esta gran cohorte unicéntrica de personas con VIH, un peor estado cardiometabólico o una mayor resistencia archivada fueron factores clave asociados a la inclusión de inhibidores de la integrasa o de la proteasa, respectivamente, en los regímenes 2DR.

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Factors associated with the use and composition of two-drug regimens in a large single-centre HIV cohort

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Objectives: We aimed to assess the clinical characteristics associated with the use of two-drug regimens (2DRs) and the factors associated with specific antiretrovirals in 2DRs in a large single-centre HIV cohort.

Methods: Retrospective analysis of demographics, HIV characteristics and AIDS events, antiretroviral prescription, virological failure and genotypic resistance testing, and laboratory results from all adult people with HIV (PWH) prospectively followed at the Hospital Clinic of Barcelona who were receiving a 3DR or a 2DR in January 2020. We assessed factors associated with the probability of receiving 2DRs relative to three-drug regimens (3DRs) using a logistic regression model, controlling for age, sex and year of HIV diagnosis. The same methodology was applied to identify factors associated with the prescription of integrase inhibitor-based regimens or PI-based regimens among PWH receiving 2DRs.

Results: There were 3432 (88%) PWH receiving 3DRs and 463 (12%) receiving 2DRs. In the final adjusted model, $\geq$2 previous virological failures, previous resistance mutations, previous AIDS diagnosis, longer time on current regimen, higher total cholesterol or triglycerides and lower baseline haemoglobin were independent factors associated with 2DRs. The majority of 2DRs included an integrase inhibitor or/and a PI. We identified independent factors associated with the inclusion of integrase inhibitors (lower HDL cholesterol) or PIs (prior AIDS, prior genotypic resistance mutations and lower CD4/CD8 ratio) in the 2DR.

Conclusions: In this large single-centre HIV cohort, a worse cardiometabolic status or more archived resistance were key factors associated with inclusion of integrase inhibitors or PIs, respectively, in 2DRs.

Introduction

Major guidelines have long-established three-drug regimens (3DRs) consisting of two NRTIs plus a third drug as the gold standard of ART.[1–3] Antiretroviral drugs have improved over time, becoming more effective, simpler and better tolerated. However, for some patients, standard 3DRs may still be challenging because of antiretroviral-related adverse effects, negative impact on comorbidities, risk of interactions, archived resistance or other reasons, therefore justifying the need for an individualized therapeutic approach with fewer than three drugs.[4,5] PI[6] and dolutegravir[7] monotherapy are inferior to standard triple therapy and are discouraged, but the efficacy of two-drug regimens (2DRs) has been confirmed in clinical trials[8] and they have been recently incorporated in major guidelines.[1–3] Recent analyses from EuroSIDA and RESPOND cohorts suggest that virological, immunological and clinical outcomes in people with HIV (PWH) on 2DRs are similar to PWH on 3DRs.[9,10] Knowing the characteristics associated with 2DRs in real life will help to better define the profile of patients who are satisfactorily taking them. We aimed to assess the clinical characteristics associated with the use of 2DRs and the factors associated with specific antiretrovirals in 2DRs in a large single-centre HIV cohort.

Methods

Participants

This retrospective analysis used registered data from all adult PWH prospectively followed at the Hospital Clinic of Barcelona (Spain) who were receiving combination ART with a 3DR or a 2DR in January 2020, when the administrative database was locked for the purpose of this analysis. PWH with last clinical visit before January 2019 were considered lost to follow-up and excluded from the analysis. In our centre, PWH data are routinely registered into a clinical history database approved by the Local Institutional Review Board that includes detailed information on demographics, HIV characteristics and AIDS events, antiretroviral

prescription, virological failure and genotypic resistance testing and laboratory results.

Ethics

According to current Spanish regulations, the study was classified as a post-authorization study with a non-prospective design by the Spanish Agency for Medicine and Health Products;[11] it was approved by the Local Institutional Review Board and informed consent was not required.

Statistical methods

Summary statistics of quantitative and qualitative variables were reported using mean and SD or median and IQR, using frequency and percentage, respectively. Comparisons between groups were based on *t*-test, Wilcoxon rank sum, chi-squared and Fisher's exact tests. First, we described the characteristics of all PWH and compared them in those receiving 3DRs versus 2DRs. We then compared the patients with missing values with those with valid values for all variables in order to identify whether there was a pattern in whether values were missing. Factors associated with the probability of receiving a 2DR relative to a 3DR were assessed using a logistic regression model, controlling for age, sex and also for the characteristic capturing the mechanism of missing values (year of HIV positivity). Considering clinical judgement and statistical criteria (*P* value < 0.1), variables were selected for the final model in a stepwise fashion. Classification tables and ROC curves were generated by 10-fold cross-validation to avoid an over-optimistic estimate of predictive performance.

Because the drugs more commonly used in 2DRs in this cohort were PIs and integrase inhibitors, the same methodology was applied to identify factors associated with the prescription of integrase inhibitor-based regimens or PI-based regimens among PWH receiving 2DRs. We primarily report risk factors considering two non-exclusive categories: integrase inhibitor-containing versus -non-containing regimens, and PI-containing versus -non-containing regimens, but we explored the factors associated with 2DRs based on both PIs and integrase inhibitors to see whether this group represented a special population. The statistical package used was Stata Release 15 (StataCorp 2017, College Station, TX, USA).

Results

Population characteristics of 2DRs versus 3DRs

There were 3895 PWH included in this analysis: 3432 (88%) receiving 3DRs and 463 (12%) receiving 2DRs. The populations were well distinguished according to demographics. PWH on 2DRs were significantly older [50 years (SD = 11), $n = 463$ versus 44 years (SD = 11), $n = 3432$; $P < 0.0001$] and more commonly female [$n = 98$ (21%) versus $n = 543$ (16%); $P = 0.0036$].

Differences were also evident regarding HIV characteristics and AIDS events, virological failure and genotypic resistance testing. PWH receiving 2DRs had been more commonly infected through injecting drug use [$n = 93$ (21%) versus $n = 385$ (12%); $P < 0.0001$], longer diagnosed with HIV [23 years (IQR 14–28), $n = 458$ versus 13 years (IQR 8–21), $n = 3322$; $P < 0.0001$], more commonly diagnosed with AIDS events [$n = 139$ (30%) versus $n = 502$ (15%); $P < 0.0001$], less commonly on their initial antiretroviral regimen [$n = 11$ (2%) versus $n = 596$ (17%); $P < 0.0001$], longer exposed to ART [17 years (IQR 8–22), $n = 463$ versus 8 years (IQR 4–15), $n = 3432$; $P < 0.0001$], longer on their current regimen [3 years (IQR 2–3), $n = 463$ versus 2 years (IQR 1–3), $n = 3432$; $P < 0.0001$], more commonly had prior virological failure [$n = 230$ (49%) versus $n = 744$ (22%); $P < 0.0001$] and resistance mutations detected [$n = 261$ (56%) versus $n = 1161$ (34%); $P < 0.0001$] but also more commonly had undetectable plasma HIV RNA at the time of initiation of their current regimen [$n = 404$ (87%) versus $n = 2743$ (81%); $P = 0.0006$].

Differences were also found in several laboratory parameters. PWH on 2DRs had higher metabolic parameters at the time of initiation of their current drug regimen: total cholesterol [192 mg/dL (IQR 166–223), $n = 449$ versus 177 mg/dL (IQR 150–240), $n = 3251$; $P < 0.0001$], LDL cholesterol [117 mg/dL (IQR 94–143), $n = 444$ versus 108 mg/dL (IQR 87–131), $n = 3251$; $P < 0.0001$], HDL cholesterol [43 mg/dL (IQR 36–53), $n = 449$ versus 42 mg/dL (IQR 35–51), $n = 3248$; $P = 0.0241$], triglycerides [134 mg/dL (IQR 96–203), $n = 449$ versus 108 mg/dL (IQR 77–157), $n = 3251$; $P < 0.0001$] and glucose [95 mg/dL (IQR 88–105), $n = 449$ versus 93 mg/dL (IQR 85–101), $n = 3253$; $P = 0.0001$]. In contrast, PWH on 2DRs had significantly lower haemoglobin at the time of initiation of their current drug regimen [147 g/L (IQR 137–154), $n = 449$ versus 148 g/L (IQR 139–157), $n = 325$; $P = 0.0015$].

Three thousand three hundred and seventy-five (86.6%) PWH with no missing data contributed to the multivariate analysis of factors associated with the use of 2DRs. In the final model adjusted for age, gender and year of HIV diagnosis, the following independent factors were identified: two or more previous virological failures (adjusted OR 1.69; 95% CI: 1.24–2.31; $P = 0.0039$), previous resistance mutations (adjusted OR 2.15; 95% CI: 1.70–2.72; $P < 0.0001$), previous AIDS diagnosis (adjusted OR 1.34; 95% CI: 1.03–1.74; $P = 0.0274$), longer time on current regimen (adjusted OR 1.14 per year increase; 95% CI: 1.07–1.21; $P = 0.0001$), higher total cholesterol (adjusted OR 1.32 per 50 unit increase; 95% CI: 1.14–1.53; $P = 0.0003$) or triglycerides [adjusted OR 1.34 per natural log-transformed (Ln) triglycerides unit increase; 95% CI: 1.08–1.66; $P = 0.0074$] at the initiation of the current regimen and lower haemoglobin at the initiation of the current regimen (adjusted OR 0.18 per Ln haemoglobin unit increase; 95% CI: 0.06–0.51; $P = 0.0013$).

Types of 2DRs

There were eight types of regimens identified among the 463 (12%) PWH receiving 2DRs in the cohort. The most common ones were one integrase inhibitor plus one NRTI ($n = 112$), followed by one integrase inhibitor plus one PI ($n = 109$), one PI plus one NRTI ($n = 82$), and one integrase inhibitor plus one NNRTI ($n = 80$). Other less common 2DRs consisted of one PI plus one NNRTI ($n = 49$), one PI plus maraviroc ($n = 24$), one integrase inhibitor plus maraviroc ($n = 5$), and two NRTIs ($n = 2$). Dolutegravir ($n = 199$; 65%) ranked first among integrase inhibitors, followed by raltegravir ($n = 107$; 35%). Darunavir ($n = 240$; 91%) was the most common among PIs, followed by atazanavir ($n = 16$, 6%) and lopinavir ($n = 8$; 3%). Lamivudine ($n = 190$; 96%) represented the overwhelming majority of NRTIs, followed by tenofovir ($n = 8$; 4%). Rilpivirine ($n = 74$; 57%) was the most common NNRTI, followed by etravirine ($n = 49$; 38%) and nevirapine ($n = 6$; 5%). The vast majority of patients ($n = 452$; 98%) were not on their first antiretroviral regimen.

Factors associated with integrase inhibitor-based 2DRs

Among PWH on 2DRs without missing data, there were 291 PWH prescribed a regimen containing integrase inhibitors and 150

prescribed a regimen not containing integrase inhibitors contributing to this analysis. Lower HDL cholesterol at the initiation of 2DR and longer regimen duration were identified as independent factors associated with an integrase inhibitor in the 2DR (Table 1).

Factors associated with PI-based 2DRs

Among patients on 2DRs without missing data, there were 251 PWH prescribed a regimen containing PIs and 188 prescribed a regimen not containing PIs contributing to this analysis. Prior AIDS, prior genotypic resistance mutations, lower CD4/CD8 ratio and shorter regimen duration were identified as independent factors associated with a PI in the 2DR (Table 2). Having previous mutations, previous virological failure and AIDS events were also factors identified when we assessed the population receiving 2DRs based on both PIs and integrase inhibitors.

Discussion

In our cohort, 1 out of 10 PWH receiving combination ART had 2DRs. Relative to 3DRs, PWH on 2DRs were older and more virologically suppressed, with a longer history of HIV infection and exposure to ART, prior AIDS, prior virological failure and genotypic resistance mutations, higher plasma lipids and lower haemoglobin. These findings are in agreement with previous reports showing that 2DRs have been preferentially addressed to older PWH with a good HIV status but limited therapeutic options because of resistance, cumulative antiretroviral toxicity or concomitant comorbidities.[5,9,12,13]

The vast majority of 2DRs in this cohort included an integrase inhibitor, a PI or both. We identified different profiles of factors associated with having either an integrase inhibitor or a PI included in the 2DR. Lower baseline HDL cholesterol and longer duration were independent factors associated with having an integrase inhibitor-containing 2DR. Prior AIDS, prior genotypic resistance mutations, lower CD4/CD8 ratio and shorter duration were independent factors associated with having a PI-containing 2DR. The differences in the duration of the 2DR prescription may be related, at least in part, to the better tolerability and lower risk of drug–drug interactions of integrase inhibitors compared with PIs. Use of PIs was associated with a worse HIV status and prior resistance mutations. Use of integrase inhibitors was associated with lower baseline HDL cholesterol. Low HDL cholesterol is a criterion of metabolic syndrome and a marker of insulin resistance and cardiovascular risk.[14] We also explored the factors associated with 2DRs based on both PIs and integrase inhibitors, which included having previous mutations, previous virological failure and AIDS events. Therefore, it was the presence of prior virological failure with resistance mutations that was related to inclusion of PIs with or without integrase inhibitors.

In this large single-centre HIV cohort, 2DRs had been tailored according to the clinical characteristics of PWH and usually contained PIs or/and integrase inhibitors. A worse cardiometabolic status or more archived resistance were key factors

Table 1. Univariate and multivariate analysis of factors associated with the inclusion of an integrase inhibitor among patients prescribed a 2DR, adjusted for age at the initiation of two-drug therapy and gender

	Univariate analysis		Multivariate analysis	
Factor	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Presumed route of HIV infection MSM	0.60 (0.29–1.24)	0.1680	—	
Years since HIV diagnosis	0.97 (0.94–1.01)	0.1608	—	
Prior AIDS	1.58 (0.80–3.14)	0.1881	—	
Years on ART	1.02 (0.98–1.07)	0.3089	—	
Years on 2DR	1.26 (1.01–1.57)	0.0387	1.26 (1.00–1.58)	0.0459
Previous blips[a]	0.75 (0.43–1.33)	0.3275	—	
Previous virological failure	1.63 (0.90–2.93)	0.1048	—	
Prior genotypic resistance mutations	0.86 (0.50–1.47)	0.5772	—	
CD4 cells[b,c]	0.98 (0.94–1.02)	0.3233	—	
CD4/CD8 ratio[a,c]	0.89 (0.51–1.54)	0.6789	—	
Plasma HIV-1 RNA <50 copies/mL[c]	0.86 (0.38–1.96)	0.7205	—	
Total cholesterol[b,c]	0.68 (0.49–0.94)	0.0199	—	
LDL cholesterol[b,c]	0.69 (0.47–1.03)	0.0685	—	
HDL cholesterol[b,c]	0.27 (0.10–0.71)	0.0077	0.27 (0.10–0.73)	0.0092
Ln triglycerides[a,c]	1.23 (0.75–2.02)	0.4061	—	
AST[b,c]	1.59 (0.55–4.64)	0.3938	—	
Creatinine[a,c]	1.17 (0.53–2.62)	0.6976	—	
Ln haemoglobin[a,c]	0.26 (0.02–3.73)	0.3244	—	
Ln glucose[a,c]	0.75 (0.14–4.08)	0.7417	—	

[a]Adjusted OR per unit increase.
[b]Adjusted OR per 50 unit increase.
[c]Laboratory values at the initiation of two-drug therapy.

Table 2. Univariate and multivariate analysis of factors associated with the inclusion of a PI among patients prescribed a 2DR, adjusted for age at the initiation of two-drug therapy and gender

	Univariate analysis		Multivariate analysis	
Factor	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Presumed route of HIV infection MSM	0.63 (0.37–1.08)	0.0947	—	
Years since HIV diagnosis	0.94 (0.91–0.97)	0.0001	—	
Prior AIDS	2.16 (1.30–3.56)	0.0027	1.80 (1.01–3.20)	0.0474
Years on ART	1.04 (1.01–1.08)	0.0190	—	
Years on 2DR	0.82 (0.70–0.96)	0.0154	0.78 (0.66–0.93)	0.0051
Previous blips[a]	1.29 (1.05–1.59)	0.0160	—	
Previous virological failure	1.46 (1.22–1.76)	0.0001	—	
Prior genotypic resistance mutations	5.35 (3.34–8.58)	<0.0001	6.03 (3.61–10.08)	<0.0001
CD4 cells[b,c]	0.97 (0.94–1.00)	0.0471	—	
CD4/CD8 ratio[a,c]	0.41 (0.25–0.67)	0.0004	0.51 (0.29–0.89)	0.0168
Plasma HIV-1 RNA <50 copies/mL[c]	0.37 (0.18–0.76)	0.0063	—	
Total cholesterol[b,c]	1.34 (1.03–1.74)	0.0266	—	
LDL cholesterol[b,c]	1.30 (0.96–1.77)	0.0851	—	
HDL cholesterol[b,c]	1.47 (0.66–3.27)	0.3500	—	
Ln triglycerides[a,c]	1.45 (0.98–2.14)	0.0654	—	
AST[b,c]	0.80 (0.41–1.55)	0.5093	—	
Creatinine[a,c]	0.66 (0.36–1.19)	0.1671	—	
Ln haemoglobin[a,c]	0.68 (0.11–4.04)	0.6694	—	
Ln glucose[a,c]	3.24 (0.84–12.57)	0.0886	—	

[a]Adjusted OR per unit increase.
[b]Adjusted OR per 50 unit increase.
[c]Laboratory values at the initiation of two-drug therapy.

associated with the inclusion of integrase inhibitors or PIs, respectively, in 2DRs.

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Transparency declarations

A. Gonzalez-Cordon, A. Inciarte, M. Martinez-Rebollar, M. Laguno, J. Ambrosioni, B. Torres, J. Mallolas, J. L. Blanco, J. M. Miro and E. Martinez have received honoraria for lectures or advisory boards and their institution has received research grants from Gilead, Janssen, MSD and ViiV. E. de Lazzari, A. Ugarte and L. de la Mora: none to declare.

Author contributions

E. Martinez designed the study. E. de Lazzari undertook the statistical analyses. All authors were involved in the interpretation of data. E. Martinez and E. de Lazzari drafted the manuscript. All authors critically reviewed and subsequently approved the final version.

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Trabajo 2

Clinical use and effectiveness of Dolutegravir and lamivudine: a long-term, real-world, retrospective study.

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Resumen

Objetivos: El uso de dolutegravir/lamivudina se basa en ensayos clínicos sólidos; sin embargo, los datos del mundo real siguen siendo limitados. Con el presente estudio pretendemos proporcionar datos sobre el uso clínico y la efectividad de dolutegravir/lamivudina en personas con VIH en un escenario real.

Métodos: Estudio retrospectivo, unicéntrico y observacional. Incluimos a todos los adultos que recibieron dolutegravir/lamivudina desde noviembre de 2014. Se describieron todas las variables demográficas, virológicas e inmunológicas al inicio del estudio y se evaluó la efectividad on-treatment (OT), por ITT modificado (mITT) e ITT, en aquellas personas que alcanzaron los 6 y 12 meses de seguimiento (M6 y M12).

Resultados: De las 1058 personas con VIH, 9 eran naïves al tratamiento; el análisis final incluyó a 1049 personas con experiencia previa al tratamiento. La mediana de seguimiento [rango intercuartíl (RIC)] fue de 1 (0.3; 1.6) años, con 81% y 63% de personas que alcanzaron M6 y M12, respectivamente. El uso más prolongado de dolutegravir/lamivudina fue de 7.4 años. Por OT, mITT e ITT, la proporción de personas con ARN-VIH < 50 copias/ml fue 97%, 92% y 81% (M6) y 98%, 90% y 80% (M12), respectivamente. Mujeres [riesgo relativo ajustado, aRR (IC 95%): 1.69 (1.19; 2.40)]; régimen inmediato previo basado en IP [aRR (IC 95%): 1.67 (1.09; 2.56)]; y ARN-VIH≥ 50 copias/ml en el momento de empezar la pauta con

dolutegravir/lamivudina [aRR (IC 95%): 3.36 (2.32; 4.88] se asociaron de forma independiente con la falta de efectividad a los 12 meses; otras variables demográficas, inmunológicas y virológicas como las sustituciones previas de M184V/I o el fracaso virológico, no presentaron esa asociación. Del total, 944 (90%) continuaron con dolutegravir/lamivudina. La razón conocida más frecuente de discontinuación fue la toxicidad [48 (46%)].

Conclusiones: En nuestra experiencia en el mundo real, las tasas de supresión virológica fueron altas para las personas con experiencia previa al tratamiento que recibieron dolutegravir/lamivudina; sin embargo, identificamos subgrupos con un mayor riesgo de falta de efectividad en el M12, que pueden beneficiarse de un seguimiento más cercano.

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Journal of Antimicrobial Chemotherapy

Clinical use and effectiveness of dolutegravir and lamivudine: a long-term, real-world, retrospective study

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Background: The use of dolutegravir/lamivudine is based on solid clinical trials; however, real-world data remain limited.

Objectives: To provide data on the clinical use and effectiveness of dolutegravir/lamivudine in persons with HIV in a real-world scenario.

Patients and methods: Retrospective, single-centre and observational study. We included all adults starting dolutegravir/lamivudine since November 2014. We reported all demographic, virological and immunological variables at baseline and assessed effectiveness [on treatment (OT), modified ITT (mITT) and ITT in those persons who reached 6 and 12 month follow-ups (M6 and M12).

Results: Of the 1058 persons, 9 were treatment-naive; the final analysis included 1049 treatment-experienced people with HIV. Median (IQR) follow-up was 1 (0.3–1.6) years, with 81% and 63% persons reaching M6 and M12, respectively. The longest use of dolutegravir/lamivudine was 7.4 years. Per OT, mITTand ITT, HIV-RNA < 50 copies/mLwas 97%, 92% and 81% (M6) and 98%, 90% and 80% (M12), respectively. Females [adjusted risk ratio, aRR (95% CI): 1.69 (1.19–2.40)]; immediate, previous PI-based regimen [aRR (95% CI): 1.67 (1.09–2.56)]; and viral load (VL) ≥ 50 copies/mL at dolutegravir/lamivudine initiation [aRR (95% CI): 3.36 (2.32–4.88)] were independently associated with lack of effectiveness at M12; other demographic, immunological and virological variables like previous M184V/I substitutions or virological failure, were unrelated. Of the total, 944 (90%) continued dolutegravir/lamivudine. The most frequent known reason for discontinuation was toxicity [48 (46%) cases].

Conclusions: In our real-world experience, virological suppression rates were high for treatment-experienced persons on dolutegravir/lamivudine; however, we identified subgroups with a higher risk of lack of effectiveness at M12, who may benefit from closer follow-ups.

Introduction

Current ART regimens recommended for both treatment-naive (TN) and treatment-experienced (TE) people with HIV include the combination of two or more drugs from the main yet different drug families [integrase strand-transfer inhibitors (InSTIs), NRTIs, NNRTIs and PIs].[1–3] Given the higher efficacy and favourable safety profile compared with other families, InSTI-based regimens currently represent the preferred combinations for ART initiation and simplification.[1–3] The association of dolutegravir (an InSTI) plus lamivudine (an NRTI) in treating persons with HIV has shown non-inferiority compared with three-drug regimens in clinical trials[4–6] with a follow-up reaching 3 years in both TN[7] and TE persons.[8]

Different real-world studies have also tested dolutegravir/lamivudine.[9–14] Real-world studies complement information provided by clinical trials and provide a more accurate view of the clinical use and effectiveness of the different treatments prescribed. This varies far from the controlled conditions of clinical trials, in which adherence to therapy is promoted throughout

the study. Moreover, given these favourable results in clinical trials, real-world use of dolutegravir/lamivudine has expanded beyond the initially approved indications. In a recent meta-analysis of real-world studies, high virological suppression was achieved and maintained at 48 weeks in many different persons with HIV, with good tolerance of dolutegravir/lamivudine, small impact on comorbidities and a low dropout rate due to side effects.[15] Studies with long-term follow-up are, however, lacking. In addition, the benefits of simplifying treatment regimens not only lie in maintaining the same efficacy with fewer drugs, which reduces the possibility of adverse effects; such a change could also result in economic savings.[16] Considering the near-normal life expectancy of persons with HIV following long-term ART compared with the general population[17] and the current requirement of lifelong ART, providing ART with the highest possible efficacy and the lowest possible toxicity may represent important cost reductions.

The aim of this study is to determine the real clinical use and effectiveness of dolutegravir/lamivudine in persons with HIV in a tertiary referral centre for HIV/AIDS over a long period (since 2014 to current date).

Patients and methods

Hospital Clinic is a community hospital that provides health and care services for a population of 600000 inhabitants in the city of Barcelona (Spain). At the same time, the institution operates as a reference care facility for specific diseases, such as HIV infections for all of Catalonia (https://www.clinicbarcelona.org/en). The hospital currently provides ambulatory care, ART and hospitalization, if necessary, for more than 6000 adults with HIV. Indeed, Hospital Clinic is the largest HIV care centre in Spain. It has been also providing post-exposure prophylaxis for HIV since 2003, and pre-exposure prophylaxis (PrEP) for HIV since its approval by the Spanish National Health System in November 2019.

This was a single-centre, observational and retrospective study. The study population included all people living with HIV who had received a dolutegravir/lamivudine regimen (either separately as dolutegravir+ lamivudine or co-formulated dolutegravir/lamivudine) since November 2014—initiation date of clinical use of these combined drugs—until 30 June 2022 (corresponding to closing of the dataset). Furthermore, TN individuals were very few (1%) and excluded from the study. We provide information on demographics, HIV-related characteristics and comorbidities, as well as previous ART regimens and reasons for discontinuation of the last previous ART. We performed the whole study with information collected for routine clinical work and entered in our database.

The main endpoint of this study was to determine the proportion of persons with HIV with an undetectable viral load (VL, defined as VL < 50 RNA copies/mL) at 6 and 12 month follow-ups (M6 and M12, respectively, with a 3 month window), if reached. Additional secondary objectives were to evaluate both safety of this ART regimen and suppression rates in those individuals with known resistance substitutions (such as M184V/I for lamivudine and InSTI substitutions).

We assessed effectiveness (VL < 50 RNA copies/mL) on the basis of on treatment (OT; discontinuation/missing= excluded), modified ITT (mITT; discontinuation= failure, missing= excluded) or ITT (discontinuation/missing= failure) for all subjects receiving at least one dose of dolutegravir/lamivudine.

We performed resistance testing until May 2015, using Sanger population sequencing. After that date onwards, we employed ultra-deep sequencing (UDS) using a 1% frequency threshold for variant detection. For UDS, we reported the proportion of sequences in which we detected substitutions.

Statistical analyses

Data were retrieved from the HIV Unit [Hospital Clinic Barcelona (HCB)] electronic health record systems. Summary statistics were based on frequency and percentage for qualitative variables, while mean (SD) or median (IQR) were used for quantitative characteristics. The discontinuation rate was presented as the number of events per 100 person-years and reported throughout the CI.

The association between baseline variables and detectable VL (VL ≥ 50 copies/mL) was estimated as risk ratio (RR) using either the Poisson regression model with robust standard errors or, in the case of sparse data (genotypic resistance and previous M184V/I substitution), penalized logistic regression via data augmentation. In the latter, we set the prior RR at 1. For the regression model, we performed a backward stepwise selection of variables, setting the *P* value for removal from the model equal to 0.1. Tests were two-tailed, and the significance level was set at 5%.

We performed statistical analyses using Stata 17 software (StataCorp LLC, College Station, TX, USA).

Ethics

The Institutional Ethics Committee approved this study (HCB. 2022.012).

Results

Baseline cohort

Between 20 November 2014 and 30 June 2022, 1058 persons with HIV received at least one dose of dolutegravir/lamivudine, either separately (dolutegravir + lamivudine) or co-formulated (dolutegravir/lamivudine). There was a limited number of TN individuals ($n = 9$); therefore, we focused the analysis on TE persons. The baseline cohort included 1049 (18% of the total cohort of people on ART) TE persons (Figure 1).

The median (IQR) follow-up time on dolutegravir/lamivudine was 1 (0.3–1.6) year. The median (IQR) time for VL determination after dolutegravir/lamivudine switch was 22 weeks (11–24); the median (IQR) number of VL determinations from switch to M6 was 0 (0–1) and from switch to M12 was 1 (1–2). The longer follow-up was 7.4 years in a person who started dolutegravir+ lamivudine in November 2014. Afterwards, between 20 and 100 subjects started this combination per year until 2020. There was then a noteworthy increase to approximately 400 initiations per year, coinciding with the availability of co-formulated dolutegravir/lamivudine in February 2020. Figure S1 (available as Supplementary data at *JAC* Online) shows the number of dolutegravir/lamivudine (dolutegravir + lamivudine and dolutegravir/lamivudine) initiations per year and semester. The first person who started dolutegravir+ lamivudine was a 63-year-old man who developed renal failure due to tenofovir disoproxil fumarate use and was positive for HLA-B5701, contraindicating the use of abacavir. Tenofovir alafenamide was not available at that time, and the subject started dolutegravir+ lamivudine in November 2014 (more than 5 years before the publication of 48 week (48W) results of the TANGO clinical trial). The subject continues with dolutegravir + lamivudine, which was simplified to co-formulated dolutegravir/lamivudine in 2020, after it became available. At the moment of closing the dataset, he was on dolutegravir/lamivudine (7.4 years with this regimen).

Of the 1049 persons included in the baseline cohort, 85% were male and the median (IQR) age was 47 (35–59) years.

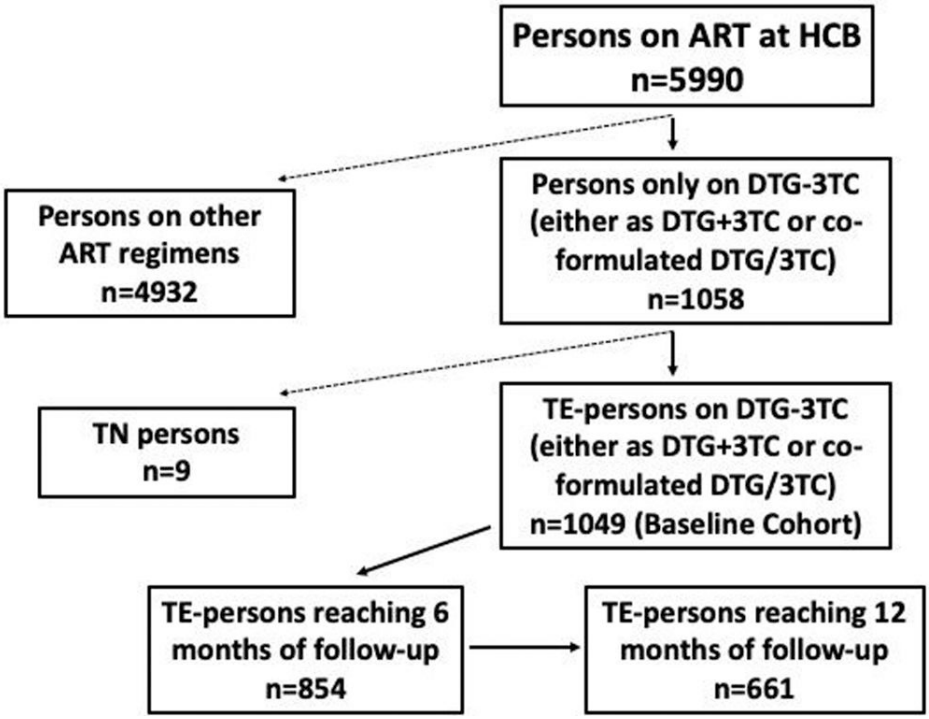

Figure 1. Flow chart of the persons with HIV cohort who received at least one dose of dolutegravir/lamivudine (DTG/3TC).

Furthermore, 58% of the patients were younger than 50 years old, and 70% were infected via sexual contact among MSM. The median (IQR) years since diagnosis to dolutegravir/lamivudine initiation was 11.9 (6.7–19.5) years. Additionally, 97% had undetectable VL at dolutegravir/lamivudine initiation with a median (IQR) CD4 count of 728 (546–959) cells/mm^3. Only 2% had a CD4 of less than 200 cells/mm^3; 15% had positive HCV serology; 7% had estimated glomerular filtration rates by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) at 30–59 mL/min (12 subjects, 1% were <30 mL/min), whilst the remaining were above 60 mL/min; and 14% of those who underwent a DXA scan presented osteoporosis. Baseline characteristics did not differ according to sex, although females had a slightly lower proportion of undetectable VL at dolutegravir/lamivudine initiation (95%). Table 1 shows the baseline characteristics of the entire cohort.

The reasons for discontinuation of the last previous ART and subsequent dolutegravir/lamivudine prescription were known in 945 (90%) cases, with the most common reason being simplification (72%) followed by toxicity (9%). Table 2 details the reasons for discontinuation of the last previous ART. Data about previous ART regimens were available in 968 (92%) cases; the median (IQR) number of previous ART regimens before dolutegravir /lamivudine initiation was 3 (2–5). Most cases started dolutegravir/lamivudine after a last regimen based on InSTI triple therapy (69%), and the single most frequent previous regimen was co-formulated dolutegravir/lamivudine/abacavir (n = 485). However, 50% of cases (n = 484) came from other triple-, double- or single-drug ART regimens. Table 3 reports data about the last previous ART regimen.

Follow-up of cohort at M6 and M12

Figure 1 shows the flow chart and distribution of the cohorts. Of the 1049 persons included in the TE baseline cohort, 854 and 661 reached M6 and M12 of follow-up, respectively. At M6, there were 40 discontinuations and 98 cases with missing data; at M12 there were 47 (39 of them with detectable VL) and 72, respectively. A hundred and ninety-five subjects (19%) started a dolutegravir/lamivudine regimen shortly before the database lock and had less than 6 months of follow-up (Figure 1). The baseline cohort of 1049 subjects provided a total of 1305.9 person-years of follow-up. Only 105 discontinued dolutegravir/lamivudine throughout the follow-up period, with the rate of discontinuation being 8.0 discontinuations per 100 person-years (95% CI 6.6–9.7). The most common reason for discontinuation was toxicity, in 46% of cases; of these, 44% were neuropsychiatric side effects, 23% gastrointestinal, 12.5% weight gain, 20% other types and 17% experienced more than one type of toxicity. Other discontinuation reasons included transfer to another institution (19%), death (10%, all unrelated to dolutegravir/lamivudine), personal preference (8%), simplification and loss of efficacy (4% each), to avoid drug–drug interactions (3%) and pregnancy (1%); in 5% of cases, the reason for discontinuation was unknown. Rates of dolutegravir/lamivudine discontinuation did not differ between sexes, although there was a trend of higher discontinuation among females (17% versus 10%, P = 0.07).

Suppression rates at M6 and M12

Suppression rates were reported according to the three predefined definitions, as shown in Figure 2. Suppression rates were

Table 1. Baseline characteristics of 1049 persons with HIV who received at least one dose of dolutegravir/lamivudine (DTG/3TC)

Characteristic	*N*=1049
DTG/3TC initial formulation	
DTG/3TC (co-formulated), *n* (%)	881 (84)
DTG+ 3TC, *n* (%)[a]	168 (16)
Sex at birth male, *n* (%)	894 (85)
Age (years), mean (SD) [*n*]	47 (12) [1049]
<50, *n* (%)	607 (58)
≥50, *n* (%)	442 (42)
Mode of infection, *n* (%)	
MSM/bisexual	735 (70)
Heterosexual intercourse	216 (21)
Injection drug use	48 (5)
Other/unknown	50 (5)
HIV-related characteristics	
Years since diagnosis, median (IQR) [*n*]	11.9 (6.7–19.5) [1022]
Years on ART previous to DTG/3TC, median (IQR)	9.1 (4.7–15.9)
ART regimens previous to DTG/3TC, median (IQR)	3 (2–5)[b]
HIV-1 RNA <50 copies/mL, *n* (%)	1015 (97)
HIV-1 RNA 50–199 copies/mL, *n* (%)	15 (1)
HIV-1 RNA ≥200 copies/mL	19 (1)
CD4 count, cells/mm^3, median (IQR) [*n*]	728 (546–959) [1049]
CD4 count <200 cells/mm^3, *n*(%)	16 (2)
CD4 count 200–499 cells/mm^3, *n*(%)	193 (18)
CD4 count ≥500 cells/mm^3, *n*(%)	840 (80)
Comorbidities and coinfections	
HBsAg negative, *N* = 708, *n* (%)	707 (100)
IgG HCV negative, *N* = 1043, *n* (%)	888 (85)
CKD-EPI median (IQR) [*n*]	87 (74–90) [1047]
CKD-EPI ≥90 mL/min, *n* (%)	463 (44)
CKD-EPI 60–89 mL/min, *n* (%)	501 (48)
CKD-EPI 30–59 mL/min, *n* (%)	71 (7)
CKD-EPI <30 mL/min, *n* (%)	12 (7)
DXA scan available data, *n* (%)	728 (69)
DXA scan-evidenced osteopenia	367 (35)
DXA scan-evidenced osteoporosis	100 (10)

[a]One hundred and five (63%) individuals switched to co-formulated DTG/3TC when it became available, and on 30 June 2022 (when database was locked) 10 patients were receiving 3TC+ DTG and 53 had discontinued it.
[b]There were 38 events of virological failure (VF) in 32 persons (27 persons had a single VF, 4 persons had two previous VFs and 1 person had 3).

Table 2. Reasons for discontinuation of last previous ART regimen in 945 persons with HIV starting dolutegravir/lamivudine (DTG/3TC)

Reasons for discontinuation	*n* (%)
Simplification	679 (72)
Toxicity	86 (9)
Avoidance of drug–drug interactions	29 (3)
Patient's preference	9 (1)
ART discontinuation without medical indication	6 (1)
Other causes	136 (14)[a]

[a]Including 50 cases included in the open-label DOLAM trial (EudraCT 201500027435).

Table 3. Last previous ART regimen in 968 persons with HIV

Previous ART	
Triple ART, *n* (%)	844 (87)
InSTI-based, *n* (%)	669 (69)
Dolutegravir-based, *n*	513[a]
Elvitegravir/cobicistat-based, *n*	83
Raltegravir-based, *n*	47
Bictegravir-based, *n*	26
NNRTI-based, *n* (%)	137 (14)
Rilpivirine-based, *n*	45
Efavirenz-based, *n*	44
Nevirapine-based, *n*	40
Etravirine-based, *n*	6
Doravirine-based, *n*	2
PI-based, *n* (%)	38 (4%)
Darunavir-based, *n*	19
Atazanavir-based, *n*	18
Lopinavir-based, *n*	1
Other triple combinations, *n* (%)	2 (0)
Double ART, *n* (%)	75 (8)
INSTI-based[b]	40 (4)
PI-based[c]	30 (3)
PI+ InSTI	5 (1)
Other ART, *n* (%)	49 (5)
PI monotherapy	27 (3)
InSTI monotherapy	19 (2)
Other combinations	3 (0)

[a]Four hundred and eighty-five cases corresponded to co-formulated dolutegravir/lamivudine/abacavir.
[b]Including 29 cases of raltegravir/lamivudine and 1 case of dolutegravir/tenofovir disoproxil fumarate.
[c]Including 19 cases of boosted darunavir/lamivudine and 11 cases of other boosted PIs/lamivudine.

remarkably high at both M6 and M12 (97% and 98% respectively, OT). Suppression rates remained similar after we removed DOLAM trial participants (97% and 97% OT at M6 and M12, respectively).

Resistance analysis and suppression rates in patients carrying antiretroviral (ARV)-resistant substitutions

At least one set of genotypic resistance test (GRT) data was available from 551 cases. We found at least one relevant substitution in 292 (53%) cases in the cumulative resistance profile. Of these persons, 29 (10%) had either M184V or M184I substitution. We detected M184V/I as the only substitution in one case; in the other 28, there were substitutions accompanying M184V/I in RT (*n* = 28; 97%), protease (*n* = 18; 62%) and integrase (*n* = 3; 10%)

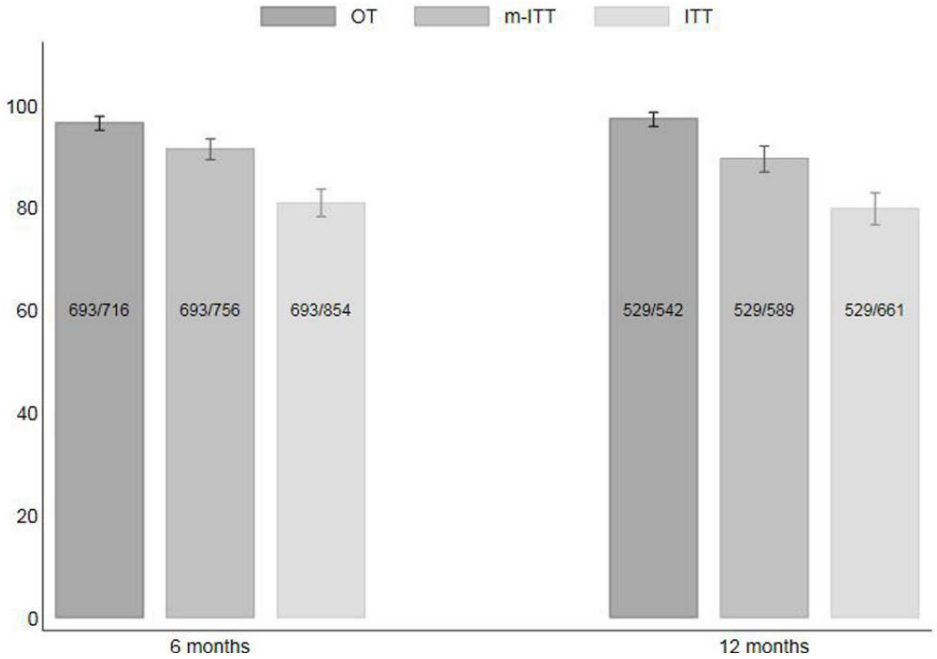

Figure 2. Suppression rates (effectiveness) of dolutegravir/lamivudine at M6 and M12.

Table 4. Analysis of variables associated with lack of effectiveness at M12 (ITT) (n = 597)[a].

Variable	uRR	(95% CI)	*P* value	aRR	(95% CI)	*P* value
Female sex at birth (versus male)	1.77	(1.24–2.52)	<0.01	1.69	(1.19–2.40)	0.0033
Age (per 5 year increase)	1.02	(0.96–1.09)	0.51			
MSM or bisexual (versus other)	0.63	(0.45–0.87)	<0.01			
Years since HIV diagnosis (per 5 year increase)	1.14	(1.04–1.25)	<0.01			
PHI patient (versus chronic)	0.97	(0.59–1.60)	0.89			
Previous VF (versus no)	2.34	(1.36–4.03)	<0.01			
Number of previous ART (per 1 treatment increase)	1.07	(1.04–1.11)	< 0.01			
Previous last regimen InSTI-based (versus no)	0.83	(0.58–1.19)	0.32			
Previous last regimen PI-based (versus no)	1.67	(1.10–2.55)	0.02	1.67	(1.09–2.56)	0.0183
Previous last regimen NNRTI-based (versus no)	0.94	(0.59–1.49)	0.78			
CD4 count at DTG/3TC start (≥500 versus <500 cells/mm^3)	0.75	(0.52–1.07)	0.11			
CD4:CD8 ratio at DTG/3TC start (≥1 versus <1)	1.09	(0.79–1.51)	0.59			
VL at DTG/3TC start (≥50 versus <50 copies/mL)	3.48	(2.44–4.96)	< 0.01	3.36	(2.32–4.88)	< 0.0001
Previous GRT at DTG/3TC start (done versus not done)	1.26	(0.90–1.76)	0.18			

Poisson regression model with robust standard errors. DTG, dolutegravir; 3TC, lamivudine; uRR, unadjusted RR; PHI, primary HIV infection; VF, virological failure.

[a]Cases where any of the covariables analysed had missing values were excluded.

(Table S1). In all but two recent cases, M184V was either detected in populational genotypes or in UDS at >20% of sequences. The median time that had elapsed between M184V/I detection and initiation of dolutegravir/lamivudine was 13.7 (IQR 7.7–17.1) years. The VL at dolutegravir/lamivudine initiation was undetectable in 24 (82%) persons carrying the M184V/I substitution. Due to a short follow-up since dolutegravir/lamivudine initiation in most cases, VL was available in only 11 cases at M6 (8 with VL < 50 copies/mL) and in 7 cases at M12 (6 with VL < 50 copies/mL).

Prognostic factors of lack of effectiveness

As detailed in Table 4 of the unadjusted models, factors associated with an increased risk of lack of effectiveness at M12

were: female (at birth) subjects; years since HIV diagnosis; previous virological failure; number of previous ART regimens; and a previous PI-based regimen. In the adjusted model, female sex [adjusted RR, aRR = 1.69 (95% CI = 1.19–2.40)], those with the last previous PI-based regimen use [aRR = 1.67 (95% CI = 1.09–2.56)] and those starting dolutegravir/lamivudine with VL > 50 copies/mL [aRR = 3.36 (95% CI = 2.32–4.88)] were at a higher risk of detectable VL at M12. For all other demographic and virological variables (including no GRT before switching to dolutegravir/lamivudine or the presence of M184V/I substitution in historical GRT), there was no evidence of a statistical association with lack of effectiveness. The results from the model did not change (the same variables were identified) after we removed DOLAM participants.

Discussion

Based on randomized controlled trial (RCT) results, dolutegravir/lamivudine is a preferred regimen for TN and TE persons, with other studies[8,12,18–20] also strengthening real-world data on its use in both settings.[9,10,13–15,21,22] Our study provides additional and robust data to support the effectiveness of dolutegravir/lamivudine, with virological suppression rates reaching 97% and 98% at M6 and M12 (OT), respectively.

Our cohort is representative of the current HIV epidemiology in Western/Central Europe, consisting of mainly MSM, median/older age (42% patients were older than 50 years) and a very low prevalence of injecting drug users (5%). Given the low number of TN persons, the entire cohort analysed here is TE. This low number of TN is explainable for several reasons. First, both new diagnoses and infections have been decreasing in the last few years, given the expansion of ART and PrEP. Second, most TN individuals receive priority for clinical trials, especially in most tertiary reference centres. Third, most of the included study subjects started dolutegravir/lamivudine during the COVID-19 pandemic, and other combinations recommended for rapid ART initiation (active against HBV and with no need to wait for laboratory results) were given priority in these periods.[23] Moreover, the PrEP scope has largely expanded in our setting; individuals previously engaged in PrEP or in contact with PrEP settings may have a higher prevalence of M184V substitution,[24] a situation where dolutegravir/lamivudine is currently not recommended. Finally, clinicians' perception of the excellent results obtained with simplification using dolutegravir/lamivudine in several clinical scenarios may lead to much more frequent use of this line of therapy in this situation. Our cohort presented a good immunological status (80% had >500 CD4/cells/mm^3) and had a median of three previous ART regimens over a median course of 11.9 years since diagnosis.

The longest follow-up was 7.4 years. The first person who started dolutegravir + lamivudine was a 63-year-old man on a tenofovir disoproxil fumarate-based regimen (tenofovir disoproxil fumarate/lamivudine/rilpivirine) who developed renal failure in 2014, and was positive for HLA-B5701. This subject began taking dolutegravir/lamivudine in November 2014 (more than 5 years before the publication of the 48W results of the TANGO clinical trial). The early use of this combination highlights the appealing profile of dolutegravir/lamivudine among our centre's clinicians, even before the publication of results from pivotal switch trials (such as 48W in the TANGO trial).[25] However, as expected, the number of individuals receiving dolutegravir/lamivudine largely increased in recent times, following both the TANGO RCT 48W results and availability of co-formulation.

The main reason for dolutegravir/lamivudine discontinuation in our study was toxicity; however, given that only 5% of our patients had to change their ART for this particular reason, we can assume this regimen's overall safety.

Our real-world data also show the clinical use of the dolutegravir/lamivudine regimen in situations beyond those approved by regulatory agencies, such as use in individuals with known resistance substitutions or a non-undetectable status at the moment of switch. Even though we detected the M184V/I mutation in 29 persons, the statistical analysis proved that it was not independently associated with lower odds of virological suppression. These findings are in line with recent studies that found that 3 years after the switch to dolutegravir/lamivudine in patients carrying the M184V/I mutation, the probability of virological failure and blips was very low (6.9%).[26] This was particularly so if the person's VL remained undetectable for long periods since the substitution was identified.[27]

However, several points need to be addressed for these multivariable analysis findings. The median time elapsed for dolutegravir/lamivudine initiation following M184V/I was extremely long (13.7 years). This highlights the decreased relevance given by clinicians when substitutions were detected in old samples and individuals' VL remained undetectable for long periods. However, there were a few cases reaching M6 and M12 of follow-up. That stated, statistical power was very low to conclude that M184V/I was unrelated to lack of effectiveness at M12, and these results should be interpreted with caution to avoid type II statistical error. Finally, all but one case had other substitutions detected in historical GRT, indicating a long history of exposure to ART. Indeed, previous PI use was associated with lack of effectiveness in the adjusted model—perhaps illustrating this fact—with higher potency than the history of M184V/I substitution itself. Females and a detectable VL at dolutegravir/lamivudine initiation were also factors associated with lack of effectiveness at M12. Females are frequently reported as having lower virological success compared with males, especially the MSM population. This may be related to different barriers for adherence to follow-up and ART,[28,29] and not necessarily regimen-specific. Finally, detectable VL at dolutegravir/lamivudine switch (a non-approved indication) was also an independent factor for lack of effectiveness at M12. This may highlight the importance of switching to this regimen only in virologically suppressed persons; it may also indicate a lower adherence, irrespective of the ART combination used. These results may suggest that these subgroups of people could benefit from closer follow-up and a reinforcement of adherence when switching to dolutegravir/lamivudine.

Virological suppression was assessed through different methods (OT, ITT and mITT), showing overall high suppression rates. Considering this is a real-world study, OT analysis is probably the best approach in defining effectiveness since the data provided better reflect the everyday clinical reality—that is, it is common that patients are lost to follow-up. However, the proportion of individuals without virological data on window was not particularly high in our study.

We recently reported our cohort of people with HIV on bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC).[30] Some interesting differences with the cohort of those receiving dolutegravir/lamivudine, which also shows the perception of regimens by clinicians, should be mentioned. In the BIC/TAF/FTC study, only 82% of those included (in the switch group) had undetectable VL at BIC/TAF/FTC initiation, compared with 97% starting dolutegravir/lamivudine. Although both combinations are recommended for switch strategies, this varying proportion highlights a different use of such regimens: BIC/TAF/FTC is reserved for those perceived as more difficult to treat, less adherent to therapy, or even in need of viraemia resuppression or salvage regimen. In contrast, dolutegravir/lamivudine seems to be used more frequently for those perceived as highly adherent, where an improvement of the combination is desired in terms of long-term safety, without losing virological efficacy.

Our paper has several strengths. It represents a large cohort from a single centre with a typical, current people with HIV population. The number of study subjects is comparable to that of multicentre cohorts. It also provides evidence of this regimen's efficacy, supported by multiple analyses. The present wide cohort also allows for a relevant number of patients carrying mutations to be represented; moreover, the follow-up period for the first cases was extremely large (compared with previously published real-world studies). However, the paper is not exempt from some major limitations, such as the absence of data in our database regarding some relevant comorbidities (e.g. cardiovascular risk). Due to the ageing of the population of persons with HIV, such data are becoming increasingly relevant. For other comorbidities like bone disease, data were only available for a percentage of the patients. This type of information would have proven interesting in illustrating the profile of persons who were prescribed dolutegravir/lamivudine in our cohort. It also provides data only from a single hospital. Although the centre is the reference unit for the area, it may not represent some characteristics of persons with HIV residing in other regions. As this was a real-world study, a non-depreciable number of persons had missing data. Finally, many cases started this regimen recently, including those carrying ARV-resistant substitutions, so the cohort experienced significant attrition at M6 and M12.

In conclusion, in our cohort of persons with HIV, a significant proportion started dolutegravir/lamivudine as a switch strategy. It was exponentially used in recent years, although initially prescribed in selected individuals and a small subset as part of an open clinical trial. Effectiveness (OT) was remarkably high and with low levels of discontinuation. Individuals with immediate previous PI use, females and those starting dolutegravir/lamivudine with detectable VL more frequently had a lack of virological effectiveness on dolutegravir/lamivudine at M12 since initiation. They may benefit from close follow-up after simplification.

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Transparency declarations

J.A. has received research funding from ViiV and Gilead, has received personal fees from ViiV, Gilead, Janssen and MSD, has participated in Advisory Boards for ViiV, Gilead, Janssen and MSD, has participated in Data Safety Monitoring Boards for HIPRA and Grifols, all these activities outside of the current work. For all authors, no conflict of interest to declare related to this work.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at *JAC* Online.

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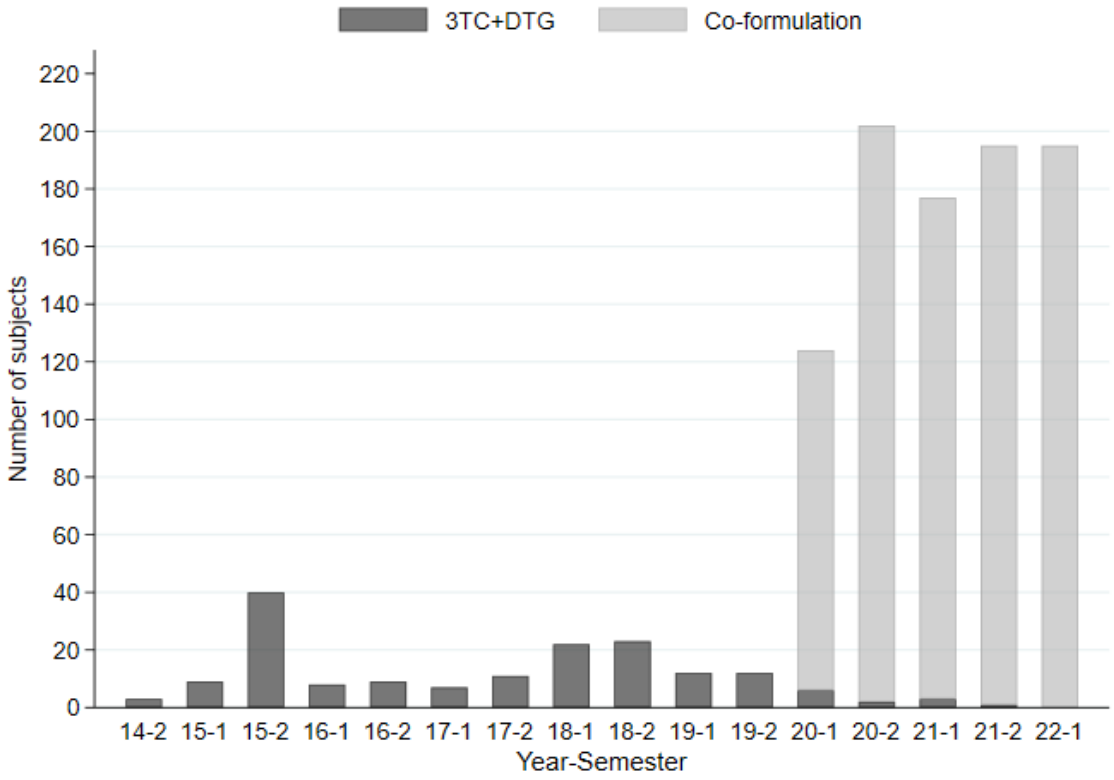
Supplemental Figure 1. Number of individuals starting DTG-3TC as separated dugs (3TC + DTG) or as co-formulated DTG/3TC in the Hospital Clinic, since second semester of 2014.



Recruitment for DOLAM study started in July 2015.

Co-formulated DTG/3TC was available in our center in the February 2020.

Trabajo 3

A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine.

Elisa de Lazzari, Montserrat Lonca, Jhon Rojas, Ana Gonzalez-Cordon, Jordi Blanch, Alexy Inciarte, Amparo Tricas, Ana Rodriguez, Maria Martinez-Rebollar, Montserrat Laguno, Josep Mallolas, Sonsoles Sanchez-Palomino, Montserrat Plana, Jose L. Blanco and Esteban Martinez.

AIDS 2019, 33: 1891–1896.

Resumen

Objetivos: Existe un creciente interés en los regímenes de dos fármacos. Planteamos la hipótesis de que la terapia de mantenimiento con raltegravir y lamivudina mantendría el VIH-1 suprimido y bien tolerado.

Métodos: Aleatorizamos (2:1) a personas adultas con VIH-1 sin fallos virológicos previos o mutaciones conocidas de resistencia a inhibidores de la integrasa o 3TC/FTC o hepatitis B crónica, a cambiar a una combinación de dosis fijas de 150 mg de lamivudina/300 mg de raltegravir dos veces al día o a continuar la misma terapia. El objetivo primario fue evaluar la proporción de pacientes libres de fracaso terapéutico (definido como fracaso viral, cambio de tratamiento por cualquier motivo, retirada del consentimiento, pérdida del seguimiento o muerte) a la semana 24. Los objetivos secundarios fueron los cambios en los parámetros de laboratorio, la composición corporal, la calidad del sueño, la adherencia y los efectos adversos.

Resultados: Se incluyeron 75 pacientes: hombres 78%; mediana de edad 50 años; mediana de CD4 622/µl. A la semana 24, 7 (9%) pacientes presentaron fallo terapéutico: raltegravir y lamivudina 2 (4%) vs. control 5 (20%). La diferencia en las proporciones de fracasos terapéuticos, raltegravir+lamivudina menos control, fue de -0.159 (IC 95%: -0.353; -0.012). Hubo una tendencia al aumento de peso con raltegravir y lamivudina, pero no hubo cambios significativos en otros resultados secundarios. El 64% de los pacientes de cada grupo

tuvieron al menos un efecto adverso. Dos (6%) pacientes en el grupo de control y 4 (7%) pacientes en el grupo de raltegravir más lamivudina tuvieron efectos adversos graves.

Conclusiones: Este estudio piloto sugiere que el cambio a raltegravir junto con lamivudina en pacientes con supresión viral mantiene la eficacia y es bien tolerado. Se requiere un estudio más amplio y de mayor duración para confirmar estos hallazgos.

A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine

Elisa de Lazzari, Montserrat Lonca, Jhon Rojas, Ana Gonzalez-Cordon, Jordi Blanch, Alexy Inciarte, Amparo Tricas, Ana Rodriguez, Maria Martinez-Rebollar, Montserrat Laguno, Josep Mallolas, Sonsoles Sanchez-Palomino, Montserrat Plana, Jose L. Blanco and Esteban Martinez

Background: There is an increasing interest in two-drug regimens. We hypothesized that maintenance therapy with raltegravir and lamivudine would keep HIV-1 suppressed and be well tolerated.

Methods: Virally suppressed HIV-1-infected adults without previous viral failures or known resistance mutations to integrase inhibitors or 3TC/FTC or chronic hepatitis B were randomized 2 : 1 to switch to fixed-dose combination 150 mg lamivudine/300 mg raltegravir twice daily or to continue therapy. Primary outcome was the proportion of patients free of therapeutic failure (defined as viral failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death) at week 24. Secondary outcomes were changes in laboratory, body composition, sleep quality, adherence, and adverse effects.

Results: There were 75 patients included: men 78%; median age 50 years; median $CD4^+$ 622/μl. At week 24, 7 (9%) patients had therapeutic failure: raltegravir and lamivudine 2 (4%) vs. control 5 (20%). The difference in proportions of therapeutic failures raltegravir and lamivudine minus control was −0.159 (95% confidence interval: −0.353 to −0.012). There was a trend to more weight gain with raltegravir and lamivudine, but no significant changes in other secondary outcomes. Sixty-four percent of patients in each arm had at least one adverse effect. Two (6%) patients in control arm and 4 (7%) patients in raltegravir and lamivudine arm had severe adverse effects.

Conclusion: This pilot study suggests that switching to raltegravir along with lamivudine in patients with viral suppression maintains efficacy and is well tolerated. A larger study of longer duration is required to confirm these findings.

AIDS 2019, **33**:1891–1896

Keywords: pilot study, randomized clinical trial, simplification of antiretroviral therapy

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Introduction

Reducing the number of antiretroviral drugs to avoid its potential negative impact on comorbidities has been long considered as a popular strategy, particularly in virally suppressed patients receiving standard three-drug regimens. Dolutegravir shares both potency and barrier to resistance with boosted protease inhibitors and recent data suggest behaviour roughly similar to that of boosted protease inhibitors in regimens with less than three drugs. Dolutegravir monotherapy has shown a higher risk of virological failure than triple standard therapy but, in contrast with protease inhibitor monotherapy, virological failures with dolutegravir monotherapy usually develop cross-resistance integrase mutations [1]. Dual therapy with dolutegravir and lamivudine has met noninferiority when compared with standard triple therapy in both antiretroviral-naïve and virologically suppressed patients and none of the few patients experiencing virologic failure in randomized clinical trials has developed drug resistance mutations so far [2–4].

Similar to dolutegravir, raltegravir does not interfere with comorbidities, has a low risk for interactions, and is better tolerated than boosted protease inhibitors [5]. Dolutegravir has shown noninferiority when compared with raltegravir as standard triple therapy in antiretroviral-naïve patients [6]. Although raltegravir is considered to have lower genetic barrier to resistance than dolutegravir, indirect evidence suggests than raltegravir may perform well in regimens with less than three fully active drugs. A post-hoc analysis of the BENCHMRK study showed that some patients in the raltegravir arm had no other drugs active as shown by the genotypic sensitivity score and yet did not experience virological failure [7]. A subanalysis of SPIRAL study looking retrospectively at patients with previous resistance failure and genotypic resistance tests available in their history database revealed that a proportion of patients were on functional dual or even monotherapy not only in the boosted protease inhibitor arm but also in the raltegravir arm and did not show virological failure [8].

Lamivudine is probably one of the safest antiretroviral drugs, with no specific toxicity profile known or major adverse effects reported after more than 25 years of use [9]. A fixed-dose combination constituting lamivudine 150 mg and a nonpoloxamer formulation of raltegravir 300 mg was approved for treatment of HIV infection under the branded name of Dutrebis by the European Medicines Agency and the US Food and Drug Administration in 2015 [10]. The objective of this fixed-dose combination was to develop an immediate release oral formulation offering at least similar pharmacokinetic properties to the equivalent individual products. Dual therapy with the fixed-dose combination raltegravir and lamivudine is a convenient regimen sparing the use of both protease inhibitors and commonly used nucleos(t)ide reverse transcriptase inhibitors tenofovir disoproxil fumarate and abacavir, which have been limited by multiple toxicities and clinically meaningful drug–drug interactions. We hypothesized that dual therapy with raltegravir/lamivudine would be feasible, able to maintain viral suppression, and well tolerated in patients with sustained viral suppression on combination antiretroviral therapy.

Methods

Study design and participants

The RALAM Study is an open-label, pilot, unicentre, randomized clinical trial. Consecutive asymptomatic and stable HIV-infected adults (≥18 years) receiving combination antiretroviral therapy for at least the previous 12 months were invited to participate if they had plasma HIV-1 RNA less than 50 copies/ml for at least 12 months prior to inclusion. In addition, participants were required not to have any of the following: prior virological failure to any regimen containing integrase inhibitors or lamivudine/emtricitabine, chronic hepatitis B, or any disease or history of disease which, in the opinion of the investigator, might confound the results of the study or pose additional risk to the patient. For women of childbearing age, a negative pregnancy test at the time of study consideration and use of anticonceptive measures throughout the study period were also required. Patients who met all inclusion criteria, none of exclusion criteria, and agreed to participate were randomized 1 : 2 to maintain their antiretroviral therapy (control arm) or to switch to the fixed-dose combination 150 mg lamivudine/300 mg raltegravir (Dutrebis) twice daily (experimental arm). We used an unequal allocation 1 : 2 that favoured the experimental arm over the control arm to increase clinical experience with the study therapy in HIV-infected patients as Dutrebis has been used only in phase I studies with healthy volunteers. The Institutional Review Board of Hospital Clínic approved the study and all participants signed informed consent prior to inclusion. The study was registered at ClinicalTrials.gov: NCT02284035.

Although the hypothesis of the study was based on consistent data to support its potential feasibility, we planned in advance that development of virological failure in at least 10% of the patients in the study arm would be unacceptable and should lead to stopping the trial. Following the request of the Institutional Review Board that approved the study, if the 24-week trial proved to be successful, an additional 48-week extension phase was planned in which patients in the experimental arm would remain treated with the dual regimen to gather long-term efficacy and safety information.

Procedures

After inclusion, each patient had four medical visits: baseline, 4, 12, and 24 weeks. At baseline, patient's characteristics including age, sex, ethnicity, and suspected route of HIV transmission were collected. At each medical

visit, participants had a complete physical examination done, a simplified adherence questionnaire [11] filled, and blood drawn for $CD4^+$ and $CD8^+$ cell counts and standard plasma HIV-1 RNA (COBAS HIV-1 Assay, limit of detection 50 copies/ml). Women of childbearing age had also a pregnancy test done at each medical visit.

At baseline and at 24 weeks: weight and height were measured; the Spanish-validated version of the Pittsburg Sleep Quality Index (PSQI) [12] was self-assessed; blood was drawn after at least an 8-h fasting period to measure blood cells and chemistry including total and high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, insulin, and 25-0H vitamin D; urine was collected to measure beta-2-microglobulin; and a dual X-absorptiometry (DXA) to measure whole body composition and lumbar and femoral bone mineral density was performed. BMI was calculated from weight and height. Estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] was calculated from plasma creatinine following a standard formula [13]. In addition, plasma and peripheral blood mononuclear cells samples were collected and stored at $-80\,^{\circ}C$ until deferred measurement of markers of inflammation and immune activation, immunophenotyping, ultrasensitive plasma HIV-1 RNA, and total and integrated HIV-1 DNA in $CD4^+$ cells (not reported here).

Outcomes

Primary end-point was the proportion of patients free of treatment failure (noncompleter = failure) at 24 weeks. Treatment failure was defined as any of the following possibilities occurring within the 24-week study framework: virological failure (defined as plasma HIV-1 RNA $\geq$50 copies/ml in two consecutive tests 2 weeks apart), discontinuation of the antiretroviral therapy schedule irrespective of the reason, consent withdrawal, lost to follow-up, pregnancy, inability to comply with the study or any other reason that could make the doctor in charge consider the cessation of the study. In the event of virological failure, plasma HIV-1 RNA would be tested for HIV reverse transcriptase, protease, and integrase mutations by population sequencing (Trugene HIV Genotyping System; Siemens Medical Solutions Diagnostics, Tarrytown, New York, USA) and ultra-deep sequencing (MiSeq platform; Illumina, San Diego, California, USA) following routine protocols. In patients with treatment failure, the investigator decided the most appropriate therapeutic option in agreement with the patient. Patients were followed for the entire trial period regardless of whether they prematurely discontinued assigned study medication.

Secondary outcomes were 24-week changes in laboratory parametres, PSQI score, body fat composition, lumbar spine and femoral bone mineral densities and *T*-scores, and incidence and intensity of adverse events. Intensity of adverse events was assessed according to the Division of AIDS table for grading the severity of adult and paediatric adverse events.

Statistical analysis

Assuming a -10% noninferiority margin, an alpha error of 0.025, a 12% treatment failure rate in the control arm, and the true difference in the proportions between groups of zero, then 68 patients (23 in the control arm and 45 in the experimental arm) would be required to achieve 80% of power to test the noninferiority with the continuity corrected *Z*-test with unspooled variance. The final sample size was established at 75 patients (25 in the control arm and 50 in the experimental arm). All randomized patients were included in the analysis. Statistical analysis was performed with the use of Stata (release 14) software (StataCorp, College Station, Texas, USA). Chi-squared or Fisher's exact tests were used to compare proportions between treatment groups. Mann–Whitney or ANOVA tests were used for comparisons of continuous variables between groups. Analysis of the primary endpoint was performed on both intent-to-treat and per-protocol populations, presenting the 95% confidence interval for the difference in proportion estimated using the Newcombe method 10 [14]. Change over time in continuous variables in each arm was calculated as a difference-in-differences estimation based on linear regression model with time, group and time-group interaction. The time to first adverse event was estimated with the Kaplan–Meier product-limit method. The incidence rate of adverse events in both arms was compared with a Poisson regression.

Results

Population

Between 27 November 2015 and 27 October 2016, 78 patients were assessed for eligibility. Three patients refused to participate because of lack of interest ($n = 2$) or lack of time ($n = 1$). Out of the 75 patients randomized, 50 were allocated to raltegravir/lamivudine and 25 to continue their baseline therapy. One patient randomized to raltegravir/lamivudine withdrew his consent prior to initiation of study medication and was excluded from the analyses.

Baseline characteristics are shown in Table 1. Twenty-three (31%) patients were on their first-line regimen. HIV-1 RNA had been maintained below detection level for a median of 56 (30–79) months before randomization. Thirty-nine (53%) patients were also taking non-HIV medications (median 2, interquartile range 0–4) being neuropsychiatric ($n = 27$ patients) and cardiovascular ($n = 21$ patients) drugs the two most common ones followed by a miscellanea of drugs.

Efficacy

Patients' disposition is shown in Supplementary Figure 1, http://links.lww.com/QAD/B507. In the intent-to-treat analysis, 47 (96%) patients in the raltegravir/

Table 1. Baseline characteristics.

	Control ($n=25$)	Raltegravir/lamivudine ($n=49$)	Total ($n=74$)
Age (years)	50 (13)	50 (12)	50 (12)
Men (%)	21 (84)	37 (76)	58 (78)
Prior ART backbone			
TDF-containing	17	26	43
ABC-containing	8	22	30
Nuke-sparing	–	1	1
Prior ART third drug			
PI	3	8	11
NNRTI	16	29	45
INSTI	5	13	19
NRTI	1	–	1
PSQI score, median (IQR)	4 (3; 9)	5 (4; 9)	4.5 (3; 9)
Adherence score, median (IQR)	19 (18.5; 20)	19 (18; 20)	19 (18; 20)
$CD4^+$ (cells/mm^3)	564 (240)	655 (295)	622 (277)
$CD8^+$ (cells/mm^3)	798 (340)	767 (342)	777 (339)
Creatinine (mg/dl)	0.84 (0.18)	0.85 (0.20)	0.85 (0.19)
eGFR (<90 ml/min/1.73 m^2), CKD-EPI	10 (40)	16 (33)	36 (35)
Triglycerides (mg/dl)	112 (53)	99 (50)	103 (51)
Total cholesterol (mg/dl)	187 (44)	189 (46)	188 (45)
LDL cholesterol (mg/dl)	115 (29)	120 (39)	118 (36)
HDL cholesterol (mg/dl)	46 (13)	48 (15)	47 (14)
Glucose (mg/dl)	96 (13)	96 (12)	96 (12)
Insulin (U/l)	16 (16)	14 (10)	14 (12)
25OH vitamin D (ng/ml)	17 (10)	17 (9)	17 (9)
Urine beta-2 microglobulin (mg/g)	595 (949)	673 (773)	651 (814)
BMI (kg/m^2) (mean, SD)	26 (4)	25 (4)	25 (4)
Fat (DXA)			
Trunk fat (g)	9891 (8052; 12611)	9232 (6587; 12976)	9738 (7140; 12976)
Trunk fat, %	30 (24; 33)	30 (22; 36)	30 (22; 36)
Upper limbs fat (g)	1950 (1538; 2765)	2420 (1370; 2920)	2290 (1508; 2912)
Upper limbs fat (%)	22 (19; 36)	29 (19; 35)	28 (19; 36)
Lower limbs fat (g)	5375 (3156; 9577)	5736 (4094; 7658)	5649 (3918; 8349)
Lower limbs fat (%)	26 (15; 37)	27 (20; 32)	27 (19; 34)
Total body fat (g)	65121 (25318; 74254)	52389 (21558; 66220)	55347 (21558; 70334)
Total body fat (%)	25 (21; 33)	29 (22; 33)	28 (21; 33)
Bone (DXA)			
Total hip BMD (g/cm^2)	0.97 (0.92; 1.04)	0.93 (0.84–1.01)	0.95 (0.89–1.02)
Femur *T*-score (mean, SD)	−0.63 (0.76)	−1.04 (0.88)	−0.90 (0.86)
L1-L4 BMD (g/cm^2)	1.16 (1.05; 1.28)	1.11 (1.00; 1.24)	1.13 (1.02; 1.23)
Lumbar spine *T*-score (mean, SD)	−0.54 (1.08)	−0.92 (1.16)	−0.79 (1.14)

Data are mean (SD) unless otherwise stated. ABC, abacavir; ART, antiretroviral therapy; BMD, bone mineral density; CKD-EPI, chronic kidney disease epidemiology collaboration; DXA, dual-X-absorptiometry; eGFR, estimated glomerular filtration rate; INSTI, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PSQI, Pittsburg Sleep Quality Index; SD, standard deviation; TDF, tenofovir disoproxyl fumarate.

lamivudine arm and 20 (80%) patients in the control arm completed the study and remained free of therapeutic failure (estimated difference 0.159; 95% confidence interval 0.012–0.353) at 24 weeks. Five (20%) of the control arm patients prematurely discontinued because of virological failure ($n=1$, week 4), discontinuation of antiretroviral therapy ($n=2$, both week 4), and lost to follow-up ($n=2$, weeks 4 and 12). In the raltegravir/lamivudine arm, two patients prematurely discontinued the study because of pregnancy (week 10) and Hodgkin lymphoma (week 20), respectively.

In the on-treatment analysis, 47 (98%) patients in the raltegravir/lamivudine arm and 20 (87%) patients in the control arm completed the study and remained free of therapeutic failure (estimated difference 0.110; 95% confidence interval 0.013–0.301) at 24 weeks.

Safety

Sixteen (64%) patients in the control arm and 32 (65%) in the raltegravir/lamivudine arm had at least one adverse event during the study. The time to first adverse event did not show differences between arms (Supplementary Figure 2, http://links.lww.com/QAD/B507). The incidence rate ratio of all adverse events was 6.9 (95% confidence interval 5.1–8.7) per 100 person-years in the raltegravir/lamivudine arm and 7.9 (95% confidence interval 4.9–11.0 per 100 person-years) in the control arm (incidence rate ratio of raltegravir/lamivudine vs. control 0.87, 95% confidence interval 0.55–1.38, $P=0.5550$). Table 2 shows the profile of adverse events; some patients had more than one adverse event. All adverse events were grade 1 or 2. Most common adverse events were muscular, gastrointestinal, and infections, with no substantial differences between arms.

Table 2. Adverse events profile.

	Control ($n=25$)	Raltegravir/ lamivudine ($n=49$)	Total ($n=74$)
Systemic	2 (8%)	–	2 (2%)
Infection	6 (23%)	12 (21%)	18 (22%)
Dermatologic	2 (8%)	2 (4%)	4 (5%)
Cardiovascular	–	1 (2%)	1 (1%)
Gastrointestinal	2 (8%)	16 (28%)	18 (22%)
Neurologic	4 (15%)	5 (9%)	9 (11%)
Muscular	5 (19%)	14 (25%)	19 (23%)
Genitourinary	–	1 (2)	1 (1%)
Ophtalmologic	–	3 (5%)	3 (4%)
Laboratory	5 (19%)	3 (5%)	8 (10%)
Total	26 (100%)	57 (100%)	83 (100%)

Some patients had more than one adverse event. Adverse events were grade 1 or 2.

There was a trend towards more weight gain and more total body fat in the raltegravir and lamivudine arm. There were no significant differences between arms in other secondary outcomes such as 24-week changes in laboratory parametres, PSQI score, and lumbar spine and femoral bone mineral densities, and *T*-scores (Supplementary Tables 1 http://links.lww.com/QAD/B507 and 2, http://links.lww.com/QAD/B507).

Discussion

This study represents a proof of concept that switching from combination antiretroviral therapy to raltegravir/lamivudine in patients with sustained viral suppression maintains viral suppression at 24 weeks and is well tolerated. The results support that raltegravir may behave similarly to dolutegravir to construct dual maintenance regimens along with lamivudine [4,15]. There were no virological failures or blips in the raltegravir and lamivudine arm through 24 weeks. However, these results should be interpreted with caution because of the short follow-up. Viral rebound in dolutegravir monotherapy studies was most commonly observed at 24 weeks or after [3,16–18].

Adverse events were not severe and did not differ between arms. This is particularly important as switching to new drugs in patients already tolerating their antiretroviral regimens usually results in an attrition effect because of tolerability issues with the new drugs. There were no more central nervous system (CNS) adverse effects in the raltegravir and lamivudine arm. CNS effects have been reported more commonly with dolutegravir than with raltegravir or elvitegravir [19–21]. In a recent meta-analysis of randomized trials [22], dolutegravir (vs. other core agents) was associated with a higher risk of insomnia. In our study, the quality of sleep as measured by the PSQI did not differ between arms. There was a nonsignificant higher weight and body fat increase in the raltegravir and lamivudine, but the size of change was small and of doubtful clinical relevance. There have been recent reports suggesting more weight gain with integrase inhibitors than with other agents [23,24]. In the NEAT022 randomized clinical trial, patients who switched from boosted protease inhibitors to dolutegravir gained approximately 1 kg in 48 weeks [25] and weight increase was associated with a decrease in adiponectin [26], a marker of insulin resistance and obesity. More data are needed to determine whether weight increase is a class effect of integrase inhibitors, and which is its clinical meaning.

Our study had limitations. There were few patients and the follow-up was short. However, this was a convenient way for planning such an intensive pilot study on a new therapeutic strategy. To compensate for these limitations, intensive virological and immunological studies were planned, and an additional 48-week extension phase is currently ongoing. Despite having been approved by FDA and EMA, the fixed-dose formulation used, Dutrebis, has never been commercially available because of a decision of the manufacturing company, Merck, but the individual products raltegravir and lamivudine are available in a once daily dose.

In summary, this pilot study suggests that switching to raltegravir and lamivudine in patients with viral suppression maintains efficacy and is well tolerated. This maintenance regimen might be a cost-effective option for patients at risk of drug–drug interactions or needing to avoid the negative impact on comorbidities or specific toxicities of certain antiretroviral drugs.

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Role of each author: E.d.L., study design, statistical analysis, draft of the manuscript. M.L., patients' recruitment, review of the manuscript. J.R., patients' recruitment, review of the manuscript; A.G.-C., patients' recruitment, review of the manuscript; J.B., analysis of the Pittsburg Sleep Quality test, review of the manuscript; A.I., patients' recruitment, review

of the manuscript; A.T., DXA scan and interpretation, sample processing, review of the manuscript. A.R., DXA scan and interpretation, sample processing, review of the manuscript; M.M.-R., patients' recruitment, review of the manuscript; M.L., patients' recruitment, review of the manuscript; J.M., patients' recruitment, review of the manuscript. S.S.P., laboratory analysis, review of the manuscript; M.P., laboratory analysis, review of the manuscript. J.L.B., patients' recruitment, review of the manuscript. E.M., secured funding, study design, patients' recruitment, review of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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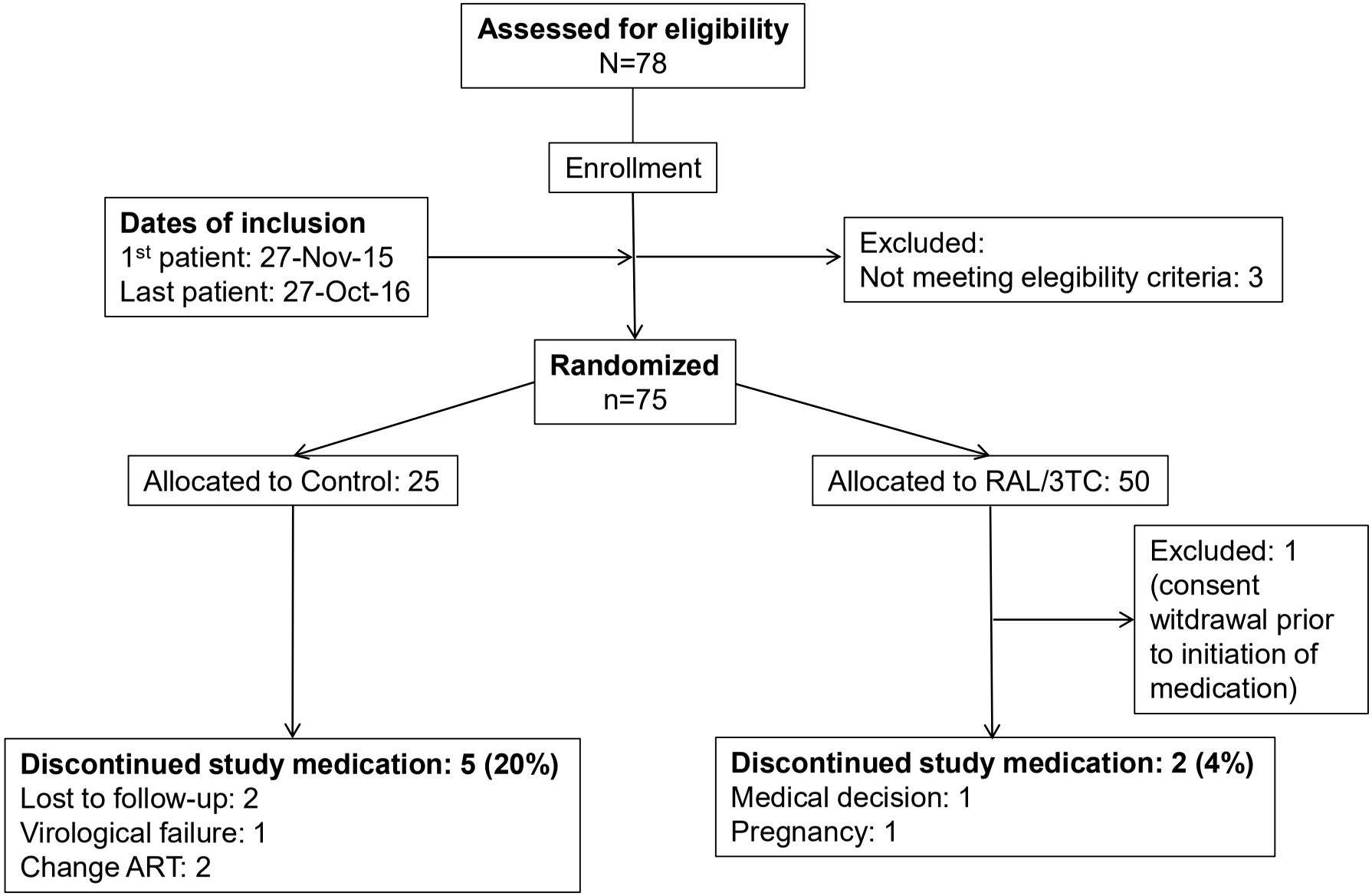
Supplementary Figure 1. Patients' disposition.



Supplementary Table 1. Change in laboratory parametres,

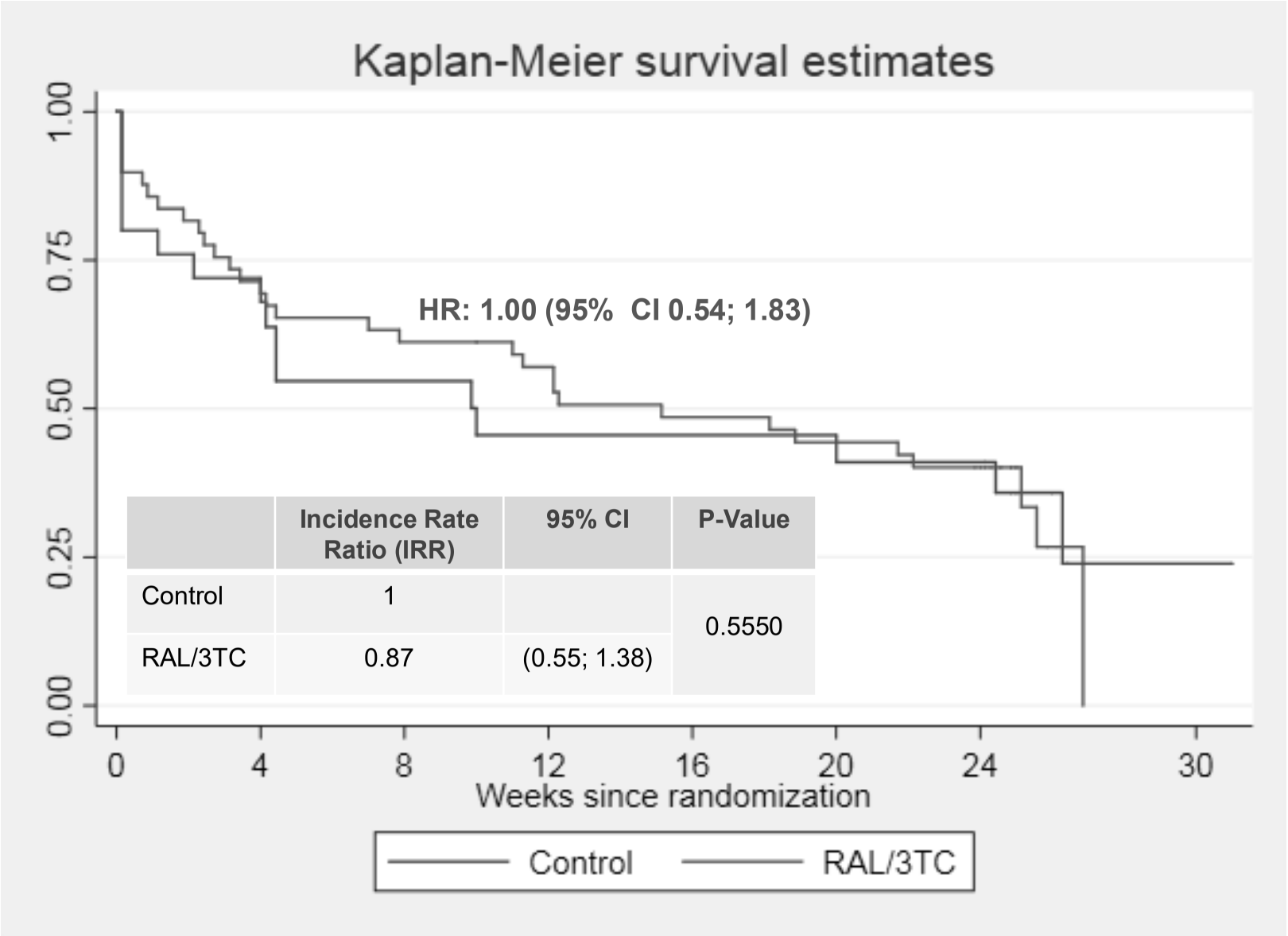
	Change in Control (n=25)	Change in RAL/3TC (n=49)	Change in RAL/3TC vs. Change in Control	P-value
PSQI score	1.088 (0.714; 1.658)	0.957 (0.716; 1.280)	0.880 (0.528; 1.468)	0.6243
Adherence, Morisky	3.309 (0.903; 12.130)	1.074 (0.471; 2.449)	0.325 (0.070; 1.512)	0.1517
CD4 cells/mm^2	0.990 (0.762; 1.287)	0.972 (0.816; 1.157)	0.981 (0.716; 1.344)	0.9054
CD8 cells/mm^2	0.867 (0.664; 1.133)	0.905 (0.757; 1.081)	1.043 (0.757; 1.438)	0.7965
Creatinine, mg/dL	1.042 (0.912; 1.190)	0.977 (0.894; 1.068)	0.938 (0.799; 1.101)	0.4318
eGFR <90 mL/min, CKD EPI	1.268 (0.529; 3.041)	0.917 (0.273; 3.081)	0.723 (0.162; 3.226)	0.6705
Triglycerides, mg/dL	0.901 (0.681; 1.191)	0.992 (0.822; 1.196)	1.101 (0.787; 1.541)	0.5744
Total cholesterol, mg/dL	-1.280 (-27.798; 25238)	0.803 (-16.986; 18.593)	2.083 (-29.849; 34.016)	0.8983
LDL cholesterol, mg/dL	2.222 (-20.663; 25.108)	-0.611 (-16.103; 14.881)	-2.834 (-30.469; 24.802)	0.8407
HDL cholesterol, mg/dL	-0.099 (-8.578; 8.380)	1.158 (-4.530; 6.845)	1.257 (-8.953; 11.466)	0.8094
Glucose, mg/dL	0.970 (0.878; 1.072)	0.922 (0.862; 0.986)	0.950 (0.843; 1.071)	0.4046
Insulin, U/L	0.866 (0.571; 1.313)	0.896 (0.666; 1.206)	1.035 (0.621; 1.727)	0.8938
25OH Vitamin D, ng/mL	1.762 (1.246; 2.490)	1.526 (1.201; 1.938)	0.866 (0.569; 1.319)	0.5034
Urine beta-2 microglobulin, mg/g	1.325 (0.278; 6.318)	0.410 (0.149; 1.123)	0.309 (0.048; 1.986)	0.2162

PSQI: Pittsburg Sleep Quality Index

Supplementary Table 2. Change in body composition parametres.

	Change in Control (n=25)	Change in RAL/3TC (n=49)	Change in RAL/3TC vs. Change in Control	P-value
BMI, kg/m^2	-0.107 (-0.261; 0.072)	0.046(--0.093; 0.144)	0.152(0.071; 0.168)	0.0532
Fat (DXA)				
Total body fat, grams	-270 (-602; 61)	51 (-189; 284)	321 (-84; 726)	0.1200
Trunk fat, grams	88 (-240; 416)	20 (-206; 245)	-69 (-467; 330)	0.7358
Bone (DXA)	Lumbar spine T-score (mean, SD)			
Total hip BMD g/cm^2	0.15 (-0.37; 0.68)	-0.067 (-0.43; 0.29)	-0.22 (-0.85; 0.42)	0.4981
Femur T-score (mean, SD)	0.01 (0; 0.02)	0 (-0.01; 0.02)	-0.01 (-0.02; 0.02)	0.3366
L1-L4 BMD g/cm^2	0.16 (-0.55; 0.78)	0.09 (-0.37; 0.55)	-0.03 (-0.84; 0.78)	0.9455
Lumbar spine T-score (mean, SD)	0 (-0.01; 0.02)	-0.01 (-0.02; 0.02)	0 (-0.02; 0.02)	0.8455

Supplementary Figure 2. Time to first adverse event and incidence rate ratio of all adverse events .



	Incidence Rate Ratio (IRR)	95% CI	P-Value
Control	1		0.5550
RAL/3TC	0.87	(0.55; 1.38)	

Trabajo 4

Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial.

Jhon Rojas*, **Elisa de Lazzari***, Eugenia Negredo, Pere Domingo, Juan Tiraboschi, Esteve Ribera, Nadia Abdulghani, Jordi Puig, Maria G Mateo, Daniel Podzamczer, Maria M Gutierrez, Roger Paredes, Bonaventura Clotet, Jose M Gatell, Jose L Blanco†, Esteban Martínez†, en nombre del grupo de studio del DOLAM

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Resumen

Objetivos: Los regímenes simplificados de terapia antirretroviral son deseables para las personas con VIH. Investigamos la eficacia y la seguridad de cambiar de triple a doble terapia con dolutegravir más lamivudina.

Métodos: El DOLAM es un ensayo de fase IV, aleatorizado, abierto y de no-inferioridad, realizado en seis clínicas de VIH de Cataluña. Las personas elegibles eran aquellas con VIH que recibían un régimen de tratamiento antirretroviral triple, con supresión virológica, un nadir CD4 ≥ 200 células/µL, que eran HBsAg negativos, y sin mutaciones de resistencia o fracasos virológicos previos. La aleatorización, generada por ordenador, fue estratificada por la clase del tercer fármaco y asignó (1:1) los participantes a cambiar a dolutegravir oral 50 mg y lamivudina 300 mg una vez al día o a continuar con la terapia triple durante 48 semanas. El criterio de valoración principal fue la proporción de personas con un valor de ARN-VIH ≥ 50 copias/ml a la semana 48 (algoritmo Snapshot de la FDA, margen de no inferioridad del 8%). Tanto los resultados primarios como los de seguridad se evaluaron en la población ITT expuesta (eITT). El estudio finalizó y se registró en EudraCT 201500027435.

Resultados: Entre el 7 de julio de 2015 y el 31 de octubre de 2018, 265 participantes fueron asignados aleatoriamente a cambiar a dolutegravir más lamivudina (n = 131) o a mantener el

tratamiento antirretroviral triple (n = 134) y todos recibieron al menos una dosis. Nueve (7%) participantes en el grupo de doble terapia y diez (7%) en el grupo de triple terapia fueron excluidos antes de las 48 semanas, principalmente debido a discontinuaciones del tratamiento o fallo virológico. Los participantes fueron predominantemente hombres (116 [87%] de 134 en el grupo triple ART y 111 [85%] de 131 en el grupo dolutegravir más lamivudina). La diferencia en la proporción de participantes con ARN-VIH ≥ 50 copias/ml a las 48 semanas entre el grupo de doble terapia (tres [2%] de 131) y el grupo de triple terapia (dos [1%] de 134) fue de 0.8 puntos porcentuales (IC 95% -3; 5.2), demostrando la no-inferioridad de la terapia doble con dolutegravir más lamivudina en comparación con el tratamiento antirretroviral triple. 73 (56%) de los 131 participantes asignados a la terapia doble tuvieron 150 efectos adversos, en comparación con 78 (58%) de 134 participantes asignados a la terapia triple que también tuvieron 150 eventos adversos (p-valor=0.68). La discontinuación del tratamiento antirretroviral debido a efectos adversos se produjo en cuatro personas del grupo de triple terapia y tres del grupo de doble terapia.

Conclusiones: Nuestros hallazgos muestran la eficacia y la seguridad del dolutegravir más lamivudina como opción de simplificación de terapia antirretroviral en personas con VIH seleccionadas, con supresión virológica en tratamiento triple.

Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial

Jhon Rojas, Elisa de Lazzari*, Eugenia Negredo, Pere Domingo, Juan Tiraboschi, Esteve Ribera, Nadia Abdulghani, Jordi Puig, Maria G Mateo, Daniel Podzamczer, Maria M Gutierrez, Roger Paredes, Bonaventura Clotet, Jose M Gatell, Jose L Blanco†, Esteban Martínez†, on behalf of the DOLAM study group‡*

Summary

Background Simplified antiretroviral therapy (ART) regimens are desirable for people with HIV. We investigated the efficacy and safety of switching from triple ART to dual dolutegravir plus lamivudine therapy.

Methods DOLAM is a phase 4, randomised, open-label, non-inferiority trial, done at six HIV clinics in Catalonia, Spain. Adults with HIV-1 receiving a triple ART regimen, aged 18 years or older, with virological suppression, a CD4 nadir of at least 200 cells per µL, who were HBsAg-negative, and without previous viral failure or resistance mutations to study drugs were eligible. Participants underwent computer-generated randomisation, stratified by the class of the third drug, and were assigned (1:1) to switch to oral dolutegravir 50 mg and lamivudine 300 mg once daily or to continue triple ART for 48 weeks. The primary endpoint was the proportion of people with an HIV RNA value of at least 50 copies per mL at week 48 (US Food and Drug Administration snapshot algorithm, 8% non-inferiority margin). Both the primary and safety outcomes were evaluated in the intention-to-treat exposed population. The study is completed and was registered with EudraCT 201500027435.

Findings Between July 7, 2015, and Oct 31, 2018, 265 participants were randomly assigned to switch to dolutegravir plus lamivudine (n=131) or to maintain triple ART (n=134) and all received at least one dose. Nine (7%) participants in the dual therapy group and ten (7%) in the triple therapy group were excluded before 48 weeks, mostly due to treatment discontinuations or virological failure. Participants were predominantly male (116 [87%] of 134 in the triple ART group and 111 [85%] of 131 in the dolutegravir plus lamivudine group). The difference in the proportion of participants with HIV RNA values of at least 50 copies per mL at 48 weeks between the dual therapy group (three [2%] of 131) and triple therapy group (two [1%] of 134) was 0·8 percentage points (95% CI −3·3 to 5·2), showing non-inferiority of dolutegravir plus lamivudine dual therapy compared with triple ART. 73 (56%) of 131 participants allocated to dual therapy had 150 adverse effects, compared with 78 (58%) of 134 participants allocated to triple therapy who also had 150 adverse events (p=0·68). Drug discontinuation due to adverse effects occurred in four people in the triple therapy group and three people in the dual therapy group.

Interpretation Our findings show the efficacy and safety of dolutegravir plus lamivudine as a simplified therapy switch option for selected people with HIV with virological suppression on triple ART.

Funding Instituto de Salud Carlos III, Red de Investigación en Sida, and ViiV Healthcare.

Introduction

Simplification of antiretroviral therapy (ART) for treating HIV has been commonly pursued.[1–3] Monotherapy has been found to be suboptimal.[4,5] A 2021 meta-analysis suggests that dual therapy could be as effective as triple therapy in people with HIV who are naive to ART and who have a CD4 count above 200 cells per µL.[6] Dolutegravir plus lamivudine has received a lot of attention as a dual HIV therapy due to its tolerability, absence of interactions, and low cost. The GEMINI trials showed non-inferiority of dolutegravir plus lamivudine versus dolutegravir plus tenofovir–emtricitabine,[7,8] leading to the inclusion of dolutegravir plus lamivudine as a preferred regimen in major guidelines for people with HIV who are naive to ART.[1–3] The effects of switching to dolutegravir plus lamivudine in adults with HIV with viral suppression on triple therapy have been assessed in several observational studies or single-arm trials.[9–12] The TANGO study showed the non-inferiority of switching to dolutegravir plus lamivudine in adults with HIV being treated with a triple regimen that contained tenofovir alafenamide,[13,14] but there are scarce randomised controlled trial data on switching from any triple regimen.[15] The SIMPL'HIV trial showed the non-inferiority of switching to dolutegravir

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical trials of dolutegravir and lamivudine for the treatment of HIV-1 infection. Our search terms included (("dolutegravir") OR ("DTG")) AND (("lamivudine") OR ("3TC")) and we looked for reports of randomised controlled trials published in English from database inception up to April 26, 2021. Dolutegravir plus lamivudine (the study regimen) has been investigated in two parallel randomised clinical trials with antiretroviral-naive HIV-infected adults (GEMINI-1 and GEMINI-2) and in two independent randomised clinicals trials with virologically suppressed antiretroviral-experienced HIV-infected adults (ASPIRE and TANGO). Non-inferiority of dolutegravir plus lamivudine to triple antiretroviral therapy based on a 12% margin was shown at 48 weeks in the ASPIRE trial, but it was a pilot study. TANGO was a fully powered clinical trial in which non-inferiority of dolutegravir plus lamivudine (single pill) based on a 4% margin was shown, but the comparator group included triple therapy containing tenofovir alafenamide only.

Added value of this study

Dolutegravir plus lamivudine is a therapeutic option for HIV infection with a lower burden of medication and a lower cost than other contemporary antiretroviral regimens. We report the first virological and safety outcomes in a phase 4 trial of switching to this regimen versus remaining on a standard triple regimen consisting of a backbone of two nucleoside reverse transcriptase inhibitors plus a third drug (protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase inhibitor) in adults with virologically suppressed HIV-1. Switching to the study regimen was non-inferior to continuing on the control regimen in terms of the proportion of patients with HIV RNA values of at least 50 copies per mL at 48 weeks. No resistance to dolutegravir or lamivudine emerged, and both groups were similarly well tolerated. Patients who switched to the study regimen had a higher weight gain, driven by regimens containing tenofovir disoproxil fumarate or integrase inhibitors before the switch, but weight changes were not correlated with changes in fasting glucose or lipids. Overall, our findings show efficacy and safety of the study regimen as a simplified therapy switch option for standard triple antiretroviral therapy in people with HIV.

Implications of all the available evidence

The study regimen is a convenient and effective antiretroviral switch option that combines the high genetic barrier to resistance of dolutegravir with the safety and cost advantages of lamivudine in adults with HIV-1 with virological suppression. The study regimen is now available in several countries as a single pill.

plus emtricitabine (rather than switching to dolutegravir plus lamivudine) in adults with HIV being treated with any triple regimen,[16] but emtricitabine is more expensive than lamivudine and is not coformulated with dolutegravir. A large, randomised clinical trial assessing whether virologically suppressed people with HIV on any triple antiretroviral can be safely switched to dual therapy with dolutegravir–lamivudine is ongoing (SALSA trial, NCT04021290).

In the DOLAM trial, we aimed to assess virological efficacy and safety of switching from contemporary triple antiretroviral regimens to the dual combination of dolutegravir plus lamivudine in selected virologically suppressed people with HIV. We chose a non-inferiority design to show that there is no important loss of efficacy if the new strategy is used instead of the standard triple ART.

Methods

Study design

The DOLAM study is a phase 4, randomised, controlled (with active treatment), open-label, parallel, clinical non-inferiority trial. The study was done at six major HIV clinics in Catalonia, Spain. Institutional review boards from all participating centres and the Spanish Agency of Medicines and Medical Devices granted ethical approval of the study.

Participants

Consecutive (by date of registration at the clinic), asymptomatic adults (aged ≥18 years) who tested seropositive for HIV-1 using standard diagnostic criteria, having received triple ART (including two nucleoside or nucleotide reverse transcriptase inhibitors [NRTIs] plus either a boosted protease inhibitor, a non-NRTI, or an integrase inhibitor) for at least the previous 12 months, with sustained viral suppression (defined by plasma HIV RNA <50 copies per mL in two or more consecutive determinations during at least the 12 months before inclusion; blips up to 200 copies per mL were admissible) were invited to participate. For women of childbearing age, a negative pregnancy test within 10 days before randomisation into the study was required. Exclusion criteria were: pregnancy, lactation, or planned pregnancy during the study period; previous virological failure (defined as plasma HIV RNA ≥50 copies per mL in two consecutive tests or >500 copies per mL in one test) to regimens containing lamivudine, emtricitabine, or integrase inhibitors; any mutation conferring resistance to lamivudine, emtricitabine, or integrase inhibitors; lowest CD4 count of less than 200 cells per µL; any disease or history of disease that might confound the results of the study or pose additional risk to the participant's treatment; and chronic hepatitis B (defined by a positive hepatitis B surface antigen test at screening). Written

informed consent was obtained from all eligible participants before randomisation.

Randomisation and masking

Participants were assigned to a treatment group using computer-generated randomisation, stratified by third drug class to ensure a balanced distribution across groups with respect to the third drug used. The assignment was centralised and implemented via MACRO Electronic Data Capture (Elsevier, Amsterdam) version 4.9.1.8852. The medical statistics core facility of August Pi i Sunyer Biomedical Research Institute (IDIBAPS; Barcelona, Spain) was in charge of the randomisation list and implementation, independently of the rest of the trial development, statistical analysis, and result interpretation. The investigators JR, EN, PD, JT, ER, NA, JP, MGM, DP, MMG, RP, BC, JLB, and EM were responsible for patients' enrolment. Allocation was open label, so investigators and participants knew who was assigned to receive each treatment. The study was developed in two phases, A and B. In phase A, eligible participants were randomly assigned in a 1:1:1 ratio to one of the following groups: to continue current triple ART (control group), to switch to dolutegravir 50 mg plus lamivudine 300 mg once daily (dual therapy group), or to switch to dolutegravir 50 mg once daily (monotherapy group), and were followed up for at least 24 weeks. Phase A was done for futility purposes to assess whether experimental groups had an unacceptable rate of viral failure (defined as ≥5%). In the planned 24-week analysis, the dolutegravir monotherapy group showed an unacceptable risk of viral failure with development of integrase inhibitor cross-resistance mutations, whereas the dolutegravir plus lamivudine dual therapy group showed no unacceptable viral failure. For this reason, the data safety monitoring board of the study recommended to stop the dolutegravir monotherapy group and to continue the study with two groups only (dolutegravir plus lamivudine dual therapy *vs* control [phase B]). Based on the phase A results, the DOLAM study protocol was amended and the sample size to complete phase B of the study was recalculated. The participants in phase B stayed in their originally randomly assigned groups, and stratification also remained the same. Phase A results have been previously published.[17] Therefore, participants recruited after this protocol amendment were randomly assigned in a 1:1 ratio to either the control group, or to switch to dolutegravir plus lamivudine dual therapy.

Procedures

Participants were randomly assigned to continue their current triple ART or to have it switched to dolutegravir 50 mg plus lamivudine 300 mg orally once daily. Participants were visited at the HIV clinic of the respective participating centres at baseline and every 12 weeks until completing at least 48 weeks of follow-up. At baseline, characteristics including age, sex assigned at birth, suspected route of HIV transmission, and anchor drug at entry were collected. At each visit, participants had a complete physical examination, including weight and height measurements, the Spanish-validated version of the Pittsburg Sleep Quality Index[18] was self-administered, and at least 8-h fasting blood was drawn for blood cells and chemistry tests including glucose, creatinine, liver tests, 25-hydroxyvitamin D, insulin, lipids, CD4 and CD8 cell counts, and plasma HIV-1 RNA (detection limit 50 copies per mL). At each follow-up visit, data on adverse events and use of drugs other than ART were collected, a simplified adherence questionnaire was administered, and a pregnancy test in women of childbearing age was done. Intensity of adverse events was assessed according to the Division of AIDS table for grading the severity of adult and paediatric adverse events.[19] Data were also collected for the following planned substudies and these will be reported elsewhere: HIV-1 RNA, inflammatory and neuronal damage markers, and dolutegravir concentrations in cerebrospinal fluid;[20] body composition and bone mineral density; proteinomics, lipidomics, and metabolomics studies; ultrasensitive plasma HIV RNA; and peripheral mononuclear blood cell HIV-1 reservoir. Changes in insulin resistance and plasma 25-OH vitamin D levels were not analysed because we were unable to obtain baseline and 48-week samples from most of the participants.

We established that a participant should be withdrawn from the study before the stipulated time in the following circumstances: confirmed virological failure (defined as ≥50 copies per mL in two consecutive determinations or a single HIV RNA value of >1000 copies per mL), interruption of treatment due to adverse events, intolerance or non-adherence during the study, concurrent process or illness that in the opinion of the investigator required withdrawal of the participant, protocol deviation that in the opinion of the sponsor required withdrawal of the participant, the participant's personal wish not to continue in the study, or other major issues, which were determined on a person-by-person basis. Confirmed virological failure was planned as a premature completion criterion because virological failure in one or both of the original experimental groups (dolutegravir-based monotherapy or dual therapy) could be associated with a higher risk of resistance. Every effort was made to maintain follow-up of all included participants.

In the event of confirmed virological failure, plasma was tested for HIV reverse transcriptase, protease, and integrase resistance mutations by population sequencing (Trugene, Siemens [Erlangen, Germany]), and peripheral blood mononuclear cells were tested for HIV reverse transcriptase, protease, and integrase resistance mutations by ultra-deep sequencing (MiSeq platform, Illumina [San Diego, CA, USA]), following routine protocols. In such scenarios, baseline peripheral blood proviral DNA genotyping was also done.

Outcomes

The primary endpoint was the proportion of people with HIV RNA values of at least 50 copies per mL at week 48 (US Food and Drug Administration [FDA] snapshot algorithm, 8% non-inferiority margin) evaluated in the intention-to-treat exposed population. Secondary endpoints were the incidence of blips (defined as a single HIV RNA value ≥50 and ≤1000 copies per mL followed by HIV RNA values <50 copies per mL), and the number of participants with one or more blips, changes in CD4 and CD8 cells, changes in fasting plasma lipids, and estimated glomerular filtration rate, proteinuria, adverse effects change in self-reported adherence as measured by the self-reported adherance (SERAD) questionnaire, and weight (as a measure of body composition) and sleep quality changes (with good sleep quality defined as a Pittsburg Sleep Quality Index score of 5 or less[18]).

Statistical analysis

Following the interim analysis at the end of phase A, which recommended interruption of treatment in the dolutegravir monotherapy group, we recalculated our sample size. On the basis of a previous ART switch study from our group[21] in which 4% of patients had HIV RNA values of at least 50 copies per mL at 48 weeks, we considered that a non-inferiority margin of 8% would require a sample size similar to that required in switch trials using the common 10–12% non-inferiority margin, that had an endpoint of treatment success (ie, HIV RNA values of <50 copies per mL). With this assumed virological failure rate, a non-inferiority margin of 8%, and an α error of 2·5%, we estimated that 117 participants per group should be recruited to achieve 80% power to prove non-inferiority with regard to the primary endpoint in the dual therapy group relative to the control group. Assuming a potential loss to follow-up of 10%, a total sample size of 260 participants was established, of whom 60 had already been recruited in the dual therapy and control groups during phase A. The test statistic used was the one-sided Z test with pooled proportions to compute the SE. This calculation was performed using Power Analysis and Sample Size Software version 15.

An FDA-derived snapshot algorithm in the intention-to-treat exposed population (non-inferiority margin 8%) was planned to assess the primary endpoint. All participants who received at least one dose of study medication were considered for the intention-to-treat analysis. The proportions of people with confirmed HIV of at least 50 copies per mL were assessed in each group and the 95% CI of the difference was based on the Newcombe method.[22] Non-inferiority would be proven if the upper bound of the CI of the difference in proportions did not cross over the prespecified margin of 8%. If the lower bound was above 0, then superiority would be assessed using the Fisher's exact test.

We also did two sensitivity efficacy analyses: an FDA-derived snapshot algorithm to assess the proportion of people with HIV RNA values of at least 50 copies per mL at week 48 in the per-protocol population, and an analysis of therapeutic efficacy defined by the proportion of people with HIV RNA values of less than 50 copies per mL in the intention-to-treat exposed population at week 48. All participants who received at least one dose of study medication and did not meet any withdrawal or dropout criteria, except if they had virological failure, were considered for the per-protocol analysis. Exploratory subgroup analyses (age, sex, baseline CD4 cell counts, baseline third drugs, and baseline NRTI drugs) of virological response of at least 50 copies per mL at 48 weeks were also assessed in the intention-to-treat exposed population.

We did a descriptive analysis of all study variables, overall and stratified by treatment groups, using medians and IQRs for the quantitative variables and using absolute frequency and percentage of each category for qualitative characteristics. Comparisons between groups were based on the Wilcoxon rank sum test for quantitative variables and on the χ^2 or Fisher's exact test for qualitative variables. Correlation between quantitative variables was assessed using Spearman's correlation coefficient because data were skewed.

Changes in weight (measured as part of basic data for body composition) and all other secondary quantitative outcomes over time were assessed by random-effect regression models. The approximation of the residuals to a normal distribution was graphically assessed using the normal probability and normal quantile plots, and was tested with the skewness and kurtosis test.

Safety outcomes were analysed descriptively in the intention-to-treat exposed population. Clinical and laboratory adverse events were reported as incidence rates per 100 person-years and Poisson regression models were done to estimate the incidence rate ratio. We did an exploratory analysis of the influence of baseline third drugs and baseline NRTI drugs on changes in fasting glucose, lipids, and kidney laboratory values using random-effect regression models including these covariables together with randomised treatment and adjusting for age and sex. Tests were two-tailed (except otherwise stated) and the significance level was set at 5%. All statistical analyses were done using Stata version 16. The study is registered at EudraCT, 201500027435.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 7, 2015, and Jan 28, 2016 (phase A) and between Oct 24, 2017, and Oct 31, 2018 (phase B), 266 people with HIV were screened for eligibility in six HIV clinics in Catalonia, Spain. 265 people were randomly assigned and one screened person withdrew

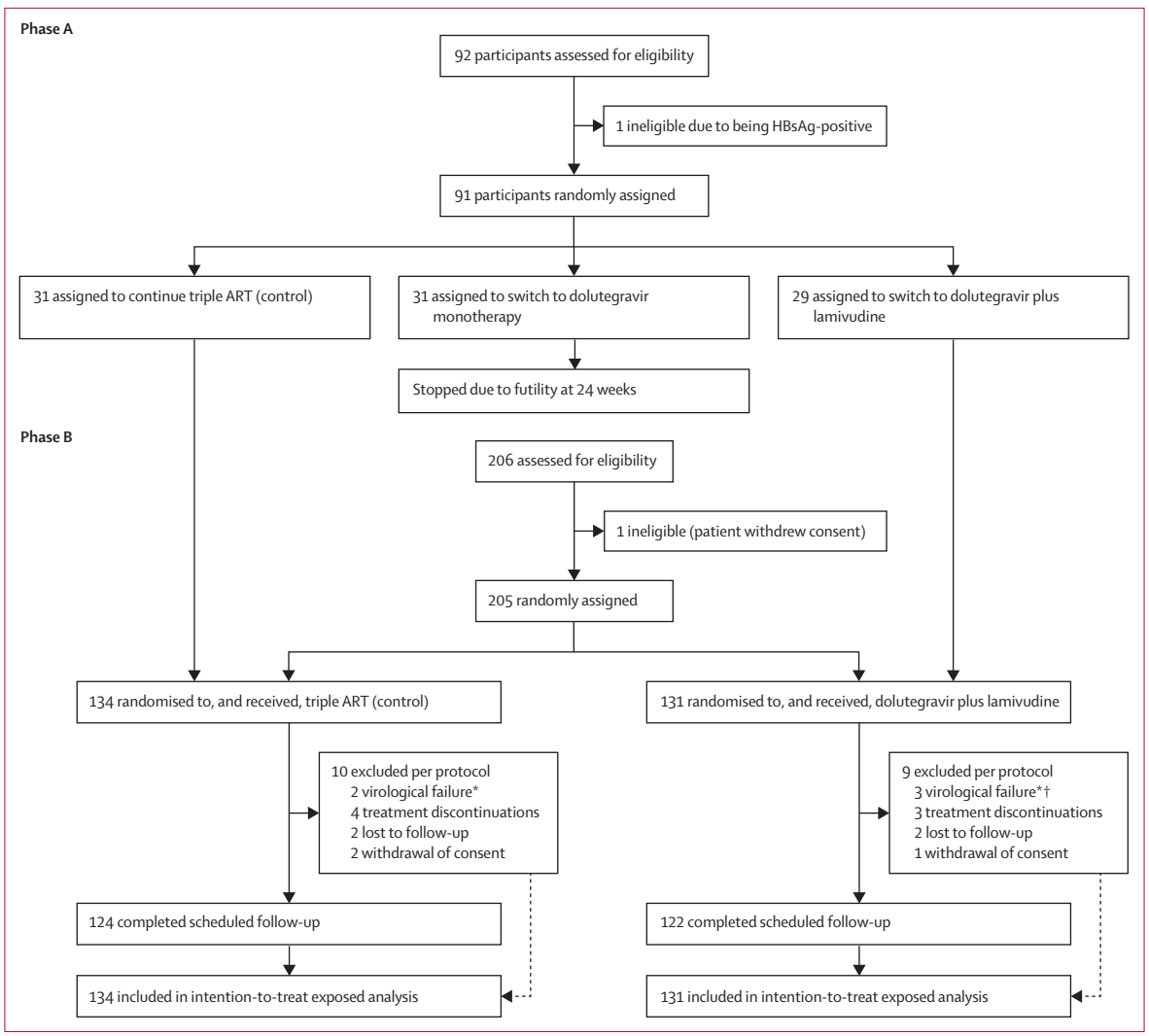

Figure 1: **Trial profile**
ART=antiretroviral therapy. *These patients were included in the per-protocol analysis; all other patients excluded per protocol were not. †Two patients had protocol-defined virological failure withdrawal, but continued follow-up and had less than 50 copies of HIV RNA per mL at 48 weeks.

their consent before randomisation (figure 1). 134 (50%) of 265 were randomly assigned to maintain their triple ART regimen and 131 (49%) were randomly assigned to switch to dolutegravir plus lamivudine. Baseline demographics and clinical characteristics were well balanced between treatment groups (table 1). Participants were predominantly male (227 [86%] of 265) and of White or Latinx ethnicities (260 [98%]). A small proportion (13 [5%] of 265) had previously experienced an AIDS-defining event and median CD4 was 712 cells per μL (IQR 555–903). 165 (62%) of the 265 participants were receiving single-pill regimens. There were roughly similar proportions of participants taking the NRTIs abacavir (98 [37%] of 265) and tenofovir disoproxil fumarate (94 [35%]), and slightly fewer taking tenofovir alafenamide (73 [28%]). There were also similar proportions of participants receiving non-NRTIs (132 [50%]) or integrase inhibitors (121 [46%]) as anchor drugs; protease inhibitors (12 [4%]) were scarcely used. 48 (18%) participants overall were taking dolutegravir-based regimens, most commonly single-pill dolutegravir–abacavir–lamivudine (12 [19%] of 134 participants in the triple ART group *vs* 19 [15%] of 131 participants in the dolutegravir plus lamivudine group).

Virological outcomes at week 48 in the intention-to-treat exposed population (n=265), using the FDA snapshot algorithm, are shown in figure 2. The difference in the proportion of participants with HIV RNA values of at least 50 copies per mL at 48 weeks between the dual therapy group (three [2%] of 131) and the triple therapy group (two [1%] of 134) was 0·8 percentage points (95% CI −3·3 to 5·2), showing non-inferiority of dolutegravir plus lamivudine dual therapy compared with triple ART because the upper bound of the CI did not cross the

	Triple ART (n=134)	Dolutegravir plus lamivudine (n=131)
Age, years	46 (39–51)	45 (37–53)
Sex at birth		
Female	18 (13%)	20 (15%)
Male	116 (87%)	111 (85%)
White	105 (78%)	106 (81%)
Latinx	25 (19%)	24 (18%)
Other	4 (3%)	1 (1%)
Suspected route of HIV transmission		
Male-to-male sex	101 (75%)	93 (71%)
Heterosexual sex	20 (15%)	24 (18%)
Injection drug use	7 (5%)	9 (7%)
Blood products	1 (1%)	1 (1%)
Unknown	5 (4%)	4 (3%)
Length of known HIV infection, years	10 (6–17)	11 (6–20)
Length of time with HIV RNA <50 copies per mL, years	5·3 (2·7–8·6)	5·2 (2·2–8·1)
Positive hepatitis C serology	7 (5%)	7 (5%)
Previous AIDS-defining events	5 (4%)*	8 (6%)†
CD4 and CD8 measurements		
CD4 cells per µL nadir	315 (261–404)	301 (253–415)
CD4 cells per µL	747 (551–891)	700 (560–940)
CD4, %	35% (32–40)	36% (31–43)
CD8 cells per µL	718 (551–902)	733 (500–962)
CD8, %	36% (30–42)	36% (28–42)
CD4:CD8 ratio	0·92 (0·75–1·08)	0·94 (0·70–1·34)
Third agent		
INSTI	63 (47%)	58 (44%)
Dolutegravir	27 (20%)	21 (16%)
Raltegravir	13 (10%)	12 (9%)
Elvitegravir	23 (17%)	25 (19%)
NNRTI	65 (49%)	67 (51%)
Protease inhibitor	6 (4%)	6 (5%)
NRTI backbone		
Abacavir–lamivudine	53 (40%)	45 (34%)
Tenofovir alafenamide–emtricitabine	35 (26%)	38 (29%)
Tenofovir disoproxil fumarate–emtricitabine	46 (34%)	48 (37%)
(Continued from previous column)		
Number of pills in antiretroviral regimen		
1	79 (59%)	86 (67%)
2	42 (31%)	24 (18%)
3	14 (10%)	18 (14%)
>3	1 (<1%)	1 (<1%)
Adherence		
≥95% weekly	117 (87%)	111 (85%)
≥95% monthly	127 (95%)	123 (94%)
Weight (kg)	72 (67–79)	75 (67–83)
Body-mass index, kg/m²	24 (23–27)	25 (23–27)
Good sleep quality (PSQI ≤5)	79 (59%)	70 (53%)
Chemistry		
Glucose, mg/dL	90 (84–98)	89 (83–95)
Triglycerides, mg/dL	107 (83–148)	117 (81–155)
Total cholesterol, mg/dL	183 (164–210)	186 (161–211)
LDL cholesterol, mg/dL	111 (89–133)	114 (89–130)
HDL cholesterol, mg/dL	46 (39–56)	43 (33–54)
Total-to-HDL cholesterol ratio	4 (3–5)	4 (3–5)
Creatinine, mg/dL	0·90 (0·81–1·04)	0·89 (0·78–1·03)
eGFR, mL/min per 1·73 m²	98 (82–107)	96 (84–106)
Proteinuria, mg/g creatinine	63 (41–85)	70 (41–98)

Data are reported as n (%) or median (IQR). ART=antiretroviral therapy. eGFR=estimated glomerular filtration rate. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. PSQI=Pittsburg Sleep Quality Index. eGFR=estimated glomerular filtration rate. *Tuberculosis (n=3), Kaposi sarcoma (n=2). †Tuberculosis (n=4), *Pneumocystis jiroveci* (n=1), Kaposi sarcoma (n=3).

Table 1: **Baseline demographics and clinical characteristics**

prespecified margin of 8%. Given that the lower bound was not above 0, we did not assess superiority. In the per-protocol exposed population (n=251) analysis at 48 weeks, the difference in the proportions of participants with HIV RNA values of at least 50 copies per mL (three [2%] of 125 in the dual therapy group *vs* two [2%] of 126 in the triple ART group) was 0·8 percentage points (95% CI –3·5 to 5·4), showing non-inferiority of dual therapy relative to triple ART. The proportions of participants with HIV RNA values of less than 50 copies per mL at week 48 in the intention-to-treat analysis were identical in both groups (122 [93%] of 131 in the dual therapy group *vs* 124 [93%] of 134 in the triple therapy group; p=0·81) and the difference between the proportions in the dual therapy group compared with the triple therapy group was 0·6 percentage points (95% CI –6·0 to 7·2). Virological outcomes across subgroups were generally consistent with those in the overall population (figure 3).

At 48 weeks, 112 (93%) of 120 participants in the dual therapy group and 117 (94%) of 125 in the triple therapy group had weekly adherence scores of at least 95%, and 114 (95%) of 120 participants in the dual therapy group and 118 (94%) of 125 in the triple therapy group had monthly adherence scores of at least 95%. In the dual therapy group, adherence scores lower than 90% at any one timepoint were recorded in 26 (20%) of 131 participants (weekly) and 6 (5%) of 131 participants (monthly). In the triple therapy group, adherence scores lower than 90% at any one timepoint occurred in 32 (24%) of 134 (weekly) and 4 (3%) of 134 (monthly).

Five participants met the criteria for confirmed virological failure, two in the triple therapy group (both at week 48) and three in the dual therapy group (two in

week 12, and one in week 36). In all five cases, HIV RNA was detectable at low concentrations (<200 copies per mL) in two consecutive determinations, and these participants had weekly and monthly adherence scores lower than 90% at the time of virological failure. One of the participants with virological failure in the dual therapy group, at week 12, has been previously described.[16] No resistance mutations were detected in the plasma of this participant, but Lys70Glu, Lys219glu, Gly190Arg, and Met230Ile were detected in peripheral blood mononuclear cells; these mutations were not found in baseline proviral DNA. This participant was switched to dolutegravir–abacavir–lamivudine and his HIV RNA was less than 50 copies per mL by week 24 when he withdrew his consent. No mutations were detected in either of the other two participants with virological failure in the dual therapy group. These participants decided to maintain assigned therapy, committed to improve their adherence, and agreed to continue being followed up within the study. In both participants, HIV RNA was less than 50 copies per mL by week 48. In the three participants from the dual therapy group who had virological failure, ARTs at entry were the single-pill regimens efavirenz–tenofovir disoproxil fumarate–emtricitabine, rilpirivirine–tenofovir disoproxil fumarate–emtricitabine, and dolutegravir–abacavir–lamivudine. In one of the participants with virological failure in the triple therapy group at 48 weeks, ART at entry was rilpivirine–tenofovir disoproxil fumarate–emtricitabine, and resistance mutations Lys219Arg, Glu138Lys, and Met230Ile were found both in plasma and peripheral blood mononuclear cells; these mutations were not found in baseline proviral DNA. In the other participant in the triple therapy group, therapy consisted of abacavir–lamivudine–dolutegravir and no resistance mutations in plasma and peripheral blood mononuclear cells were found. In both participants, therapy was switched to darunavir–cobicistat–tenofovir alafenamide–emtricitabine and HIV RNA returned to less than 50 copies per mL 3 months later.

25 (9%) of 265 participants had blips. There were 17 blips in 15 (11%) of the 134 participants assigned to dual therapy and 11 blips in ten (7%) of the 131 participants assigned to triple therapy (p=0·27). The incidence of blips was 14·7 episodes per 100 patient-years in the dual therapy group versus 9·3 episodes per 100 patient-years in the triple therapy group (incidence rate ratio [IRR] 1·58, 95% CI 0·74–3·37, p=0·23). None of the participants with blips had virological failure.

The mean change (adjusted by strata) in the number of CD4 cells per µL at 48 weeks compared with baseline was 32 (95% CI –11 to 75) in the triple therapy group and 30 (–15 to 74) in the dual therapy group (p=0·94). The mean change in the number of CD8 cells per µL was –7 (95% CI –56 to 41) in the triple therapy group versus 24 (–26 to 74) in the dual therapy group (p=0·39). The mean change of the ratio of CD4 to CD8 cells was 0·08 (95% CI 0·01 to 0·15) in the triple therapy group versus 0·06 (–0·01 to 0·13) in the dual therapy group (p=0·71).

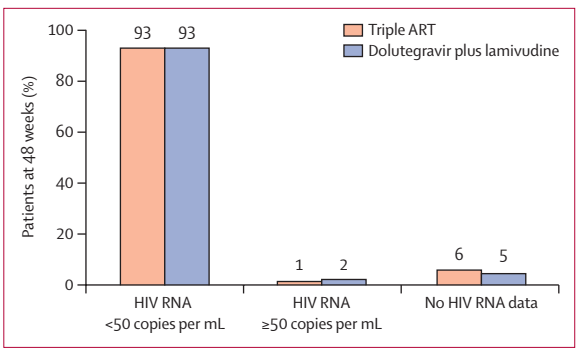

Figure 2: **Virological outcomes at week 48 in the intention-to-treat exposed population by the US Food and Drug Administration snapshot algorithm**
ART=antiretroviral therapy.

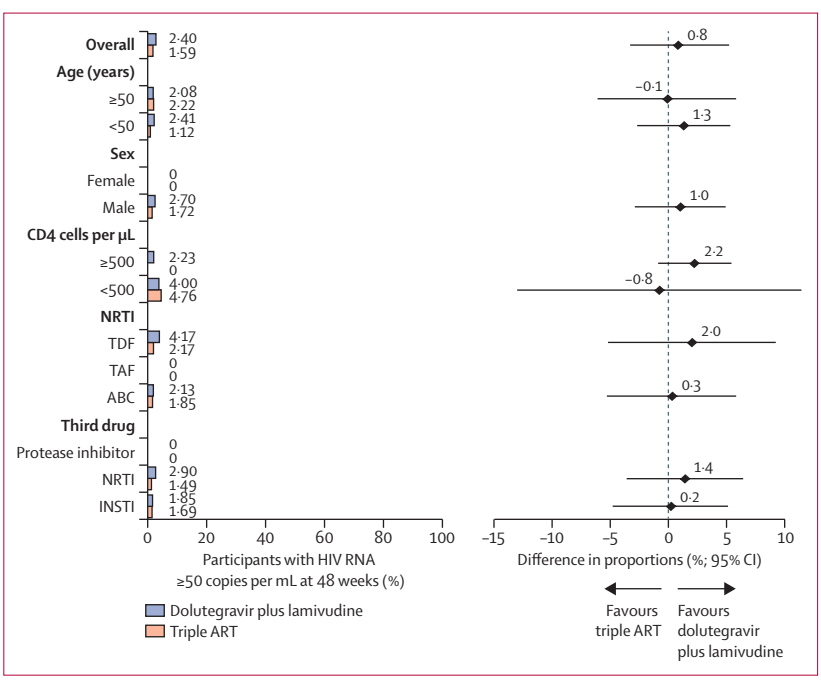

Figure 3: **Virological failure (≥50 copies per mL at 48 weeks, US Food and Drug Administration snapshot algorithm) across subgroups (age, gender, baseline CD4 cell counts, baseline NRTI drugs, and baseline third drugs) in the intention-to-treat exposed population**
NRTI=nucleoside and nucleotide reverse transcriptase inhibitor. TDF=tenofovir disoproxil fumarate. TAF=tenofovir alafenamide. ABC=abacavir. INSTI=integrase strand transfer inhibitor. ART=antiretroviral therapy.

73 (56%) of 131 participants allocated to dual therapy had 150 adverse events, compared with 78 (58%) of 134 participants allocated to triple therapy who also had 150 adverse events (p=0·68). The incidence of adverse effects was 126·2 episodes per 100 person-years in the dual therapy group versus 122·2 episodes per 100 person-years in the triple therapy group (IRR 1·03, 95% CI 0·82–1·30; p=0·78). The most common adverse effects, occurring in at least 5% of participants, were infections, and gastrointestinal, systemic, respiratory, genitourinary, neurological, and dermatological events (table 2). Adverse

	Triple ART (n=134)	Dolutegravir plus lamivudine (n=131)
Adverse events		
Infections	35/150 (23%)	28/150 (19%)
Gastrointestinal	23/150 (15%)	26/150 (17%)
Systemic	16/150 (11%)	19/150 (13%)
Respiratory	17/150 (11%)	18/150 (12%)
Musculoskeletal	19/150 (13%)	16/150 (11%)
Genitourinary	16/150 (11%)	12/150 (8%)
Neurological	8/150 (5%)	14/150 (9%)
Dermatological	8/150 (5%)	14/150 (9%)
Laboratory	5/150 (3%)	1/150 (1%)
Cardiovascular	3/150 (2%)	0/150
Ocular or visual	0/150	2/150 (1%)
Severity		
Mild (grade 1)	107/150 (71%)	118/150 (79%)
Moderate (grade 2)	37/150 (25%)	29/150 (19%)
Severe (grade 3)	6/150 (4%)	3/150 (2%)
Relationship to treatment		
Not related	145/150 (97%)	129/150 (86%)
Unlikely related	4/150 (3%)	4/150 (3%)
Possibly related	1/150 (1%)	8/150 (5%)
Probably related	0/150	9/150 (6%)

Data are the number of events/total number of adverse events (%). Some people presented with more than one adverse event. ART=antiretroviral therapy.

Table 2: **Adverse events**

	Triple ART			Dolutegravir plus lamivudine			$p_{interaction}$ value*
	Mean (95% CI)	n	p value†	Mean (95% CI)	n	p value†	
Total cholesterol (mg/dL)	..	..	0·59	..	..	0·57	0·43
Baseline	186 (179–192)	119	..	188 (180–193)	116	..	..
48 weeks	187 (181–194)	118	..	185 (178–192)	116	..	..
LDL cholesterol (mg/dL)	..		0·97	..	..	0·99	0·97
Baseline	112 (106–119)	108	..	112 (107–118)	102	..	..
48 weeks	114 (108–121)	113	..	112 (106–118)	105	..	..
HDL cholesterol (mg/dL)	..	..	0·031	..	..	0·0039	0·59
Baseline	47 (44–49)	115	..	47 (45–49)	114	..	..
48 weeks	50 (47–52)	118	..	48 (46–51)	115	..	..
Total-to-HDL cholesterol ratio	..	..	0·17	..	..	0·0001	0·28
Baseline	4·07 (3·87–4·27)	115	..	4·36 (4·16–4·56)	114	..	..
48 weeks	3·88 (3·68–4·08)	118	..	4·05 (3·85–4·25)	115	..	..

ART=antiretroviral therapy. *For the difference between groups in the change over time. †For the difference between baseline and 48 weeks within a group.

Table 3: **Plasma lipids at baseline and at 48 weeks, estimated by a mixed-effects regression model adjusted for backbone, anchor drug, sex, and age**

effects were usually mild or moderate and considered unrelated to study drugs. Five (4%) participants in the triple therapy group had serious adverse events (*Listeria monocytogenes* bacteraemia, bacterial endocarditis, appendicitis, severe aortic stenosis, and bowel perforation), compared with three (2%) participants in the dual therapy group (liver abscess, appendicitis, and hip fracture). There were no AIDS-defining events or deaths. Study drug discontinuation due to adverse effects occurred in four people in the triple therapy group (due to osteoporosis, sleep disturbance and dizziness, decompensated heart failure, and diarrhoea) and three people in the dual therapy group (due to insomnia, headache, and dizziness and nightmares).

There were significant increases in HDL cholesterol in both groups at 48 weeks and a significant decrease in the ratio of total to HDL cholesterol in the dual therapy group only, but the differences in changes in fasting lipids between groups were not significant (table 3). We found significant total cholesterol changes at 48 weeks in the 94 participants from regimens containing tenofovir disoproxil fumarate (mean change 9 mg/dL [95% CI 2 to 16], p=0·011) and in the 73 participants from a tenofovir alafenamide-containing regimen (–10 mg/dL [–18 to –2], p=0·018). LDL cholesterol changes were significant in participants on regimens containing tenofovir alafenamide (mean change –11 mg/dL [95% CI –18 to –4], p=0·0021), but were not significantly different in participants on regimens containing tenofovir disoproxil fumarate (5 mg/dL [–0·99 to 11], p=0·10]. HDL cholesterol changes were significant in the participants on regimens containing tenofovir disoproxil fumarate (mean change 5 mg/dL [95% CI 3 to 7], p<0·0001) and in the 121 participants on regimens containing integrase inhibitors (3 mg/dL [1 to 5], p=0·0034). In 258 participants (251 at baseline and 231 at 48 weeks) estimated glomerular filtration rate significantly decreased in the dual therapy group relative to the triple therapy group (mean change –3·1 mL/min per 1·73 m² [95% CI –5·8 to –0·5], p=0·021). There were significant changes in estimated glomerular filtration rate from regimens containing tenofovir alafenamide (n=73; mean change –7 mL/min per 1·73 m² [95% CI –9 to –4], p<0·0001) and from abacavir (n=98; –4 mL/min per 1·73 m² [–6 to –2], p<0·0001). There were no significant changes in proteinuria between groups (data not shown).

In both groups, the quality of sleep did not change over time. The odds ratio of having good sleep quality at 48 weeks compared with baseline was 1·36 (95% CI 0·65–2·86; p=0·42) in the triple therapy group and 1·05 (0·51–2·16; p=0·89) in the dual therapy group. The change in sleep quality over time did not differ between groups: the ratio of the odds ratios in quality of sleep changes in the dual therapy group versus the triple therapy group was 0·77 (95% CI 0·28–2·18, p=0·63). On restricting the analysis to those participants who were not taking integrase inhibitors at study entry, the odds ratios of having good sleep quality at 48 weeks relative to

baseline in both the triple therapy group or the dual therapy group were not significant (data not shown).

In an exploratory analysis, weight change from baseline increased significantly in the dual therapy group (mean change 1·6 kg [95% CI 0·9 to 2·4], p<0·0001) but not in the triple therapy group (0·1 kg [–0·6 to 0·8], p=0·78). The difference between the dual therapy group versus the triple therapy group in mean weight change at 48 weeks was 1·5 kg (95% CI 0·5 to 2·5, p=0·0049). There were significant effects on weight on regimens containing tenofovir disoproxil fumarate (mean change 1·5 kg [95% CI 0·5 to 2·5], p=0·0023) or integrase inhibitors (mean change 1·1 kg [0·2 to 1·9], p=0·011). Participants switching from a regimen containing raltegravir or elvitegravir to dolutegravir plus lamivudine had greater weight increases than those who were already on a dolutegravir-containing regimen (data not shown). Changes in weight were not correlated with changes in fasting glucose, total cholesterol, LDL cholesterol, or HDL cholesterol.

Discussion

After 48 weeks of follow-up, switching to dolutegravir plus lamivudine was found to be a non-inferior HIV therapy to remaining on a triple therapy regimen, with an 8% margin. Very few participants had virological failure and HIV RNA was low when virological failure developed. Virological failure was associated with suboptimal adherence in both groups. No resistance mutations to study drugs were detected in participants with protocol-defined virological failure on dual therapy, thus supporting the high genetic barrier of the drug combination.[23] We did not find differences in efficacy according to the type of third drug or NRTI at baseline, CD4 cell count, sex, or age. The presence of blips was not associated with virological failure.

The results of the DOLAM study support the results of the TANGO study and other smaller studies.[13–16] The DOLAM study unrestrictedly included adults with HIV on any triple therapy and the dual combination therapy was given as two separate pills thus exploring more broadly the applicability of the switching strategy. Even though about two in three participants assigned to dolutegravir plus lamivudine came from single-pill antiretroviral regimens, switching did not negatively affect adherence or virological outcomes. Switching from triple therapy to dolutegravir plus emtricitabine has previously been shown to lead to an improvement in quality-of-life scores.[16] Mathematical modelling has suggested that dolutegravir plus lamivudine dual therapy regimen would be cost-effective and cost-saving in the USA.[24]

The safety of dolutegravir plus lamivudine in the DOLAM study was consistent with the safety profile previously reported in first-line studies and switching studies. Most adverse effects were mild or moderate. There were almost identical numbers of participants with at least one adverse effect or overall adverse effects in both groups. This finding is outstanding as a switching study, in which participants in the study group are exposed to a new medication whereas those in the control group continue with a previously tolerated medication.[25]

Although we did not see significant changes in fasting glucose and lipids between groups overall, participants on triple regimens based on tenofovir disoproxil fumarate or tenofovir alafenamide revealed significant opposite effects on total cholesterol and LDL cholesterol in accordance with previous reports.[26] There was an expected reduction in estimated glomerular filtration rate in the dolutegravir plus lamivudine group, due at least in part to inhibition of tubular creatinine secretion by dolutegravir without affecting glomerular filtration itself.[27]

Participants' weight increased significantly more in the dual therapy group than in the triple therapy group, in accordance with the SIMPL'HIV study results.[16] Of note, weight gain was significant when participants were on triple regimens containing tenofovir disoproxil fumarate or integrase inhibitors. In antiretroviral-naive adults with HIV, greater weight gain has been associated with integrase inhibitors in general, and more specifically with dolutegravir and bictegravir, than with other anchor drugs, and with tenofovir alafenamide than with other NRTIs.[28] Although long-term trends and potential clinical implications of the weight increase at 48 weeks detected in patients switching to dolutegravir plus lamivudine are still unknown, we did not see any correlation between changes in weight and changes in metabolic parameters.

There were no differences between groups in sleep quality changes. The Pittsburg Sleep Quality Index score has been validated in adults with HIV and we have shown discriminative results in previous randomised controlled studies.[27] Initiation of dolutegravir-containing therapy has been associated with an increased risk of neuropsychiatric symptoms, the most specific one being insomnia.[29] Reports of insomnia in people with HIV and being treated with dolutegravir were frequent when dolutegravir became clinically available. However, major clinical trials[7,8,13,14,30–32] have not found any substantial clinical effect of dolutegravir-containing therapy on sleep.

This study had limitations. The open-label design might have led to ascertainment bias; however, because the primary outcome and many secondary endpoints were measured objectively, ascertainment bias was less likely to occur than if they had been subjective measures. We justified and chose an 8% non-inferiority margin, which is higher than the 4% recommended by major health agencies, but were able to show non-inferiority of the dolutegravir plus lamivudine switch relative to standard triple therapy using this 8% margin. The biphasic design made the trial last longer than if we had done the trial in a single phase. Although the methods were similar in both phases, the real management of virological failure in participants assigned to dual therapy probably differed from the one originally planned because the clinical knowledge of and confidence in

the dual dolutegravir plus lamivudine combination increased over time. Dolutegravir and lamivudine were taken as separate drugs because the fixed combination was not available over the study period; although adherence to the dual combination was high throughout follow-up, it is possible that it could have been even better with a fixed-dose combination. As most participants were White or Latinx men, the results of this study should be interpreted with caution in women or people of other races or ethnicities. We did not assess diet or physical exercise, although the randomised design should have precluded any potential imbalance between groups.

In conclusion, the results of the DOLAM study provide supporting evidence that switching to dolutegravir plus lamivudine in selected virologically suppressed adults with HIV is virologically non-inferior and as safe as continuing triple ART.

Contributors

JMG, JLB, and EM conceived and designed the study. JR, EN, PD, JT, ER, NA, JP, MGM, DP, MMG, RP, BC, JLB, and EM were responsible for patients' inclusion, clinical follow-up, and data collection. EdL constructed the database, did the analysis, and took responsibility for the integrity of the data and the accuracy of the data analysis. EdL and EM verified the data. EM wrote the manuscript. All authors critically revised the manuscript and gave their approval for the final version. All authors had access to the data, were involved in the interpretation of data and development of the manuscript, and read and approved the final version. All authors shared the final responsibility to submit the manuscript for publication.

Declaration of interests

PD reports grants and personal fees from Gilead Sciences, ViiV Healthcare, and Janssen & Cilag, and personal fees from Merck, Sharp & Dohme and Theratechnologies, outside the submitted work. JT reports personal fees from Gilead Sciences, ViiV Healthcare, Merck, Sharp & Dohme, and Janssen, outside the submitted work. ER reports personal fees from Merck, Sharp & Dohme, Gilead Sciences, Janssen, and ViiV Healthcare, outside the submitted work. DP reports research grants and honoraria for advisory boards and conferences from Viiv Healthcare, Pfizer, Bristol Myers Squibb, Gilead Sciences, Janssen, and Merck, Sharp & Dohme, outside the submitted work. RP reports grants from ViiV Healthcare during the conduct of the study, and grants and personal fees from Merck, Sharp & Dohme and Gilead Sciences, outside the submitted work. JMG is currently a full employee at ViiV Healthcare, reports grants from ViiV Healthcare during the conduct of the study, and personal fees from ViiV Healthcare, outside the submitted work. JLB reports grants, personal fees, and non-financial support from ViiV Healthcare and Janssen, and personal fees and non-financial support from Merck, Sharp & Dohme, Gilead Sciences, and Theratechnologies, outside the submitted work. EM reports grants from Instituto de Salud Carlos III and ViiV Healthcare during the conduct of the study, grants and personal fees from Merck, Sharp & Dohme and ViiV Healthcare, and personal fees from Gilead Sciences and Janssen, outside the submitted work. All other authors declare no competing interests.

Data sharing

The full protocol can be made available upon request. Deidentified participant data and a data dictionary defined in the set can also be made available upon request. The protocol and data can be requested from the corresponding author, and a signed data access agreement will be required for access.

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Trabajo 5

Multiomics plasma effects of switching from triple antiretroviral regimens to dolutegravir plus lamivudine

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Resumen

Objetivos: El ensayo DOLAM reveló que el cambio de la terapia antirretroviral triple (3DR) a uno doble (2DR) con dolutegravir más lamivudina fue virológicamente no inferior a continuar con el régimen 3DR después de 48 semanas de seguimiento. El peso aumentó con el régimen 2DR respecto a 3DR, pero no impactó en parámetros metabólicos. Con el presente estudio pretendemos conocer mejor si este cambio terapéutico podría afectar vías biológicas específicas.

Métodos: Se realizó el perfil plasmático multiómico para conocer mejor si este cambio terapéutico podría afectar vías biológicas específicas. El DOLAM (EudraCT 201500027435) es un ensayo de fase 4, aleatorizado, abierto y de no-inferioridad en el que personas que viven con VIH tratadas con 3DR se asignaron aleatoriamente (1:1) a cambiar a 2DR o continuar con 3DR durante 48 semanas. Los análisis de proteómica, metabolómica y lipidómica no dirigidos se realizaron al inicio y a las 48 semanas. Se realizaron análisis univariados y multivariados para identificar cambios en moléculas clave entre ambos grupos de terapia.

Resultados: El cambio de 3DR a 2DR mostró un impacto multiómico en la concentración plasmática circulante de N-acetilmuramoil-L-alanina amidasa (Q96PD5), proteína de unión al factor de crecimiento insulínico 3 (A6XND0), alanina y TG (48:0). Los análisis de correlación

identificaron una asociación entre la regulación de estas cuatro moléculas en personas tratadas con 2DR.

Conclusiones: Estudios de perfiles multiómicos no segmentados identificaron cambios moleculares potencialmente asociados con las vías inmunitarias de la inflamación y con el metabolismo de los lípidos y la glucosa. Aunque estos cambios podrían estar asociados con posibles consecuencias metabólicas o cardiovasculares, su importancia clínica sigue siendo incierta. Es necesario seguir trabajando para confirmar estos hallazgos y evaluar sus consecuencias clínicas a largo plazo.

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Multiomics plasma effects of switching from triple antiretroviral regimens to dolutegravir plus lamivudine

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Introduction: The DOLAM trial revealed that switching from triple antiretroviral therapy (three-drug regimen; 3DR) to dolutegravir plus lamivudine (two-drug regimen; 2DR) was virologically non-inferior to continuing 3DR after 48 weeks of follow-up. Weight increased with 2DR relative to 3DR but it did not impact on metabolic parameters.

Methods: Multiomics plasma profile was performed to gain further insight into whether this therapy switch might affect specific biological pathways. DOLAM (EudraCT 201500027435) is a Phase 4, randomized, open-label, non-inferiority trial in which virologically suppressed persons with HIV treated with 3DR were assigned (1:1) to switch to 2DR or to continue 3DR for 48 weeks. Untargeted proteomics, metabolomics and lipidomics analyses were performed at baseline and at 48 weeks. Univariate and multivariate analyses were performed to identify changes in key molecules between both therapy arms.

Results: Switching from 3DR to 2DR showed a multiomic impact on circulating plasma concentration of *N*-acetylmuramoyl-L-alanine amidase (Q96PD5), insulin-like growth factor-binding protein 3 (A6XND0), alanine and triglyceride (TG) (48:0). Correlation analyses identified an association among the up-regulation of these four molecules in persons treated with 2DR.

Conclusions: Untargeted multiomics profiling studies identified molecular changes potentially associated with inflammation immune pathways, and with lipid and glucose metabolism. Although these changes could be associated with potential metabolic or cardiovascular consequences, their clinical significance remains uncertain. Further work is needed to confirm these findings and to assess their long-term clinical consequences.

Introduction

Antiretroviral drugs have improved over time, becoming more effective, simpler and better tolerated. However, for some patients current ART may still be challenging.[1] Despite better tolerability, some patients may experience direct toxicities with contemporary antiretrovirals. The risk for most potential toxicities is usually cumulative and may further depend on specific individual factors. Beyond direct short-term harm, antiretroviral toxicities may have a long-term impact on the development or progression

of comorbidities. Medications for comorbidities may further increase the risk of significant interactions with some antiretrovirals. Switching antiretrovirals for reasons other than virological failure is a common and evolving strategy in clinical practice.[2]

The effects of switching to dolutegravir plus lamivudine (a two-drug regimen; 2DR) in adults suppressed on triple therapy have been assessed in several observational studies or single-arm trials and three large randomized clinical trials.[3–9] The results of all these studies support that switching to 2DR in selected adults with HIV is virologically non-inferior and as safe as continuing triple ART (three-drug regimen; 3DR).

Whether switching from 3DR to 2DR might be associated with better long-term tolerability due to the reduction of antiretroviral drug burden has not been proven yet.[10] Conversely, integrase inhibitors in general, including dolutegravir, have been associated with higher risk of weight gain, diabetes, hypertension and cardiovascular disease, although the not entirely consistent data leave many unknowns.[11]

In the DOLAM (EudraCT 201500027435) study and SALSA (NCT00295620) study, switching to 2DR was associated with weight gain at 48 weeks compared with continuing 3DR but there were no differences in lipid parameters between arms.[8] It was the discontinuation of tenofovir disoproxil fumarate that was associated with 48 week increases in total cholesterol and weight in persons switched to 2DR.[8]

Omics approaches have emerged as robust and powerful tools for a better understanding of immunometabolism in HIV pathogenesis. Proteomics-based approaches offer a high-throughput method not only to identify biomarkers for diagnostic antigens and therapeutic targets but also to investigate mechanisms of drug action in persons with HIV.[12–14] Along with proteomics, metabolomics and lipidomics technologies have yielded new insights into the key role of cellular metabolism in the activity of immune cells and the treatment-induced metabolic derangements in the context of HIV infection.[15–17]

An untargeted multiomics plasma profile, including proteomics, metabolomics and lipidomics data, was pre-planned as a substudy of the DOLAM study to gain insight on whether some immunometabolic pathways might be affected by this therapy switch. The untargeted approach was selected for a more comprehensive and systemic analysis of both unknown and known plasma compounds to discover new biomarkers to be selected for more accurate quantitation and annotation in future studies (targeted).

Methods

Study design

The DOLAM study is a Phase 4, multicentre, randomized, controlled with active treatment, open-label, parallel clinical trial. The study was done at six major HIV clinics in Catalonia (Spain). Institutional review boards from all participating centres and the Spanish Agency of Medicines and Medical Devices approved the study. Participants were randomly assigned to continue their current 3DR (control arm) or to switch to 2DR once daily (dual-therapy arm). Major results of the DOLAM study have already been published.[8]

Study participants and data collection

Consecutive asymptomatic adults (≥18 years old) with HIV on stable (defined as at least the previous 12 months) 3DR including two NRTIs plus either a boosted PI, an NNRTI, or an integrase inhibitor with sustained viral suppression (defined by plasma HIV RNA < 50 copies/mL in two or more consecutive determinations during at least the 12 months before inclusion; blips up to 200 copies/mL were admissible) were invited to participate. For women of childbearing age, a negative pregnancy test within 10 days before randomization into the study was required. Exclusion criteria were: pregnancy, lactation or planned pregnancy during the study period; prior virological failure (defined as plasma HIV RNA ≥ 50 copies/mL in two consecutive tests or >500 copies/mL in one test) to regimens containing lamivudine, emtricitabine or integrase inhibitors; any mutation conferring resistance to lamivudine, emtricitabine or integrase inhibitors; CD4 nadir <200 cells/μL; any disease or history of disease that might confound the results of the study or pose additional risk to participant's treatment; and chronic hepatitis B, defined by a positive hepatitis B surface antigen (HBsAg) result at screening. Written informed consent was obtained from all eligible participants before randomization.

Participants were visited at baseline and every 12 weeks until completing at least 48 weeks of follow-up. At baseline and at 48 weeks, 10 mL EDTA blood samples were collected after at least 8 h of fasting and processed immediately; plasma samples were split into 1 mL aliquots and stored at −80°C for deferred multiomics studies.

Determination of the proteomic profile

Detailed information about protein extraction and identification can be found in the Supplementary Methods (available as Supplementary data at *JAC* Online). MS analyses were performed on an LTQ-Orbitrap Velos Pro from Thermo Fisher by an enhanced FT-resolution MS spectrum (R = 30 000 FHMW) followed by a data-dependent FT-MS/MS acquisition (R = 15 000 FHMW, 40% NCE HCD) from the 10 most intense parent ions with a charge state rejection of one and dynamic exclusion of 0.5 min. Protein identification/quantification was performed on Proteome Discoverer software v.1.4.0.288 (Thermo Fisher Scientific, CA, USA) by Multidimensional Protein Identification Technology (MudPIT) combining the two raw data files obtained from each sample. For protein identification, all MS and MS/MS spectra were analysed using the Mascot search engine (v.2.5). The workflow was set up using two different Mascot nodes combining a *Homo sapiens* database (74 449 entries) and a contaminants database (247 entries), both searches assuming trypsin digestion. Two missed cleavages were allowed and an error of 0.02 Da for FT-MS/MS fragmentation mass and 10.0 ppm for an FT-MS parent ion mass were allowed. TMT-10plex was set as quantification modification and oxidation of methionine and acetylation of N-termini were set as dynamic modifications, whereas carbamidomethylation of cysteine was set as static modification. The false discovery rate (FDR) and protein probabilities were calculated by Percolator. For protein quantification, the ratios between each TMT label against 126-TMT label were used and quantification results were normalized based on the protein median. The results are a ratio of reporter ion abundance and are dimensionless.

Determination of the metabolomic profile (analytical method)

Detailed information about the analytical method for metabolomic identification can be found in the Supplementary Methods. Samples were analysed on a 7200 GC-qTOF from Agilent Technologies (Santa Clara, CA, USA). The chromatographic separation was based on the Fiehn method.[18] Targeted compounds were identified using pure standards with a mass accuracy of 20 ppm and different internal standards were used to correct signal response. Chromatographic peaks were deconvoluted using Unknowns Analysis software (version B.09.00, from Agilent) based on the exact mass. Identification of compounds was tentatively made by comparing the mass spectra and retention time of all detected compounds with the Fiehn 2013 Mass Spectral RTL Library and the National Institute of Standards and Technology (NIST) library 11 (2014)

also using the Unknowns software. The identity of the main compounds was confirmed with commercial pure standards. After direct (with pure standards) or putative (with a library) identification of metabolites, these were semiquantified in terms of internal standard response ratio. For this relative quantification, the area of specific fragments for each metabolite was divided by the area of its specific internal standard to provide a reliable, accurate and reproducible relative concentration of metabolites.

Determination of the lipidomic profile (analytical method)

Lipid extraction procedure can be found in the Supplementary Methods. The identification of lipid species was performed using the Agilent MassHunter Profinder B.08 software. First, a feature extraction deconvolution was made; accurate mass and tandem mass spectrum, when available, was then matched to Metlin-PCDL (2017) from Agilent containing more than 40 000 metabolites and lipids, allowing a mass error of 20 ppm and a score higher than 80 for isotopic distribution. To ensure the tentative characterization, the chromatographic behaviour of pure standards for each family and corroboration with the Lipid Maps database (www.lipidmaps.org) was used to ensure their putative identification. Afterwards, matched entities were selected to perform a targeted MS/MS acquisition on the LC-QTOF-MS instrument to corroborate the identification. Lipid species were then semiquantified in terms of internal standard response ratio using one internal standard for each lipid family.

Statistical analysis

To further delineate semiquantitative differences between groups due to the switching effect, a ratio between data from samples at 48 weeks and data from baseline timepoints was performed in each participant before statistical analyses. Only those proteins, metabolites and lipids that were present in >60% of the samples in at least one of the experimental groups were considered. In addition, $\log_2$ transformations were applied to the data (proteomics, lipidomics and metabolomics) for variance stabilization, data range compression and making the data more normally distributed. This transformation was performed by Mass Profiler Professional software v.15.1 from Agilent Technologies. Regression model such as partial least squares discriminant (PLSD) was performed from compounds in each comparison and random forest (RF) analyses were performed to determine those molecules with higher accuracy to differentiate both groups. An unpaired *t*-test (Mann–Whitney *U*-test) was then performed between ratios (48 weeks/baseline) from experimental groups (control and case). In each comparison, its significant level (*P* value) was corrected for multiple testing using the FDR with the Benjamin–Hochberg procedure and a *P* value cut-off of <0.05 was applied. Associations between quantitative variables were evaluated using the Spearman correlation test and receiver operating characteristic (ROC) curves were employed to confirm the statistical relevance of molecules in the switching from 3DR to 2DR. The protein network was constructed with the online String software (version 11.5).

Statistical analyses were performed using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA), and graphical representations were generated with GraphPad Prism (version 5.0, GraphPad Inc., San Diego, CA, USA), MetaboAnalyst 5.0 software and Open Office software. The results were considered significant at *P* values < 0.05.

Ethics

Institutional review boards from all participating centres and the Spanish Agency of Medicines and Medical Devices granted ethical approval of the study. Written informed consent was obtained from all eligible participants before randomization.

Table 1. Baseline demographic and clinical characteristics

	Triple therapy (3DR)	Dolutegravir plus lamivudine (2DR)
Age, years	47 (39–51)	44 (37–53)
Sex at birth		
Female	12 (14)	17 (16)
Male	72 (86)	86 (84)
BMI, kg/m^2	24 (23–26)	25 (23–27)
Suspected route of HIV transmission		
Male-to-male sex	62 (74)	71 (68)
Heterosexual sex	13 (15)	19 (18)
Injection drug	4 (5)	6 (6)
Other/unknown	3 (7)	7 (8)
CD4 and CD8 measurements		
CD4 cells/μL	746 (553–919)	698 (577–938)
CD4, %	35 (31–40)	36 (31–43)
CD8 cells/μL	795 (591–931)	731 (502–959)
CD8, %	36 (31–43)	35 (27–42)
CD4:CD8 ratio	0.88 (0.72–1.02)	0.92 (0.69–1.09)

Data are reported as *n* (%) or median (IQR).

Results

Patient characteristics

There were 198 (75%) out of 265 participants with valid samples for this substudy, 85 receiving 3DR and 113 receiving 2DR.[8,9] Their baseline characteristics were like those of the main study. Participants were predominantly male (158; 84%) with a median (IQR) age of 45 (38–52) years. Roughly similar proportions were taking abacavir (35%), tenofovir disoproxil fumarate (37%) or tenofovir alafenamide (28%) before study entry (Table 1, Figure 1).

Switching from 3DR to 2DR is associated with the p53 signalling pathway

A total of 136 proteins were identified in plasma samples (Table S1) and the ratio between data from samples at 48 weeks and data from basal timepoint was compared between 3DR and 2DR groups. The PLSD regression model showed a group-average effect, although the two groups overlapped (Figure 2a). Case–control samples were then compared using a non-parametric test corrected by multiple test (FDR < 0.05), and 3 of 136 proteins were found to be statistically different between 3DR and 2DR groups (Figure 2b). *N*-acetylmuramoyl-L-alanine amidase (Q96PD5) ($P = 0.035$), insulin-like growth factor-binding protein 3 (IGFBP3) (A6XND0) ($P = 0.043$) and LPS-binding protein (LBP) (P18428) ($P = 0.05$) had elevated plasma concentrations in the 2DR group compared with the 3DR group. Furthermore, Q96PD5 and A6XND0 were consistent with those proteins that had the highest discriminatory power between groups (random forest analysis) (Figure 2c). Thus, by using a combination of univariate and multivariate approaches, Q96PD5 and A6XND0, which showed a positive correlation (ρ 0.247, $P < 0.001$), were

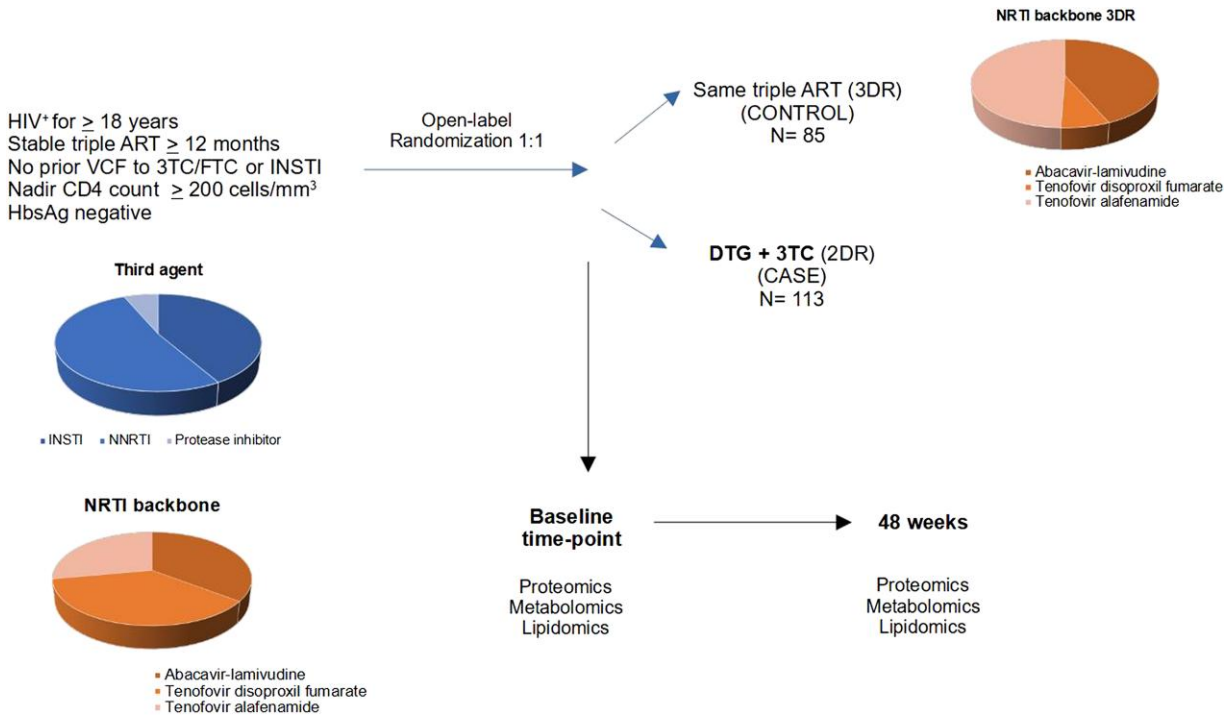


Figure 1. Study design. The study cohort comprised 198 PLHIV on stable triple ART for more than 12 months and with nadir CD4 T cell count greater or equal to 200 cells/mm^3. Participants were assigned to a treatment group using computer-generated randomization. 3TC, lamivudine; DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside or nucleotide reverse transcriptase inhibitor; VCF, virological failure. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

discovered as the main proteins significantly increased in therapy simplification. These proteins were subjected to an ROC curve analysis to confirm their statistical relevance in the switching from 3DR to 2DR (Figure 2d). Both Q96PD5 and A6XND0 yielded significant AUC values (0.616, $P=0.005$ and 0.613, $P=0.04$, respectively) and the combination of both proteins resulted in an AUC of 0.624 (0.547–0.702, $P=0.003$). Network mapping identified an interconnecting cluster between LBP and A6XND0 (confidence score 0.4) and STRING database analysis confirmed the interaction between switching from 3DR to 2DR and proteins associated with the p53 signalling pathway (FDR=0.03, impact 0.05).

Switching from 3DR to 2DR is associated with increased alanine and TG 48:0

A total of 97 metabolites were identified in plasma samples (Table S2) and as previously performed with proteomics data, the ratio between metabolomics data from samples at 48 weeks and data from basal timepoint was compared between 3DR and 2DR groups. PLSD analysis also showed a group-average effect in the relative concentration of metabolites (Figure 3a). The univariate non-parametric test corrected by multiple test identified five metabolites statistically different between 3DR and 2DR groups; relative to 3DR, two were significantly decreased (2-hydroxybutyric acid, $P<0.001$; and benzoic acid, $P=0.03$) and three were significantly increased (2-hydroxy isobutyric acid, $P<0.001$; nonanoic acid, $P=0.04$; and alanine, $P=0.05$) in 2DR. However, the multivariate analysis revealed alanine only as the main metabolite significantly increased by therapy simplification (Figure 3b and c). Of interest, circulating alanine levels positively correlated with A6XND0 levels ($\rho=0.141$, $P=0.018$).

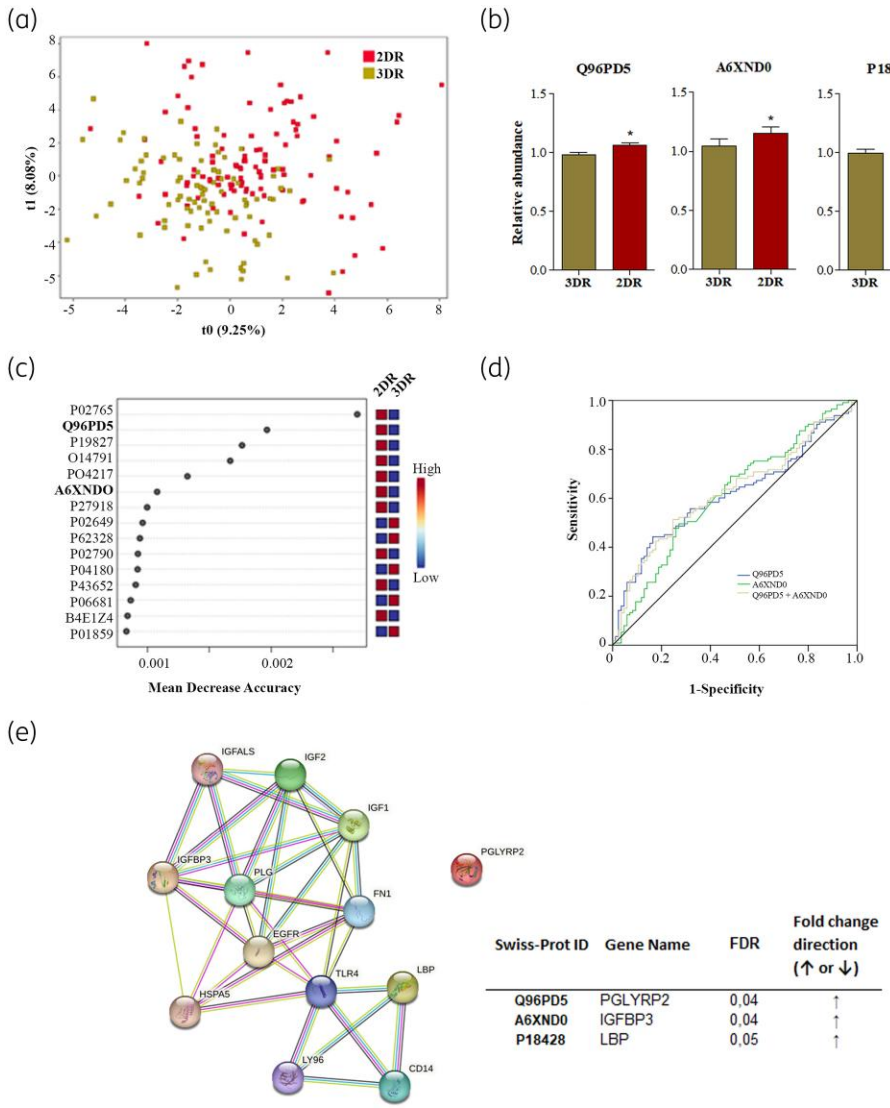
Regarding lipidomics analysis, a total of 117 lipid species were identified in plasma samples and the regression model (PLSD) also showed a group-average effect in the relative concentration of lipid species (Figure 3a). However, the univariate analysis corrected by multiple tests (FDR) only identified TG 48:0 as significantly increased in the 2DR group compared with the 3DR group ($P=0.018$) (Figure 3c). The first number indicates the acyl carbon atoms, and the second number indicates the number of unsaturations.

Thus, alanine and TG 48:0 were analysed in combination to evaluate their association in therapy simplification. Correlation analyses confirmed a positive association between circulating alanine and TG 48:0 levels ($\rho=0.2134$, $P=0.003$) (Figure 3d) and the combination of both features were evaluated using the ROC curve, obtaining an AUC of 0.601 (95% CI 0.503–0.706) (Figure 3e).

No significant association was found between proteins and metabolites identified in the switching from 3DR to 2DR.

Discussion

Similar to other randomized clinical trials such as TANGO or SALSA, the DOLAM study showed that switching from 3DR to 2DR in selected virologically suppressed adults with HIV is virologically non-inferior and as safe as continuing 3DR.[7,9] However, dolutegravir has been associated with weight increase



Swiss-Prot ID	Gene Name	FDR	Fold change direction (↑ or ↓)
Q96PD5	PGLYRP2	0,04	↑
A6XND0	IGFBP3	0,04	↑
P18428	LBP	0,05	↑

Figure 2. Changes in plasma proteins when switching from 3DR to 2DR. (a) A PLSD regression model plot is shown based on relative protein levels. (b) Circulating levels of the three proteins with significant expression among groups by univariate analysis corrected by multiple tests (FDR) results for positive mode features (FDR ≤ 0.05). (c) RF analysis. The top 15 metabolites with the highest discriminatory power between both groups are listed. (d) ROC curve for proteins selected based on the combination of univariate and multivariate analyses. AUC for Q96PD5 was 0.616 (95% CI 0.538–0.694), AUC for A6XND0 was 0.613 (95% CI 0.534–0.693) and AUC for the combination of both proteins (Q96PD5+A6ZND0) was 0.624 (95% CI 0.547–0.702). (e) STRING database analysis confirmed the interaction between switching from 3DR to 2DR and proteins associated with the p53 signalling pathway (FDR = 0.03, impact 0.05). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

in both naive and treated persons with HIV and there are concerns that it could also be associated with diabetes and cardiovascular disease.[19,20] In the DOLAM study, persons living with HIV (PLHIV) assigned to 2DR significantly gained more weight and there were more overweight or obese persons at 48 weeks relative to those continuing 3DR, but we were unable to detect significant changes in body fat, lean mass or bone mineral density (BMD) between arms.[8] Taking advantage of omic approaches for a better understanding of cellular metabolism, we attempted to explore if there were any plasma molecular alterations affected by the switch from 3DR to 2DR.

The combination of untargeted proteomics, metabolomics (polar compounds) and lipidomics evidenced that switching from 3DR to 2DR was related to a few circulating metabolomic perturbations. Specifically, the multiomic approach identified two proteins, one metabolite and one lipid differentially expressed in the 2DR group compared with 3DR. Correlation analyses identified an association among the up-regulation of these four molecules in the 2DR arm.

At 48 weeks of follow-up, participants receiving 2DR showed increased plasma concentration of Q96PD5 and A6XND0 compared with 3DR. Q96PD5 is a protein encoded by the peptidoglycan recognition protein 2 (PGLYRP2) gene, a gene from the peptidoglycan recognition proteins (PGLYRPs) family. PGLYRPs are proteins that are conserved from insects to mammals, acting in inflammation and immune responses independently of their

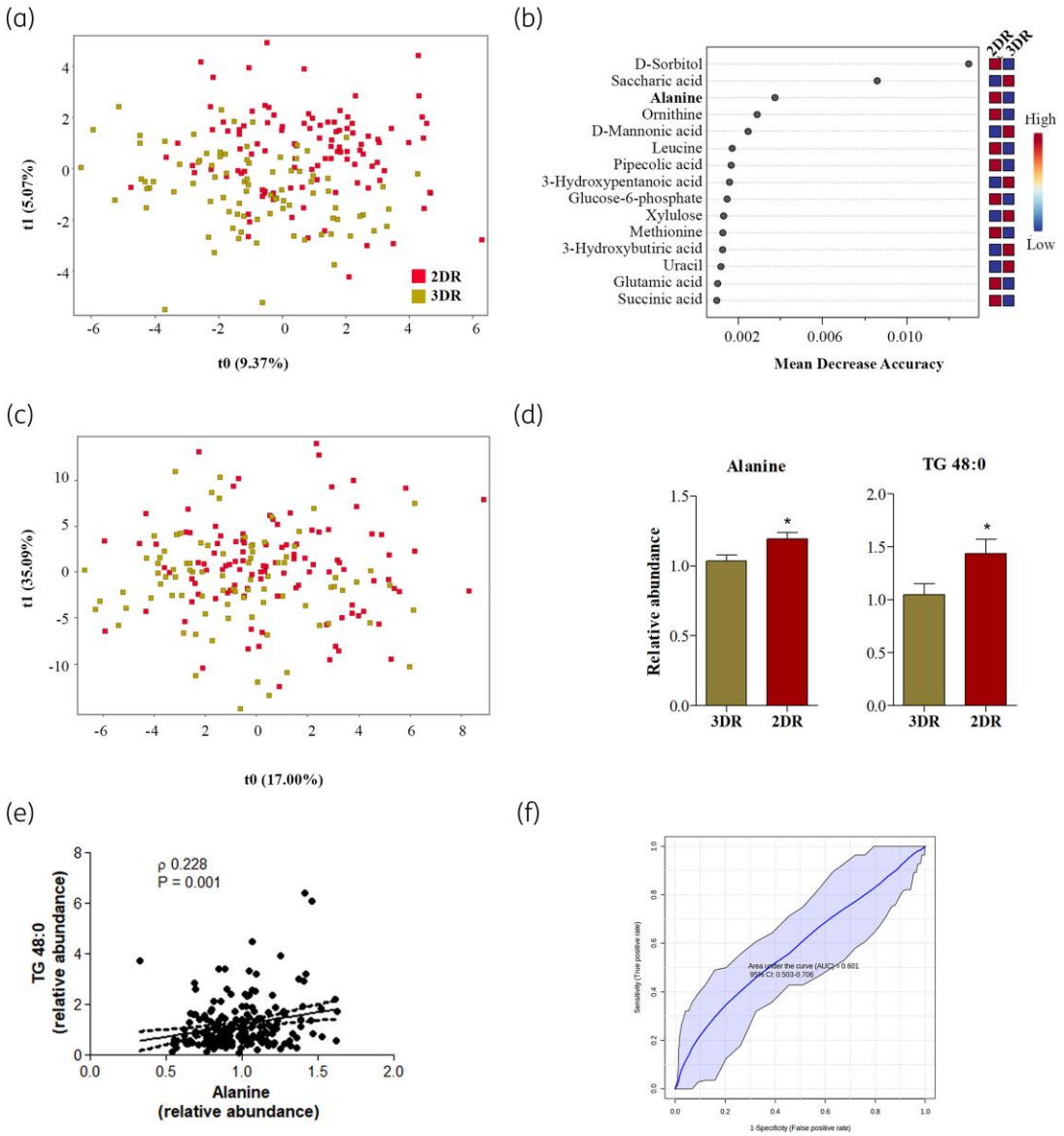


Figure 3. Changes in plasma metabolites and lipid species of switching from 3DR to 2DR. (a) A PLSD regression model plot is shown based on relative metabolite levels. (b) RF analysis. The top 15 metabolites with the highest discriminatory power between both groups are listed. (c) A PLSD regression model plot is shown based on relative lipid species levels. (d) Circulating differences between the significant metabolite and lipid species by univariate analysis corrected by multiple tests (FDR ≤ 0.05). (e) Correlation analysis between alanine (metabolite) and TG 48:0 (lipid species). The Spearman (ρ) correlation coefficient and *P* value are indicated inside the graphical representation. (f) ROC curve model for the combination of alanine and TG 48:0 to evaluate the feature of these molecules in the therapy simplification. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

bactericidal and enzymatic activities.[21] Specifically, PGLYRP2 has shown both anti-inflammatory and pro-inflammatory properties, probably related to its link to the transcription factor family nuclear factor κB (NF-κB).[22–25] NF-κB represents a family of inducible transcription factors involved in the regulation of genes belonging to immune and inflammatory pathways (including cytokines, chemokines and inflammasome) whose expression has been linked to the p53 signalling pathway.[24,26] Our results suggested a possible association between the differentially expressed proteins associated with therapy simplification and the p53 signalling pathway. Of interest, a recent study also showed a positive correlation between PGLYRP2 and ApoB/A1 in patients with systemic lupus erythematosus (SLE), which suggested a potential role of PGLYRP2 in the dyslipidaemia and cardiovascular disease risks in SLE patients.[27] In the present study, no association was found between Q96PD5 and the lipid species differentially identified among groups (TG 48:0), but Q96PD5 was shown to be significantly related to A6XND0, whose gene expression (IGFBP3) was previously related to lipid metabolism.[28] In serum, IGFBP-3 is the most abundant protein of the IGFBP family that

functions in an IGF-dependent (delivery of IGF and activation of IGF downstream signalling) manner, as well as in an IGF-independent (interaction with proteins) manner.[29] Although some studies unveiled its role in metabolic regulation, the exact role of IGFBP3 in glucose and lipid metabolism remains unclear, even in PLHIV.[29,30] Some studies suggested that serum IGFBP3 could be involved in HIV disease progression and related to insulin resistance, but on the other hand, 3 months of treatment with IGF-I/IGFBP-3 improved whole-body glucose, glucose tolerance and fasting TGs in men living with HIV with excess abdominal adiposity and insulin resistance.[31–33] Based on our results, the role of an increase in plasma IGFBP3 concentration in the 2DR arm remains uncertain as no significant metabolic alterations were clinically observed between 3DR and 2DR groups at 48 weeks of therapy randomization.[8] However, it is important to highlight that our results suggested a positive relationship between A6XND0 and plasma alanine levels, and between plasma alanine levels and TG (48:0). At the molecular level, participants in the 2DR group showed increased plasma concentrations in both circulating plasma alanine and TG (48:0) compared with the 3DR group. Increased circulating alanine concentrations could indicate an alteration in the glucose-alanine cycle in which alanine can be synthesized from pyruvate deriving from skeletal muscle through the enzymatic reaction of ALT and then transported to the liver to be used for gluconeogenesis. High circulating alanine concentration has been related to the risk of incident type II diabetes while reduced rates of glucose-alanine cycling have been associated with the regulation of hepatic mitochondrial oxidation.[34,35] Regarding the monoacid triglyceride TG (48:0), previous studies have considered the saturated TG (48:0) as a key lipid species in biomarker panels related to liver-fat content.[36,37]

This study had limitations. The multiomic analysis was performed from baseline to 48 weeks after randomization, a period in which potential metabolic consequences of weight gain had not been apparent. Multiomics data integration can bring several problems and requires several attention to combine high-throughput data obtained from different molecular layers. To reduce the heterogeneity across the three different omics technologies applied and the difficulty of interpreting multilayered system models derived from the combination of omics data and non-omic data (clinical data), single analysis was preferred for the present work focused on the antiretroviral simplification. Performing a multiomic analysis after a longer follow-up would be of great interest. As a strength, this study provides novel and valuable information, as no multiomic analysis investigating changes after switching from 3DR to 2DR has been previously published to our knowledge.

Conclusions

In summary, 48 weeks of dolutegravir plus lamivudine (2DR) represents a reduction in antiretroviral drug burden that is virologically non-inferior, safe and without apparent clinical metabolic derangement compared with continuing triple ART (3DR). Switching from 3DR to 2DR, however, was related to some plasma metabolomics perturbations, in which four soluble compounds were involved. Plasma changes in Q96PD5, A6XND0, alanine and TG (48:0) might be associated with the activation of inflammation and immune pathways but also with an alteration in lipid and glucose metabolism. Although these changes could be associated with potential metabolic or cardiovascular consequences, their clinical significance remains uncertain. Further work is needed to confirm these findings and to assess their long-term clinical consequences.

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Transparency declarations

Esteban Martínez has received funds for research from ViiV Healthcare. Jose M. Gatell is a full-time employee of and owns stock in ViiV as Senior Global Medical Director since 1 May 2018. All other authors: none to declare.

Author contributions

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Data availability

The datasets used and analysed during the current study may be made available by the corresponding author upon reasonable request.

Supplementary data

Supplementary Methods, Figures S1 to S3 and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

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MULTIOMICS PLASMA EFFECTS OF SWITCHING FROM TRIPLE ANTIRETROVIRAL REGIMENS TO DOLUTEGRAVIR PLUS LAMIVUDINE

Running title: Plasma profile from 3DR to 2DR

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Supplementary Material

Supplementary Figures

Representative nanoLC-(Orbitarp) MS/MS chromatograms for protemics (1), GC-(qTOF)MS chromatogram for metabolomics (2) and UHPLC-(qTOF)MS chromatogram for lipidomics (3).

Supplementary Tables

S2. Detected compounds during the proteomics (1), the metabolomics (2) and lipidomics (3) analyses on the LC-MS platform, including the theoretical mass-to-charge ratio (*m/z*) and retention time (RT) values**.**

Proteomics analysis

Before proteomic analysis, depletion of the most abundant plasma proteins (albumin, IgG, antitrypsin, IgA, transferrin, haptoglobin and fibrinogen) was performed to increase the number of identified/quantified proteins. Thus, 12 µL of each sample were passed twice through the Human-7 Multiple Affinity Removal Spin (MARS) cartridge from Agilent Technologies and the flow-through fractions were collected for proteomic analysis following manufacturer protocol. Flow-through fractions were concentrated, and buffer exchanged to about 100 µL of 6M urea in 50 mM ammonium bicarbonate (ABC) by using 5K MWCO spin columns (Agilent 5185-5991). Thirty µg of total protein (quantified by Bradford's method) were reduced with 4 mM 1.4-Dithiothreitol (DTT) for 1-hour at 37°C and alquilated with 8 mM iodoacetamide (IAA) for 30 min at 25ºC in the dark. Afterwards, samples were overnight digested (pH 8.0, 37ºC) with sequencing-grade Trypsin/Lys-C Protease Mix (ThermoFisher Scientific, CA, USA) at enzyme:protein ratio of 1:50. Digestion was quenched by acidification with 1% (v/v) formic acid and peptides were desalted on Oasis HLB SPE column (Waters, Massachusetts, USA) before TMT 11-plex labelling (Thermo Fisher Scientific, CA, USA) following manufacturer instructions.

To normalize all samples in the study along the different TMT-multiplexed batches used, a pool containing all the samples was labelled with TMT-126 tag and included in each TMT batch (see the attached excel file TMT Plex Organization). The different TMT 11-plex batches were desalted on Oasis HLB SPE columns before the nanoLC-MS analysis. Labelled and multiplexed peptides were loaded on a trap nano-column (100 µm I.D.; 2cm length; 5µm particle diameter, ThermoFisher Scientific, CA, USA) and separated onto a C-18 reversed-phase (RP) nano-column (75µm I.D.; 15cm length; 3µm particle diameter, Nikkyo Technos Co. LTD, Japan) on an EASY-II nanoLC from ThermoFisher. The chromatographic separation was performed with a 180 min gradient using Milli-Q water (0.1% formic acid) and acetonitrile (0.1% formic acid) as mobile phase at a flow rate of 300 nL/min.

Metabolomic analysis

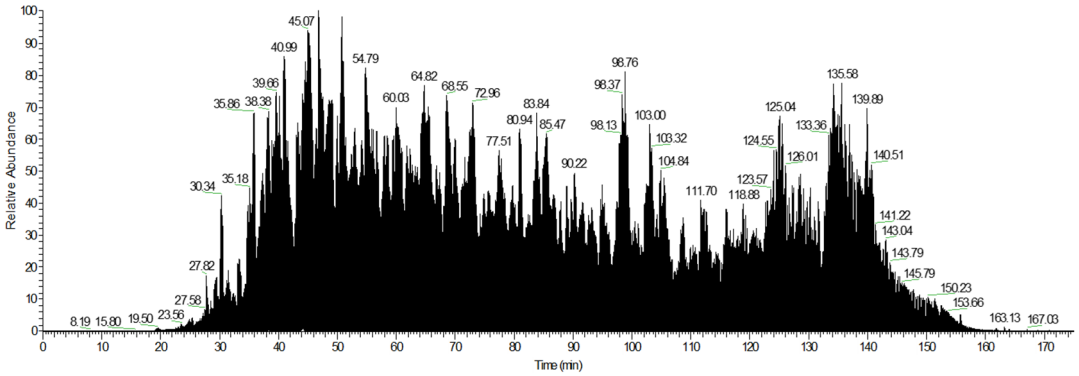
A protein precipitation extraction was performed by adding eight volumes of methanol: water (8:2) containing an internal standard mixture to plasma samples. Samples were mixed and incubated at 4ºC for 10 min, centrifuged at 21,000g and supernatant evaporated to dryness before compound derivatization (methoxyamine hydrochloride and N-Methyl-N-trimethylsilyltrifluoroacetamide + 1% Trimethylsilyl chloride (MSTFA +1% TMCS)). The chromatographic separation was based on Fiehn Method, using a J&W Scientific HP5-MS (30 m x 0.25 mm i.d., 0.25 µm) film capillary column and helium as carrier gas using an

oven program from 60 to 325ºC.18 Ionization was done by electronic impact (EI), with electron energy of 70eV and operated in full scan mode, recording data in a range between 35 and 700 m/z at a scan rate of 5 spec/s.

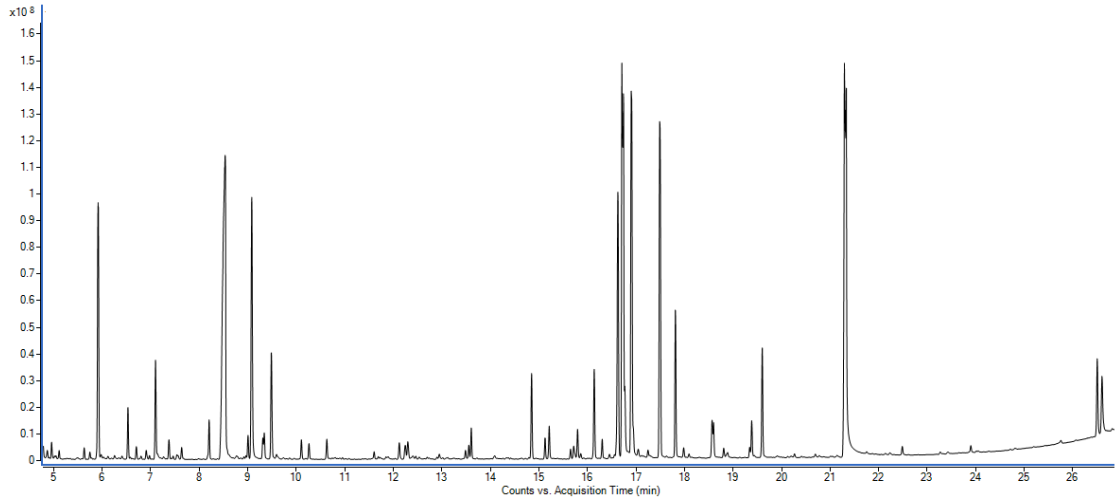
Lipidomic analysis

For the extraction of hydrophobic lipids, liquid-liquid extraction with chloroform:methanol (2:1) based on the Folch procedure was performed by adding four volumes of chloroform: methanol (2:1) containing internal standard mixture (Lipidomic SPLASH® Avanti Polar Lipids, Birmingham, AL, USA) to plasma. Then, the samples were mixed and incubated at -20ºC for 30 min. Afterwards, 1/10 volumes of NaCl 0.8 % were added and the mixture was centrifuged at 15,000 rpm. The lower phase was recovered, evaporated to dryness and reconstituted with methanol:methyl-tert-butyl ether (9:1) and analyzed on a 1290 Infinity UHPLC coupled to a 6550 qTOF mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) in positive electrospray ionization mode. The chromatographic elution consists of a ternary mobile phase containing water (A), methanol (B), 2-propanol (C) and 200 mM ammonium formate and 2% formic acid (D). The gradient was as follow: 0 minutes, 10% B, 35% C and 5% D; 0.5 minutes, 10% B, 45% C and 5% D; 1.5 minutes, 9.5% B, 47.7% C and 5% D; 1.6 minutes, 7.5% B, 58.5% C and 5% D; 5 minutes, 7% B, 61.2% C and 5% D; 5.1 minutes, 4% B, 77.4% C and 5% D; 7.5 minutes, 3.5% B, 80% C and 5% D; 9 minutes, 3.5% B, 80% C and 5% D; 9.5 minutes, 0% B, 100% C and 0% D; 11.5 minutes, 0% B, 100% C and 0% D; 11.6 minutes, 10% B, 35% C and 5% D; 14 minutes, 10% B, 35% C and 5% D. The stationary phase was a C18 column (Kinetex EVO C18 Column, 2.6 µm, 2.1 mm X 100 mm) that allows the sequential elution of the more hydrophobic lipids such as lysophospholipids, sphingomyelins, phospholipids, diacylglycerols, triacylglycerols and cholesteryl esters, among others.

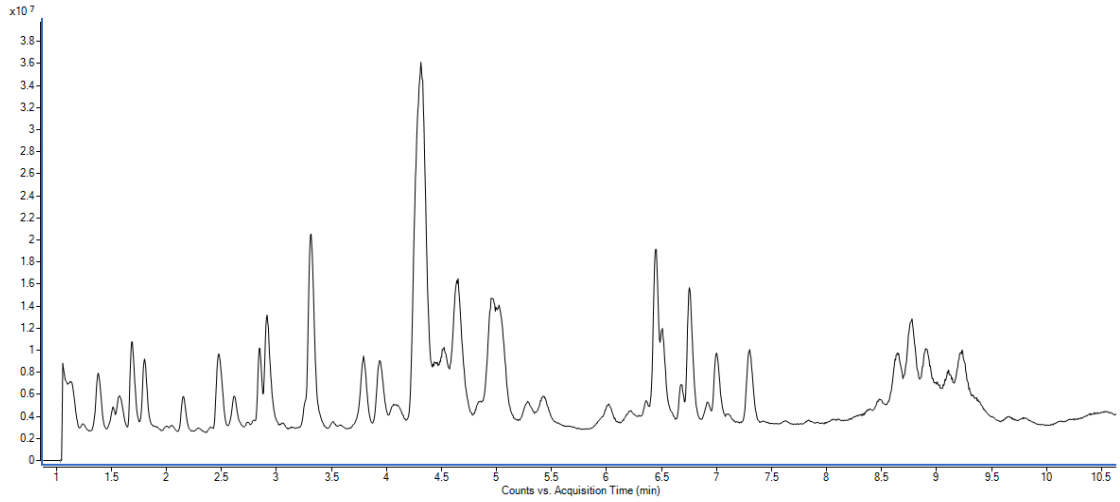
To ensure reproducibility during the analysis, a pooled matrix sample was generated by taking a small volume of each experimental sample and was used as a technical replicate throughout the analysis.



Supplementary Figure S1. Total ion chromatogram (TIC) of a pool of samples analyzed by nanoLC-Orbitrap-MS for the proteomic profile.



Supplementary Figure S2. Total ion chromatogram (TIC) of a pool of samples analyzed by GC-MS for the metabolomic profile.



Supplementary Figure S3. Total ion chromatogram (TIC) of a pool of samples analyzed by LC-MS for the lipidomic profile.

Supplementary Table S1. Detected proteins during the proteomics analysis on the nanoLC-Orbitrap-MS platform, including the Swiss-Prot ID, the number of peptides identified for that protein (Σ# Peptides), the % of the total protein covered by the identified peptides (Σ Coverage), the score provided by the MasCot search engine (Score), the number of amino acids in the protein (# AAs) and the molecular weight (MW) in kDa.

Protein	Swiss-Prot ID	Σ# Peptides	Σ Coverage	Score	# AAs	MW [kDa]
14-3-3 protein zeta/delta	P63104	7	39.59	320.71	245	27.7
Actin, gamma-enteric smooth muscle	P63267	9	23.94	511.09	376	41.8
Adiponectin	Q15848	1	6.15	106.73	244	26.4
Afamin	P43652	38	58.60	1991.27	599	69.0
Alpha-1-acid glycoprotein 1	P02763	14	59.20	3293.14	201	23.5
Alpha-1-acid glycoprotein 2	P19652	12	57.71	2069.83	201	23.6
Alpha-1-antichymotrypsin	P01011	21	51.06	2721.57	423	47.6
Alpha-1-antitrypsin	P01009	23	54.31	1463.97	418	46.7
Alpha-1B-glycoprotein	P04217	18	50.10	1559.44	495	54.2
Alpha-2-antiplasmin	P08697	18	46.23	829.80	491	54.5
Alpha-2-HS-glycoprotein	P02765	11	44.69	1543.77	367	39.3
Alpha-2-macroglobulin	P01023	87	63.23	35961.34	1474	163.2
Alpha-actinin-1	P12814	13	16.26	491.18	892	103.0
Angiotensinogen	P01019	13	27.84	1704.97	485	53.1
Antithrombin-III	P01008	33	65.52	1574.84	464	52.6
APOC4-APOC2 readthrough (NMD candidate)	K7ER74	6	37.08	408.47	178	20.0
Apolipoprotein A-I	P02647	36	81.27	9562.65	267	30.8
Apolipoprotein A-II	P02652	10	67.00	1926.48	100	11.2
Apolipoprotein A-IV	P06727	35	69.44	2151.68	396	45.3
Apolipoprotein B-100	P04114	198	46.55	13725.15	4563	515.3
Apolipoprotein C-I (Fragment)	K7ERI9	5	37.66	369.39	77	8.6
Apolipoprotein C-III	P02656	5	55.56	784.47	99	10.8
Apolipoprotein C-IV	P55056	2	12.60	58.49	127	14.5
Apolipoprotein D	P05090	8	34.92	848.31	189	21.3
Apolipoprotein E	P02649	21	59.31	813.90	317	36.1
Apolipoprotein F	Q13790	3	18.10	359.79	326	35.4
Apolipoprotein L1	O14791	9	32.66	217.34	398	43.9
Apolipoprotein M	O95445	4	17.55	206.44	188	21.2

Apolipoprotein(a)	P08519	9	27.18	243.58	4548	501.0
Attractin	O75882	9	7.35	264.42	1429	158.4
Beta-2-glycoprotein 1	P02749	16	57.10	1545.41	345	38.3
Beta-Ala-His dipeptidase	Q96KN2	5	14.00	147.68	507	56.7
Biotinidase	P43251	4	8.29	151.92	543	61.1
C4b-binding protein alpha chain	P04003	22	37.86	1044.54	597	67.0
C4b-binding protein beta chain	P20851	3	15.87	101.77	252	28.3
Carbonic anhydrase 1 (Fragment)	E5RH81	3	15.43	191.85	175	19.2
Carboxylic ester hydrolase	F8WF14	3	4.98	150.58	562	63.4
Carboxypeptidase B2	A0A087WSY5	6	15.80	148.05	386	44.0
Carboxypeptidase N catalytic chain	P15169	6	14.41	213.98	458	52.3
Carboxypeptidase N subunit 2	P22792	12	29.72	513.29	545	60.5
CD5 antigen-like	O43866	3	13.83	90.60	347	38.1
cDNA FLJ55673, highly similar to Complement factor B	B4E1Z4	53	41.63	3040.30	1266	140.9
Ceruloplasmin	P00450	49	57.37	5732.81	1065	122.1
Ceruloplasmin (Fragment)	H7C5R1	39	54.23	4528.98	852	97.7
Clusterin	P10909	17	34.97	1070.69	449	52.5
Coagulation factor IX	P00740	6	18.00	167.42	461	51.7
Coagulation factor X	P00742	10	22.13	360.29	488	54.7
Coagulation factor XI	P03951	4	7.68	83.92	625	70.1
Coagulation factor XII	P00748	19	37.89	855.53	615	67.7
Coagulation factor XIII A chain	P00488	10	19.40	538.70	732	83.2
Coagulation factor XIII B chain	P05160	15	31.16	655.79	661	75.5
Cofilin 1 (Non-muscle), isoform CRA_a	G3V1A4	2	15.44	140.78	149	16.8
Complement C1q subcomponent subunit A	P02745	7	28.57	225.91	245	26.0
Complement C1q subcomponent subunit B (Fragment)	A0A0A0MSV6	7	31.58	480.26	228	24.0
Complement C1q subcomponent subunit C	P02747	5	22.86	440.85	245	25.8
Complement C1r subcomponent	A0A3B3ISR2	29	55.32	1009.49	705	80.1
Complement C1r subcomponent-like protein	Q9NZP8	7	12.73	164.36	487	53.5
Complement C1s subcomponent	P09871	21	44.48	1142.39	688	76.6
Complement C2	P06681	14	22.61	672.56	752	83.2
Complement C3	P01024	141	83.76	24850.01	1663	187.0
Complement C4-A	A0A0G2JPR0	100	65.08	7127.77	1744	192.8
Complement C4-A	A0A140TA32	97	64.61	7042.69	1698	187.6

Complement C4-A	P0C0L4	99	64.33	7053.16	1744	192.7
Complement C4-B	P0C0L5	100	65.08	7310.50	1744	192.6
Complement C4-B	A0A140TA29	97	64.61	7213.11	1698	187.5
Complement C5	P01031	65	45.64	3050.80	1676	188.2
Complement component C6	P13671	28	36.08	1157.21	934	104.7
Complement component C7	P10643	31	48.52	1326.58	843	93.5
Complement component C8 alpha chain	P07357	14	34.76	738.80	584	65.1
Complement component C8 beta chain	F5GY80	20	46.69	727.82	529	60.0
Complement component C8 beta chain	P07358	20	41.12	708.61	591	67.0
Complement component C8 gamma chain	P07360	10	58.91	517.51	202	22.3
Complement component C9	P02748	25	40.61	1224.41	559	63.1
Complement factor D	P00746	1	9.49	43.83	253	27.0
Complement factor H	A0A0D9SG88	27	75.06	1903.21	449	51.0
Complement factor H	P08603	62	58.73	4993.28	1231	139.0
Complement factor H-related protein 1	Q03591	14	43.94	710.94	330	37.6
Complement factor H-related protein 2	V9GYE7	7	33.46	392.48	254	28.9
Complement factor I	G3XAM2	21	42.01	1502.73	576	65.0
Condensin complex subunit 3	Q9BPX3	1	0.89	40.57	1015	114.3
Corticosteroid-binding globulin	P08185	6	16.54	315.32	405	45.1
C-reactive protein	P02741	3	16.52	196.87	224	25.0
Cysteine-rich secretory protein 3 (Fragment)	I3L0A1	1	4.19	48.22	191	21.6
Deleted in malignant brain tumors 1 protein (Fragment)	A0A590UJF8	1	13.86	76.35	202	21.6
Dermcidin	P81605	2	20.00	150.87	110	11.3
Extracellular glycoprotein lacritin	Q9GZZ8	1	7.97	75.93	138	14.2
Extracellular matrix protein 1	Q16610	16	35.19	469.00	540	60.6
Fermitin family homolog 3	Q86UX7	3	5.25	104.76	667	75.9
Fetuin-B	Q9UGM5	4	14.66	105.70	382	42.0
Fibrinogen alpha chain	P02671	30	36.37	1794.10	866	94.9
Fibrinogen beta chain	P02675	22	54.79	1827.10	491	55.9
Fibrinogen gamma chain	P02679	22	55.85	1271.78	453	51.5
Fibronectin	P02751	97	48.93	8032.22	2477	272.2
Fibulin-1	P23142	5	10.81	161.09	703	77.2
Ficolin-3	O75636	4	20.74	306.13	299	32.9
Gelsolin	P06396	31	41.43	1553.78	782	85.6

Glutathione peroxidase	A0A087X1J7	2	14.22	151.47	225	25.4
Haptoglobin	P00738	25	65.02	1622.00	406	45.2
Haptoglobin-related protein	P00739	15	30.17	846.32	348	39.0
Hemoglobin subunit alpha	P69905	8	67.61	856.39	142	15.2
Hemoglobin subunit beta	P68871	11	88.44	1977.75	147	16.0
Hemoglobin subunit delta	P02042	6	41.50	649.97	147	16.0
Hemopexin	P02790	28	62.77	5650.12	462	51.6
Heparin cofactor 2	P05546	18	33.27	1362.05	499	57.0
Hepatocyte growth factor activator	Q04756	6	10.08	175.70	655	70.6
Histidine-rich glycoprotein	P04196	21	45.52	1776.01	525	59.5
Hyaluronan-binding protein 2	Q14520	5	10.89	208.86	560	62.6
Ig-like domain-containing protein (Fragment)	A0A0J9YY99	3	24.79	173.03	117	13.0
Ig-like domain-containing protein (Fragment)	A0A0J9YWU9	1	7.76	56.86	116	12.9
Immunoglobulin heavy constant alpha 1	P01876	13	45.89	1259.13	353	37.6
Immunoglobulin heavy constant alpha 2 (Fragment)	A0A0G2JMB2	8	25.88	689.58	340	36.5
Immunoglobulin heavy constant delta	P01880	2	10.16	122.95	384	42.3
Immunoglobulin heavy constant gamma 1	P01857	13	56.06	2608.14	330	36.1
Immunoglobulin heavy constant gamma 2	P01859	8	33.74	800.65	326	35.9
Immunoglobulin heavy constant gamma 3 (Fragment)	A0A4W9A917	10	37.67	1246.50	377	41.3
Immunoglobulin heavy constant gamma 4	P01861	9	36.70	1086.71	327	35.9
Immunoglobulin heavy constant mu	P01871	15	39.96	830.57	453	49.4
Immunoglobulin heavy variable 1-18	A0A0C4DH31	1	9.40	68.37	117	12.8
Immunoglobulin heavy variable 1-69D	A0A0B4J2H0	1	9.40	73.24	117	12.7
Immunoglobulin heavy variable 3/OR16-12 (non-functional) (Fragment)	A0A075B7B8	2	18.80	119.00	117	12.9
Immunoglobulin heavy variable 3-7	P01780	2	17.09	115.59	117	12.9
Immunoglobulin heavy variable 3-72	A0A4W8ZXM2	2	25.74	206.20	101	11.2
Immunoglobulin heavy variable 3-74	A0A0B4J1X5	3	24.79	121.48	117	12.8
Immunoglobulin J chain (Fragment)	C9JA05	1	17.14	92.84	70	8.2
Immunoglobulin kappa constant	P01834	8	84.11	2252.45	107	11.8
Immunoglobulin kappa variable 1-5	P01602	1	9.40	51.14	117	12.8
Immunoglobulin kappa variable 2-30	P06310	3	16.67	142.47	120	13.2
Immunoglobulin kappa variable 2D-28	A0A5H1ZRS2	2	19.61	142.47	102	11.0
Immunoglobulin kappa variable 3-20	P01619	2	21.55	158.71	116	12.5
Immunoglobulin kappa variable 3D-11	A0A0A0MRZ8	2	13.91	54.44	115	12.6

Immunoglobulin kappa variable 4-1	P06312	2	13.22	51.66	121	13.4
Immunoglobulin lambda constant 2	P0DOY2	7	88.68	1333.86	106	11.3
Immunoglobulin lambda variable 3-9	A0A075B6K5	1	13.91	79.62	115	12.3
Immunoglobulin lambda-like polypeptide 5	B9A064	7	42.99	838.89	214	23.0
Insulin-like growth factor II	P01344	1	5.00	74.48	180	20.1
Insulin-like growth factor-binding protein 3	A6XND0	2	6.67	58.99	270	29.7
Insulin-like growth factor-binding protein complex acid labile subunit	P35858	18	33.39	732.64	605	66.0
Inter-alpha-trypsin inhibitor heavy chain H1	P19827	26	32.05	2741.73	911	101.3
Inter-alpha-trypsin inhibitor heavy chain H2	Q5T985	39	42.25	2896.53	935	105.2
Inter-alpha-trypsin inhibitor heavy chain H3	A0A087WW43	12	21.34	438.74	670	75.0
Inter-alpha-trypsin inhibitor heavy chain H4	Q14624	42	49.14	2934.94	930	103.3
Kallistatin	P29622	12	36.07	349.32	427	48.5
Keratin, type I cytoskeletal 10	P13645	20	44.35	635.94	584	58.8
Keratin, type I cytoskeletal 9	P35527	13	27.77	766.62	623	62.0
Keratin, type II cytoskeletal 1	P04264	25	37.27	910.70	644	66.0
Keratin, type II cytoskeletal 2 epidermal	P35908	8	12.05	408.84	639	65.4
Kininogen-1	P01042	28	42.24	2446.73	644	71.9
Lactotransferrin (Fragment)	E7EQB2	13	21.55	500.51	696	76.6
Leucine-rich alpha-2-glycoprotein	P02750	7	27.95	299.56	347	38.2
Lipocalin-1	P31025	5	26.70	410.65	176	19.2
Lipopolysaccharide-binding protein	P18428	2	6.24	239.88	481	53.3
Lumican	P51884	11	37.87	781.33	338	38.4
Lysozyme	F8VV32	3	27.88	169.19	104	11.5
Mammaglobin-B	O75556	2	22.11	138.28	95	10.9
Mannan-binding lectin serine protease 1 (Fragment)	C9JMA2	3	16.18	68.13	204	23.7
Mannose-binding protein C	P11226	4	22.18	83.93	248	26.1
N-acetylmuramoyl-L-alanine amidase	Q96PD5	12	31.25	558.26	576	62.2
Phosphatidylcholine-sterol acyltransferase	P04180	3	11.36	173.60	440	49.5
Phosphatidylinositol-glycan-specific phospholipase D	P80108	10	12.86	282.15	840	92.3
Phospholipase A(2)	A0A3B3IRX2	2	15.38	48.41	117	13.0
Pigment epithelium-derived factor	P36955	14	34.93	924.15	418	46.3
Plasma kallikrein	P03952	26	38.71	946.83	638	71.3
Plasma protease C1 inhibitor	A0A7I2V2D2	18	40.04	1721.64	482	53.2
Plasma serine protease inhibitor	P05154	4	11.08	138.15	406	45.6

Plasminogen	P00747	50	63.21	2900.54	810	90.5
Platelet basic protein	P02775	5	44.53	547.18	128	13.9
Platelet factor 4	P02776	1	14.85	0.00	101	10.8
Pleckstrin	P08567	1	6.29	82.72	350	40.1
Polymeric immunoglobulin receptor	P01833	2	2.75	124.21	764	83.2
Pregnancy zone protein	P20742	22	17.14	11999.73	1482	163.8
Prenylcysteine oxidase 1	Q9UHG3	1	3.17	40.57	505	56.6
Profilin-1	P07737	4	35.71	412.43	140	15.0
Properdin	P27918	8	19.19	336.62	469	51.2
Protein AMBP	P02760	14	44.03	1288.66	352	39.0
Protein S100-A9	P06702	1	13.16	96.44	114	13.2
Protein Z-dependent protease inhibitor	Q9UK55	4	12.39	145.92	444	50.7
Proteoglycan 4	Q92954	6	4.84	88.87	1404	151.0
Prothrombin	P00734	33	61.41	2349.19	622	70.0
Retinol-binding protein	Q5VY30	11	72.36	1383.31	199	23.0
SAA2-SAA4 readthrough	A0A096LPE2	7	27.88	402.54	208	23.3
Selenoprotein P (Fragment)	A0A182DWH8	1	10.53	73.74	209	23.6
Serotransferrin	P02787	43	54.30	3029.94	698	77.0
Serum amyloid A-1 protein	P0DJI8	5	54.10	546.01	122	13.5
Serum amyloid A-2 protein	P0DJI9	4	37.70	347.54	122	13.5
Serum amyloid P-component	P02743	11	34.08	636.37	223	25.4
Serum paraoxonase/arylesterase 1	P27169	9	30.99	887.55	355	39.7
Sex hormone-binding globulin	I3L2X4	3	22.76	171.84	290	31.5
Talin-1	Q9Y490	12	6.14	474.45	2541	269.6
Tetranectin	E9PHK0	8	68.13	549.29	160	17.8
Thrombospondin-1	P07996	5	5.98	94.97	1170	129.3
Thymosin beta-4	P62328	4	61.36	69.24	44	5.0
Thyroxine-binding globulin	P05543	11	30.12	410.17	415	46.3
Transgelin-2 (Fragment)	X6RJP6	1	5.88	63.56	187	21.1
Transthyretin	A0A087WT59	12	88.70	2151.82	115	12.6
Tropomyosin alpha-4 chain	P67936	6	26.21	143.90	248	28.5
Vasodilator-stimulated phosphoprotein (Fragment)	K7EM16	1	6.56	78.11	183	20.1
Vinculin	P18206	3	3.79	96.44	1134	123.7
Vitamin D-binding protein	P02774	40	79.11	3849.54	474	52.9

Vitamin K-dependent protein C	P04070	4	9.11	195.81	461	52.0
Vitamin K-dependent protein S	A0A3B3ISJ1	11	18.28	388.83	662	73.7
Vitamin K-dependent protein Z	P22891	3	9.75	92.22	400	44.7
Vitronectin	P04004	14	30.54	1595.14	478	54.3
von Willebrand factor	P04275	27	13.33	760.96	2813	309.1
WD repeat-containing protein 1	O75083	1	3.63	48.82	606	66.2
Zinc finger C4H2 domain-containing protein	Q9NQZ6	1	3.13	50.61	224	26.2
Zinc-alpha-2-glycoprotein	P25311	17	54.70	1286.43	298	34.2
Zyxin (Fragment)	H0Y2Y8	1	2.78	65.55	540	57.6

Supplementary Table S2. Detected compounds during the metabolomics analysis on the GC-MS platform, including the theoretical mass-to-charge ratio (*m/z*) and retention time (RT) values.

Compound	*m/z*	RT	Compound	*m/z*	RT
2-Hydroxybutyric acid	131.0895	6.91	Glutamine	156.0961	15.21
2-Hydroxyglutaric acid	247.1189	12.94	Glyceric acid	189.0782	9.86
2-Hydroxyisobutyric acid	131.0895	5.96	Glycerol	218.1185	9.01
2-Hydroxyisovaleric acid	145.1061	7.46	Glycerol-1-phosphate	299.0801	15.20
2-Keto-3-methylvaleric acid	200.1102	7.68	Glycine	174.1153	9.48
2-Ketoisocaproic acid	200.1102	8.17	Glycolic acid	177.0764	6.12
3-Hydroxy(iso)butyric acid	117.0731	7.37	Heptanoic acid	187.1148	7.42
3-Hydroxypentanoic acid	204.1316	8.53	Hexanoic acid	173.1005	6.02
3-Phosphoglyceric acid	299.0741	15.69	Hippuric acid	105.0373	15.81
4-Hydroxybenzoic acid	223.1010	13.55	Hydrocinnamic acid	104.0656	10.89
4-hydroxyphenyllactic acid	179.0902	16.34	Hypoxanthine	265.1025	15.53
α-Ketoglutaric acid	198.0622	12.97	Iminodiacetic acid	232.1300	12.41
α-Ketoisovaleric acid	202.0891	7.03	Indole-3-propanoic acid	202.1064	18.28
α-Tocopherol	237.1337	26.37	Indolelactic acid	202.1064	19.23
Alanine	116.0916	6.53	Isoleucine	158.1360	9.31
Aspartic acid	233.1045	12.31	Lactic acid	190.0880	5.92
Benzoic acid	179.0559	8.57	Leucine	158.1432	9.01
Citric acid	273.1050	15.79	Linoleic acid	337.2654	19.34
Creatinine	115.0841	12.75	Malic acid	233.1030	11.92
d-Arabinose	307.1622	14.07	Maltose (isomer 1)	361.1790	24.05
d-Arabitol	319.1667	14.85	Maltose (isomer 2)	361.1790	24.13
Decanoic acid	229.1615	11.38	Meso-erythritol	202.1095	12.23
d-Fructose	307.1650	16.45	Methionine	128.0909	12.24
d-Galactitol	319.1675	17.12	Myo-Inositol	318.1569	18.57
d-Gluconic acid	292.1385	17.28	Nonanoic acid	215.1464	10.11
d-Mannitol	319.1675	16.91	Octanoic acid	201.1311	8.79
d-Mannonic acid	333.1434	17.12	Oleic acid (isomer 1)	339.2795	19.38
d-Sorbitol	319.1642	17.04	Oleic acid (isomer 2)	339.2795	19.44
d-Sucrose	361.1790	23.27	Ornithine	142.1063	15.71
d-Threitol	204.1070	12.15	Oxalic acid	131.0353	7.10
d-Xylitol	319.1667	14.66	Oxoproline	156.0853	12.30
d-Xylose	307.1622	14.02	p-Cresol	165.0738	7.19
Dodecanoic acid	257.1941	13.73	Palmitic acid	117.0382	17.81
Erythronic acid	217.1142	12.69	Phenylalanine	218.1050	13.56
Ethanolamine	174.1147	8.92	Phosphoric acid	299.0788	9.09
Ethylmalonic acid	217.1139	9.07	Pipecolic acid	156.1220	10.26
Fumaric acid	245.0752	9.97	Proline	142.1082	9.34
Galactonic acid	292.1395	17.76	Pyruvic acid	174.0629	5.75
Galactose	319.1592	16.60	Ribonic acid	292.1424	15.40
Galacturonic acid	333.1434	17.25	Saccharic acid	292.1385	17.90
Glucose 6-phosphate	387.1492	20.60	Sarcosine	116.0909	7.02

Glutamic acid	246.1392	13.49	Sedoheptulose	319.1661	19.03
Compound	**m/z**	**RT**	**Compound**	**m/z**	**RT**
Serine	204.1070	10.26	Uracil	241.0848	9.92
Stearic acid	117.0382	19.60	Urea	189.0909	8.50
Succinic acid	247.0851	9.53	Uric acid	441.1685	18.60
Tetradecanoic acid	285.2254	15.86	Valine	144.1229	8.20
Threonic acid	292.1383	12.69	Xylonic acid	292.1424	15.22
Threonine	218.1353	10.63	Xylulose	263.1405	14.31

Supplementary Table S3. Detected lipid species during the lipidomics analysis on the LC-MS platform, including the theoretical mass-to-charge ratio (*m/z*) and retention time (RT) values.

Compound	*m/z*	RT	Compound	*m/z*	RT
ChoE (16:0)	647.5737	9.43	PC 33:2	744.5538	4.25
ChoE (16:1)	645.5581	8.96	PC 34:0	762.6008	5.56
ChoE (17:0)	661.5894	10.17	PC 34:1	760.5851	4.98
ChoE (17:1)	659.5737	9.21	PC 34:2	758.5694	4.56
ChoE (18:0)	675.6050	10.06	PC 34:3	756.5538	4.23
ChoE (18:1)	673.5894	9.54	PC 34:4	754.5381	4.03
ChoE (18:2)	671.5737	9.15	PC 35:1	774.6007	5.39
ChoE (18:3)	669.5581	8.83	PC 35:2	772.5851	4.92
ChoE (20:2)	699.6050	9.53	PC 35:4	768.5538	4.33
ChoE (20:3)	697.5894	9.35	PC 36:1	788.6164	5.86
ChoE (20:4)	695.5737	9.01	PC 36:2	786.6007	5.33
ChoE (20:5)	693.5581	8.72	PC 36:3	784.5851	4.85
ChoE (22:4)	723.6050	9.51	PC 36:4	782.5694	4.65
ChoE (22:5)	721.5894	9.19	PC 36:5	780.5538	4.32
ChoE (22:6)	719.5737	8.93	PC 38:2	814.6320	6.10
DG 34:1	617.5115	6.74	PC 38:3	812.6164	5.70
DG 34:2	615.4959	6.50	PC 38:4	810.6007	5.44
DG 34:3	613.4802	6.40	PC 38:5	808.5851	4.82
DG 36:1	645.5434	6.92	PC 38:6	806.5694	4.41
DG 36:2	643.5272	6.74	PC 40:4	838.6320	6.09
DG 36:3	641.5115	6.57	PC 40:5	836.6164	5.64
DG 36:4	639.4959	6.42	PC 40:6	834.6007	5.05
DG 40:4	695.5591	9.01	SM 32:0	677.5592	3.83
LPC 15:0	482.3241	1.52	SM 32:1	675.5436	3.54
LPC 16:0	496.3398	1.74	SM 32:2	673.5279	3.28
LPC 16:0 e	482.3605	1.93	SM 33:1	689.5592	3.75
LPC 16:1 e	480.3449	1.94	SM 34:1	703.5749	4.01
LPC 18:0	524.3711	2.23	SM 34:2	701.5592	3.69
LPC 18:0 e	510.3918	2.49	SM 35:1	717.5905	4.30
LPC 18:1	522.3554	1.86	SM 36:0	733.6218	4.90
LPC 18:2	520.3398	1.61	SM 36:1	731.6062	4.62
LPC 20:0	552.4024	2.76	SM 36:2	729.5905	4.23
LPC 20:2	548.3711	2.23	SM 38:1	759.6375	5.41
LPC 20:3	546.3554	1.79	SM 38:2	757.6218	4.91
PC 30:0	706.5381	4.13	SM 39:1	773.6531	5.95
PC 31:0	720.5538	4.41	SM 40:1	787.6688	6.23
PC 32:0	734.5694	4.75	SM 40:2	785.6531	5.81
PC 32:1	732.5538	4.37	SM 41:1	801.6844	6.39
PC 32:2	730.5381	3.98	SM 41:2	799.6688	6.19
PC 33:0	748.5851	5.13	SM 42:1	815.7001	6.52
PC 33:1	746.5694	4.62	SM 42:2	813.6844	6.26

Compound	*m/z*	RT	Compound	*m/z*	RT
SM 42:3	811.6688	5.89	TG 51:3	860.7813	9.98
SM 43:1	829.7157	6.58	TG 52:1	878.8171	10.10
SM 43:2	827.7001	6.37	TG 52:2	876.8015	9.64
TG 46:0	796.7389	8.88	TG 52:3	874.7858	9.28
TG 46:1	794.7232	8.58	TG 52:4	872.7702	8.96
TG 46:2	792.7076	8.29	TG 52:5	870.7545	8.70
TG 47:0	810.7499	9.10	TG 52:6	868.7389	8.47
TG 47:1	808.7403	8.79	TG 54:2	904.8328	10.21
TG 48:0	824.7702	9.37	TG 54:3	902.8171	9.79
TG 48:1	822.7545	8.99	TG 54:4	900.8015	9.41
TG 48:2	820.7389	8.69	TG 54:5	898.7858	9.08
TG 48:3	818.7232	8.41	TG 54:6	896.7702	8.79
TG 50:0	852.8015	9.95	TG 54:7	894.7545	8.54
TG 50:1	850.7858	9.50	TG 56:5	926.8267	9.88
TG 50:2	848.7702	9.13	TG 56:6	924.8104	9.40
TG 50:3	846.7545	8.81	TG 56:7	922.7975	9.20
TG 50:4	844.7389	8.54	TG 58:8	948.8099	9.35
TG 51:2	862.7858	9.37			

Trabajo 6

Impact of coronavirus disease 2019 epidemics on prevention and care for HIV and other sexually transmitted infections.

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Resumen

Objetivos: Evaluar el impacto de las epidemias de coronavirus 2019 (COVID-19) en la prevención y atención del VIH y otras infecciones de transmisión sexual en un importante centro de referencia que presta servicios preventivos y clínicos en Cataluña, España.

Métodos: Comparamos retrospectivamente los datos anonimizados clínicos y de laboratorio de marzo a diciembre de 2020 vs. 2019. De la base de datos hospitalaria administrativa se obtuvieron datos clínicos mensuales sobre los usuarios de profilaxis previa y posterior a la exposición al VIH y sobre adultos que viven con una infección por VIH. Se recuperaron de la base de datos de laboratorio pruebas mensuales de VIH, hepatitis B y C, Treponema pallidum, Neisseria gonorrhoeae y Chlamydia trachomatis, y lípidos plasmáticos y glucosa.

Resultados: Hubo menos (↓28%, p-valor=0.003) pero más avanzadas (media de células CD4+/µl 305 vs. 370, p-valor <0.001) infecciones por VIH y más gonorrea (↑39%, p-valor <0.001) y clamidia (↑37%, p-valor <0.001) en 2020 vs. 2019. En personas con VIH, las tasas de ARN-VIH < 50 copias/ml se mantuvieron estables (11 vs. 11%, p-valor =0.147) a pesar de menos visitas programadas (↓25%, p-valor <0.001). Sin embargo,

tuvieron menos cambios en la prescripción de antirretrovirales (↓10%, p-valor =0.018), peores lípidos plasmáticos [colesterol total medio 190 vs. 185 mg/dl, p-valor <0.001; colesterol de lipoproteínas de baja densidad (LDL) medio 114 vs. 110 mg/dl, p-valor <0.001; triglicéridos medios 136 vs. 125 mg/dl, p-valor <0.001; colesterol de alta densidad (HDL) medio 47 vs. 48 mg/dl, p-valor =0.006], y un exceso de mortalidad (↑264%, p-valor =0.006) debido en gran parte no solo a COVID-19 sino también a otras causas.

Conclusiones: En nuestro entorno, las epidemias de COVID-19 se asociaron con un aumento de algunas infecciones de transmisión sexual prevalentes, con menos infecciones de VIH pero más avanzadas, y con peores resultados de salud no virológicos y mayor mortalidad en personas que viven con el VIH.

Impact of coronavirus disease 2019 epidemics on prevention and care for HIV and other sexually transmitted infections

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Objective: To assess the impact of coronavirus disease 2019 (COVID-19) epidemics on the prevention and care for HIV and other sexually transmitted infections at a major reference centre providing preventive and clinical services in Catalonia, Spain.

Design: We retrospectively compared anonymized clinical and laboratory data from March to December 2020 vs. 2019.

Methods: Monthly clinical data on HIV preexposure and postexposure prophylaxis users and on adults with HIV infection were retrieved from the administrative hospital database. Monthly tests for HIV, hepatitis B and C, *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*, and plasma lipids and glucose were recovered from the laboratory database.

Results: There were less (↓28%, $P = 0.003$) but more advanced (mean $CD4^+$ cells/μl 305 vs. 370, $P < 0.001$) HIV infections and more gonorrhoea (↑39%, $P < 0.001$) and chlamydia (↑37%, $P < 0.001$) infections in 2020 vs. 2019. In people with HIV, rates of HIV RNA at least 50 copies/ml remained stable (11 vs. 11%, $P = 0.147$) despite less scheduled visits (↓25%, $P < 0.001$). However, they had less antiretroviral prescription changes (↓10%, $P = 0.018$), worse plasma lipids [mean total cholesterol 190 vs. 185 mg/dl, $P < 0.001$; mean low-density lipoprotein (LDL) cholesterol 114 vs. 110 mg/dl, $P < 0.001$; mean triglycerides 136 vs. 125 mg/dl, $P < 0.001$; mean high-density lipoprotein (HDL) cholesterol 47 vs. 48 mg/dl, $P = 006$], and an excess of mortality (↑264%, $P = 0.006$) due in great part not only to COVID-19 but also to other causes.

Conclusion: In our setting, COVID-19 epidemics was associated with an increase in some prevalent sexually transmitted infections, with less but more advanced HIV infections, and with worse nonvirologic healthcare outcomes and higher mortality in people living with HIV.

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Keywords: coronavirus disease 2019 epidemics, HIV, impact, sexually transmitted diseases

Introduction

As of 12 October 2021, coronavirus disease 2019 (COVID-19) pandemic has caused more than 237 million confirmed cases and more than 4.8 million deaths worldwide [1]. Governments across the globe dictated severe physical and social contact restrictions aimed to drastically reduce viral transmission. Spain was one of the hardest hit countries at the beginning of the pandemic. Due to the exceptional nature of the situation, the Spanish government approved a first state of alarm on 14 March 2020 and imposed a strict home lockdown for all citizens with the exception of essential workers. With the slow but steady reduction in the number of cases, measures became more flexible from 11 May 2020 until 21 June 2020 when the first state of alarm officially ended. Unfortunately, during the summer, the number of cases progressively increased and the Spanish government declared a second state of alarm from 25 October 2020 until 9 May 2021. Mass vaccination against COVID-19 in Spain started on 27 December 2020 [2]. Figure 1 shows the epidemic curve of laboratory-confirmed COVID-19 cases in Spain along with key milestones dates through 2020.

Beyond the direct toll on morbidity and mortality, SARS-CoV-2 pandemic have severely affected healthcare access and quality throughout the world. Healthcare resources were urgently and widely prioritized for SARS-CoV-2 diagnosis and clinical care of COVID-19 patients. As a result, the screening and the diagnosis for common chronic diseases was dramatically reduced and the availability of specific therapies was significantly delayed [3,4]. These factors ultimately led to increasing morbidity and mortality because of illnesses other than COVID-19 [5,6].

The emergence of SARS-CoV-2 epidemics may have also affected established measures for the prevention and diagnosis of HIV infection and other sexually transmitted diseases and the clinical care of HIV-infected patients, although data are limited [7,8]. The WHO warned that the access to HIV medicines could be severely impacted by COVID-19 [9]. Mathematical models predicted an increase of HIV-related mortality if antiretroviral therapy supply was temporarily interrupted [10,11]. In Spain, telephone calls or electronic messaging kept minimum standards for HIV clinical care during lockdown, and antiretroviral therapy dispensation was facilitated with the

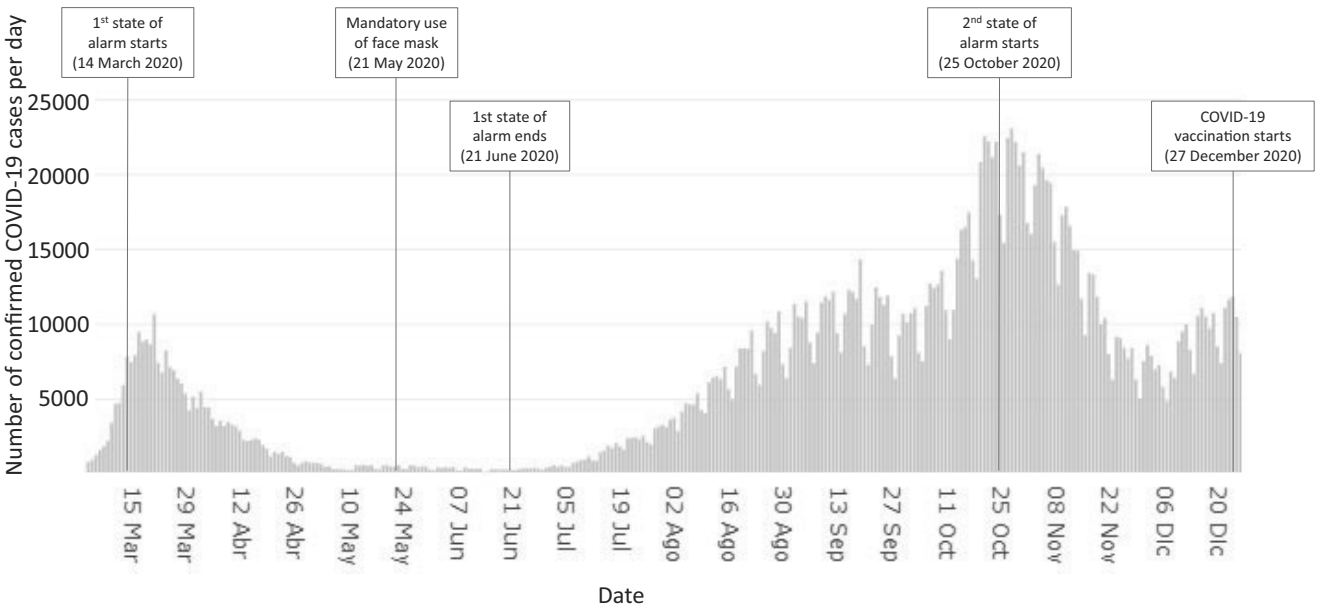

Fig. 1. Epidemic curve of laboratory-confirmed coronavirus disease 2019 cases in Spain along with key milestones dates. Adapted from: https://cnecovid.isciii.es/covid19/#provincias. Accessed on 13 September 2021.

development of home delivery programmes through the national public postal service, the national civil protection system, or private couriers [12].

The Hospital Clínic is a community hospital for an area of influence with a population of 540 000 inhabitants in the city of Barcelona (Spain), and at the same time, operates as a reference care facility for specific diseases, such as HIV infection for the whole region of Catalonia (https://www.clinicbarcelona.org/en). The hospital currently provides ambulatory care, supply of antiretroviral therapy, and hospital admission if necessary for more than 6000 adults with HIV infection being the largest HIV care centre in Spain. It has been also providing HIV postexposure prophylaxis since 2003 and HIV preexposure prophylaxis as it was approved by the Spanish National Health System in November 2019. We aimed to assess the impact of COVID-19 epidemics on the prevention and clinical care of HIV infection and on the screening and diagnosis of HIV infection and other sexually transmitted diseases in the setting of Hospital Clínic of Barcelona.

Methods

Study design

We retrospectively compared anonymized clinical and laboratory data from the first 10 months of the COVID-19 epidemics in Spain (March 2020 to December 2020) with those from the same time period 1 year earlier (March 2019 to December 2019) considered as the reference for the purpose of this study. The only exception was HIV preexposure prophylaxis as it became available in Spain from November 2019. For the sake of simplicity, we will refer as 2020 or 2019 for the corresponding study periods.

The study was approved by the local Institutional Review Board. According to current Spanish regulations [13], informed consent was waived because of the retrospective nature of the study and the use of anonymous data for the analysis.

Procedures

Monthly clinical data on HIV preexposure and postexposure prophylaxis users and on persons with HIV infection were retrieved from the hospital administrative database. By protocol, preexposure and postexposure visits include screening tests for HIV and the other sexually transmitted infections evaluated in this study. Monthly laboratory data including tests for HIV (fourth generation ELISA tests for people unknown to be HIV-positive, and plasma HIV RNA for people known to be HIV), hepatitis B (HBsAg) and C (anti-HCV, RNA VHC), *Treponema pallidum* (IgM, VDRL, PCR), *Neisseria gonorrhoeae* (PCR), and *Chlamydia trachomatis* (PCR) were obtained from the microbiology laboratory database whereas plasma lipids and glucose were recovered from the chemistry laboratory database. PCR tests for sexually transmitted infections were obtained from urinary, anal, pharyngeal sites. As fasting is explicitly requested for routine blood tests in our hospital, we assumed that plasma lipids and glucose values of chemistry tests were fasting. De novo HIV, hepatitis B, or hepatitis C-positive tests were considered when a person had a first known positive laboratory diagnosis (i.e. a positive laboratory diagnosis with previous respective tests negative or not done). Data were entered into an electronic case report form specifically designed for the purpose of this study using the Research Electronic Data Capture (REDCap) system hosted at the Hospital Clínic of Barcelona.

The following data per month were collected: number of HIV preexposure prophylaxis visits; number of HIV postexposure prophylaxis visits; number of HIV diagnostic tests performed and number of de novo positive ones; number of outpatient visits in persons with HIV; number of plasma HIV RNA tests done and number of plasma HIV RNA tests with viral load above the level of detection (50 copies/ml); mean values of total, LDL, and HDL cholesterol, triglycerides, and glucose in routine blood chemistries of persons with HIV; number of changes in antiretroviral regimens; number of hospital admissions; number and causes of deaths; number of hepatitis B tests and number of de novo hepatitis B diagnosis (defined by a positive HBsAg); number of hepatitis C tests and number of de novo hepatitis C diagnosis (defined by positive antibodies plus measurable RNA confirmation); number of *T. pallidum* tests and number of active syphilis diagnoses (defined by at least a positive IgM, a VDRL titer >1/8, or a positive PCR); number of *N. gonorrhoeae* tests and number of active gonorrhoea diagnoses (defined by a positive PCR); number of *C. trachomatis* tests and number of active chlamydia infection diagnoses (defined by a positive PCR). In people with de novo HIV diagnosis, $CD4^+$ cell counts and the presence of AIDS-defining conditions at HIV diagnosis was also collected.

Statistical analysis

The monthly and the total number of events in the 2019 and 2020 together with the 95% confidence interval estimated using the delta method was compared between the 2 years by means of the Incidence Rate Ratio (IRR) (excepting for HIV preexposure prophylaxis, as previously mentioned). The events were considered following a Poisson distribution. The trend over time in lipid profile was estimated using a mixed-effects linear regression. For triglycerides and glucose, a log-transformation was applied to improve the normality of the residuals and the predicted mean was presented as geometric mean. $CD4^+$ cell counts and the presence of AIDS-defining conditions at HIV diagnosis were compared with chi-squared and *t* tests, respectively. The statistical analysis was

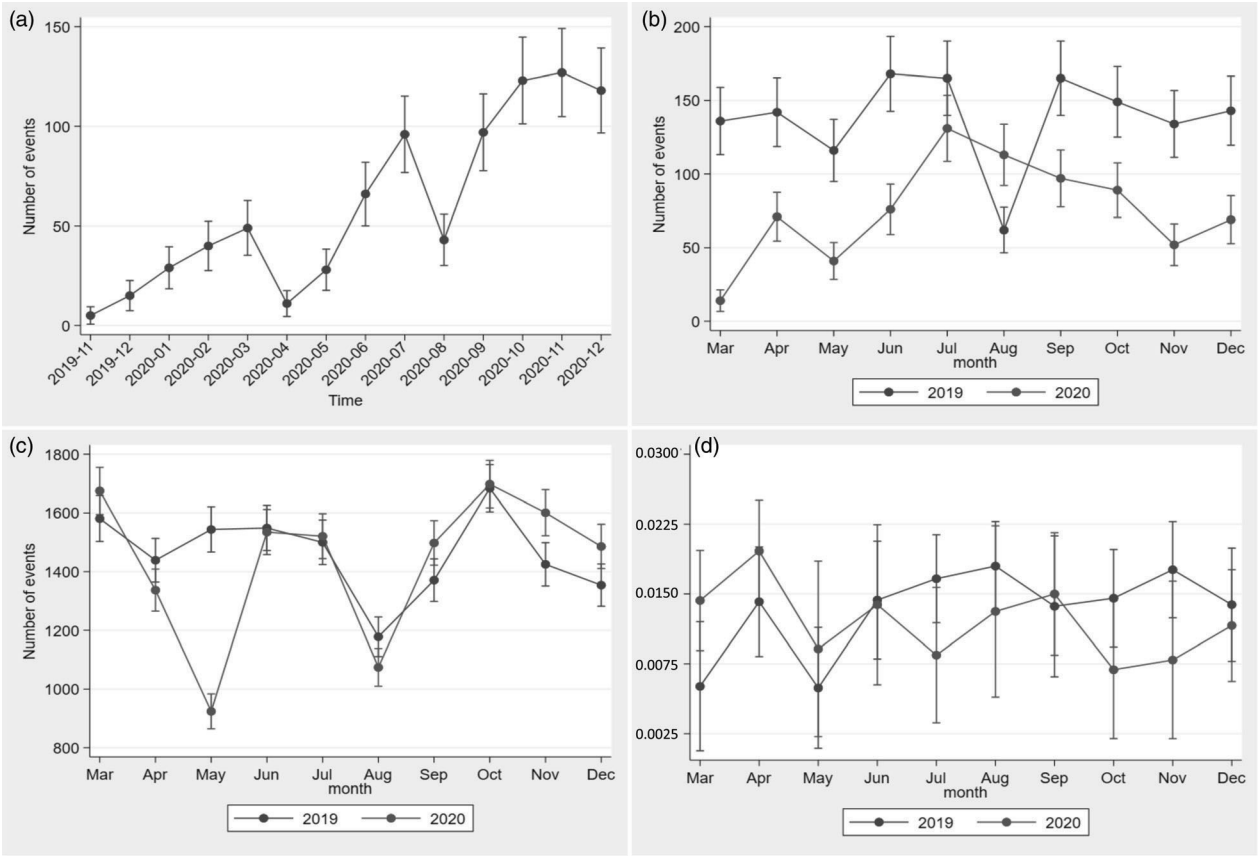

Fig. 2. Monthly data on HIV preexposure (a) and postexposure (b) prophylaxis visits, number of HIV diagnostic tests performed (c), and proportion of de novo HIV diagnoses (d).

performed using Stata (StataCorp. 2019. Stata: Release 16.1. Statistical Software; StataCorp LLC, College Station, Texas, USA).

Results

The program of preexposure prophylaxis at the hospital started on November 2019. The steady increase in the number of participants visited per month was severely impacted during the first wave (April and May 2020) and at the beginning of the second wave (August 2020), although the increasing trend in the number of visits peaked by the end of 2020. There were 753 postexposure prophylaxis visits in 2020 vs. 1380 in 2019, showing a 45% reduction (IRR 0.55, 95% CI 0.50–0.60, $P < 0.001$). There were 14 349 HIV diagnostic tests performed in 2020 vs. 14 625 in 2019, showing no significant difference (IRR 0.98, 95% CI 0.96–1.00, $P = 0.105$). There were 143 persons with a de novo diagnosis of HIV in 2020 vs. 199 in 2019, showing a 28% reduction (IRR 0.72, 95% CI 0.58–0.89, $P = 0.003$). Mean (SD) $CD4^+$ cell counts/μl at HIV diagnosis were 305 (167) in 2020 and 370 (170) in 2019 ($P < 0.001$). Twenty-six (18%) persons had AIDS-defining conditions at HIV diagnosis in 2020 as compared with 20 (10%) in 2019 ($P = 0.03$). Figure 2 shows monthly data on HIV preexposure (Fig. 2a) and postexposure (Fig. 2b) prophylaxis visits, number of HIV diagnostic tests performed (Fig. 2c), and proportion of de novo HIV diagnoses (Fig. 2d).

There were 9830 outpatient visits in persons with HIV in 2020 vs. 13 024 in 2019, showing a 25% reduction (IRR 0.75, 95% CI 0.74–0.77, $P < 0.001$). Although prior to the pandemic, all outpatient visits were done face-to-face, during the 2020 pandemic period 3851 (39%) outpatient visits were done virtually. There were 9612 plasma HIV RNA tests done in 2020 vs. 9814 in 2019, showing no significant difference (IRR 0.98, 95% CI 0.95–1.01, $P = 0.147$). There were 1068 (11%) plasma HIV RNA tests with viral load above the level of detection in 2020 vs. 1031 (11%) in 2019, showing no significant difference (IRR 0.98, 95% CI 0.95–1.01, $P = 0.147$). There were 1017 changes in antiretroviral regimens in 2020 vs. 1127 in 2020, showing a 10% reduction (IRR 0.90, 95% CI 0.83–0.98, $P = 0.018$). Figure 3 shows monthly data on

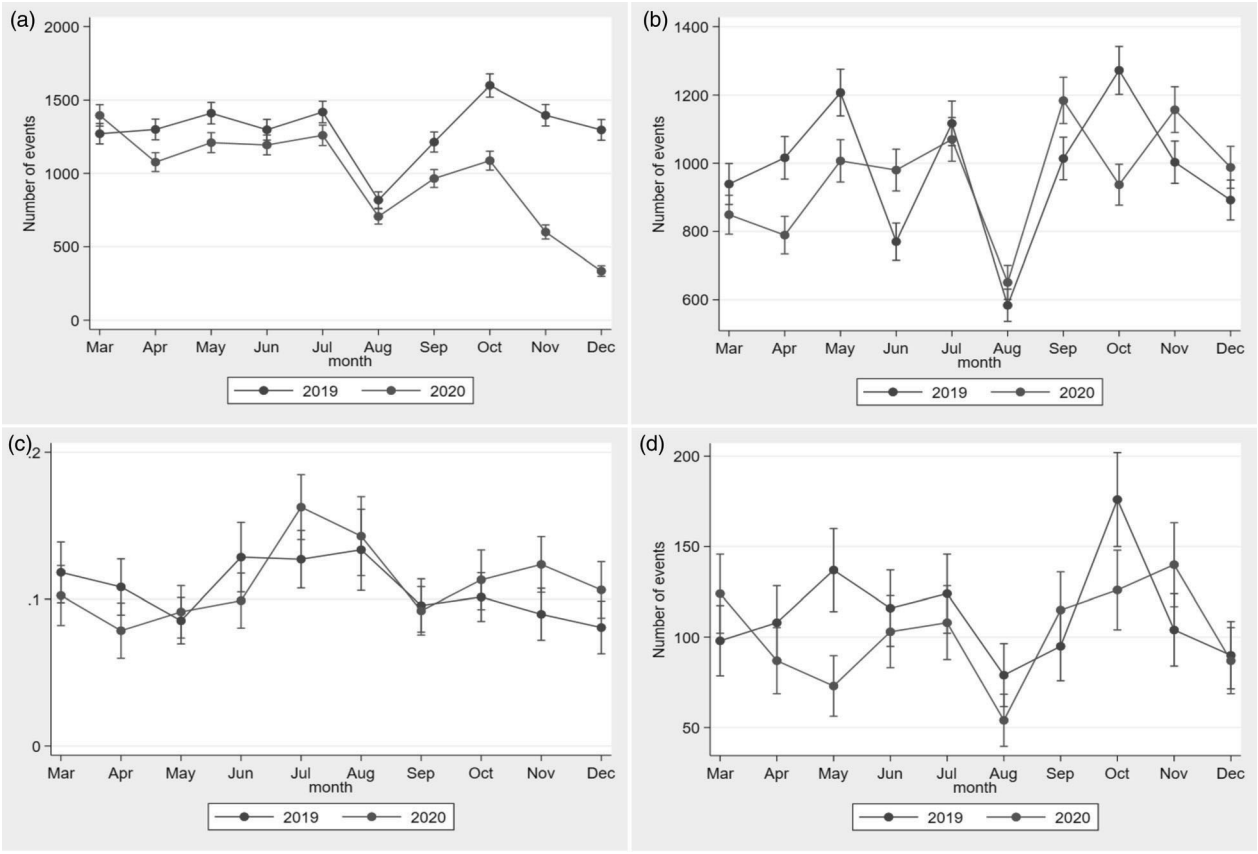

Fig. 3. Monthly data on outpatient visits in persons with HIV (a), number of plasma HIV RNA tests done (b), proportion of plasma HIV RNA tests with viral load above the level of detection per 100 HIV RNA tests performed per month (c), and changes in antiretroviral regimens (d).

outpatient visits in persons with HIV (Fig. 3a), number of plasma HIV RNA tests done (Fig. 3b), proportion of plasma HIV RNA tests with viral load above the level of detection per 100 HIV RNA tests performed per month (Fig. 3c), and changes in antiretroviral regimens (Fig. 3d).

There were 10 147 blood chemistry tests with plasma lipids and glucose determinations in persons with HIV in 2020 vs. 11 271 in 2019, showing a 10% reduction (IRR 0.90, 95% CI 0.88–0.92, $P < 0.001$). Relative to 2019, in 2020 mean total cholesterol (190 vs. 185 mg/dl, $P < 0.001$), LDL cholesterol (114 vs. 110 mg/dl, $P < 0.001$), and triglycerides increased (136 vs. 125 mg/dl, $P < 0.001$), HDL cholesterol (47 vs. 48 mg/dl, $P = 0.006$) decreased, and glucose (93 vs. 93 mg/dl, $P = 0.961$) remained unchanged. Figure 4 shows the mean monthly values of total cholesterol (Fig. 4a), LDL cholesterol (Fig. 4b), HDL cholesterol (Fig. 4c), triglycerides (Fig. 4d), and glucose (Fig. 4e) in routine blood chemistries of persons with HIV.

There were 429 hospital admissions in people with HIV during 2020 vs. 486 during 2019, showing a 12% reduction (IRR 0.88, 95% CI 0.78–1.01, $P = 0.060$). There were 29 deaths in people with HIV during the study period of 2020 vs. 11 during 2019, showing a 264% increase (IRR 2.64, 95% CI 1.32–5.28, $P = 0.006$). Causes of death included: COVID-19 ($n = 11$) (all in 2020), neoplasia ($n = 10$) (4 in 2020, and 6 in 2019), cardiovascular ($n = 8$) (7 in 2020, and 1 in 2019), non-COVID-19 infections ($n = 6$) (3 in 2020, and 3 in 2019), cirrhosis ($n = 3$) (2 in 2020, and 1 in 2019), drug overdose ($n = 1$, in 2020), and polytrauma ($n = 1$, in 2020); all the persons who died from non-COVID causes in 2020 had been SARS-CoV-2-negative confirmed. Figure 5 shows number of hospital admissions in people with HIV per month (Fig. 5a), and proportion of deaths per 100 people with HIV in the cohort per month (Fig. 5b).

There were 3202 HBsAg tests done in 2020 vs. 3208 in 2019, showing no statistical difference (IRR 1.00, 95% CI 0.95–1.05, $P = 0.940$). There were four de novo hepatitis B diagnosed in 2020 vs. 4 in 2019, showing no statistical difference (IRR 1.00, 95% CI 0.25–4.00, $P = 1$). There were 4475 hepatitis C antibodies done in 2020 vs. 5288 in 2019, showing a 15% reduction (IRR

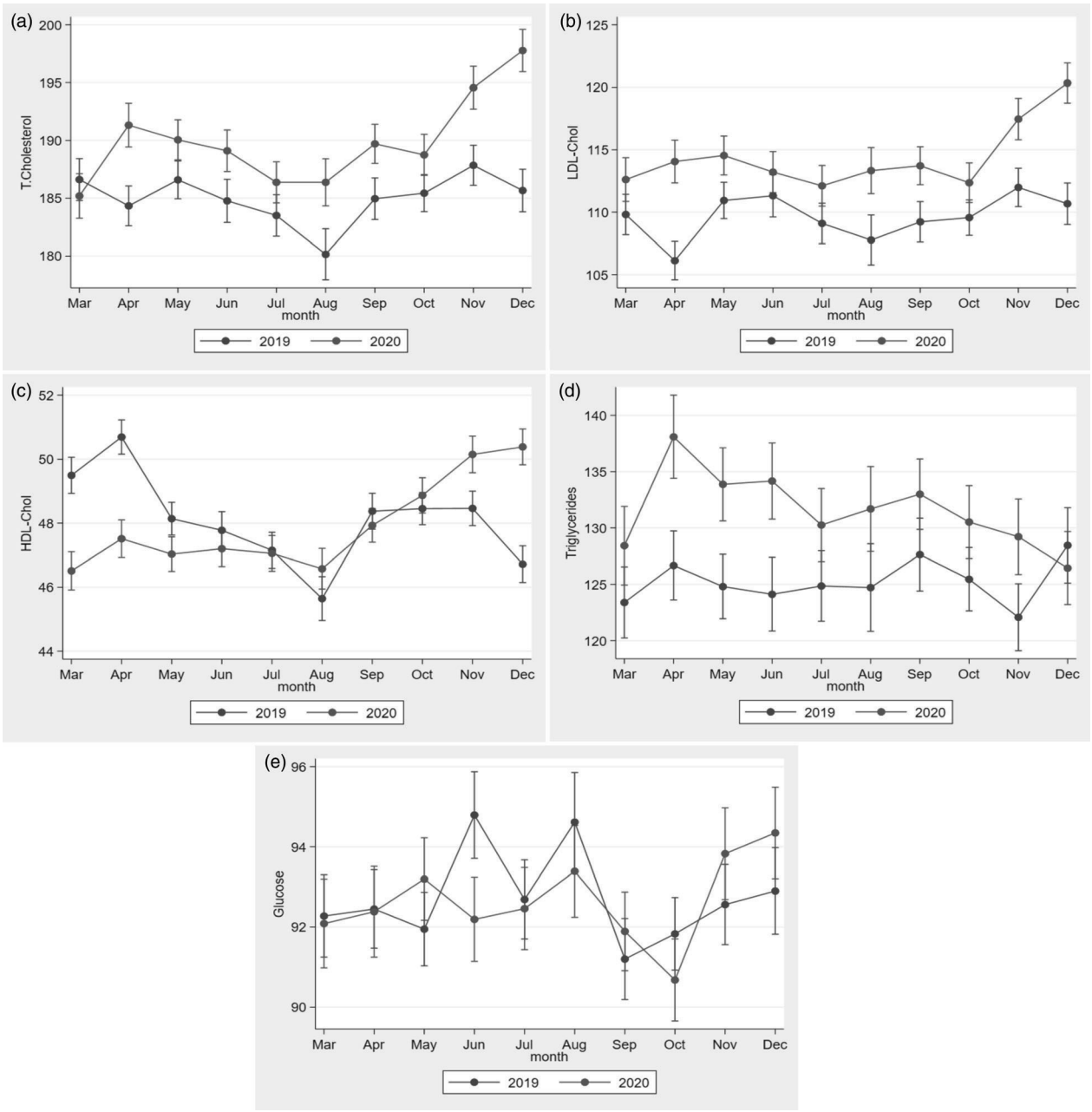

Fig. 4. Mean monthly values of total cholesterol (a), low-density lipoprotein cholesterol (b), high-density lipoprotein cholesterol (c), triglycerides (d), and glucose (e) in routine blood chemistries of persons with HIV.

0.85, 95% CI 0.81–0.88, $P < 0.001$). There were 839 hepatitis C RNA tests done in 2020 vs. 923 in 2019, showing a 9% reduction (IRR 0.91, 95% CI 0.83–1.00, $P = 0.045$). There were 86 de novo hepatitis C diagnosed in 2020 vs. 112 in 2019, showing no statistical difference (IRR 0.77, 95% CI 0.58–1.02, $P = 0.065$). Supplementary Figure 1, http://links.lww.com/QAD/C436 shows number of hepatitis B surface antigen tests done per month (Supplementary Fig. 1a, http://links.lww.com/QAD/C436), proportion of de novo hepatitis B diagnoses per 100 hepatitis B tests performed per month (Supplementary Fig. 1b, http://links.lww.com/QAD/C436), number of hepatitis C antibody tests done per month (Supplementary Fig. 1c, http://links.lww.com/QAD/C436), number of hepatitis C RNA tests done per month (Supplementary Fig. 1d, http://links.lww.com/QAD/C436), and proportion of de novo hepatitis C diagnoses per 100 hepatitis C tests performed per month (Supplementary Fig. 1e, http://links.lww.com/QAD/C436).

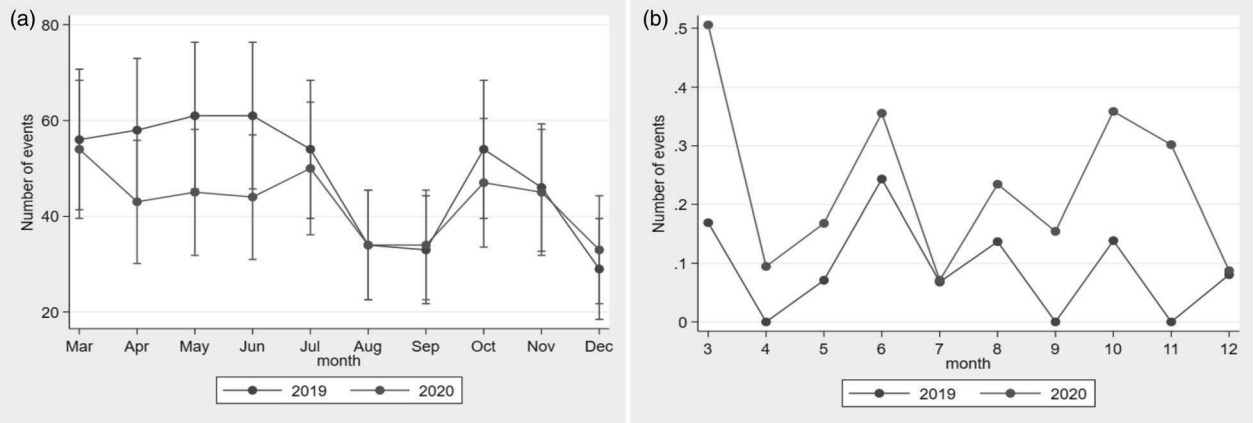

Fig. 5. Number of hospital admissions in people with HIV per month (a), and proportion of deaths per 100 people with HIV in the cohort per month (b).

There were 10 978 VDRL tests done in 2020 vs. 12 237 in 2019, showing a 10% reduction (IRR 0.90, 95% CI 0.87–0.92, $P < 0.001$). There were 1452 IgM tests done in 2020 vs. 1493 in 2019, showing no significant difference (IRR 0.97, 95% CI 0.90–1.05, $P = 0.450$). There were 310 *T. pallidum* PCR tests done in 2020 vs. 242 in 2019, showing a 28% increase (IRR 1.28, 95% CI 1.08–1.52, $P = 0.004$). There were 952 active syphilis C diagnosed in 2020 vs. 944 in 2019, showing no statistical difference (IRR 1.01, 95% CI 0.92–1.10, $P = 0.854$), although the number of syphilis diagnosis made through PCR almost doubled in 2020 ($n = 281$) vs. 2019 ($n = 143$). There were 1667 *N. gonorrhoeae* PCR tests done in 2020 vs. 1501 in 2019, showing a 11% increase (IRR 1.11, 95% CI 1.04–1.19, $P = 0.003$). There were 341 (20%) active gonorrhoea episodes diagnosed in 2020 vs. 246 (16%) in 2019, showing a 39% increase (IRR 1.39, 95% CI 1.18–1.63, $P < 0.001$). There were 1667 *C. trachomatis* PCR tests done in 2020 vs. 1501 in 2019, showing a 11% increase (IRR 1.11, 95% CI 1.04–1.19, $P = 0.003$). There were 249 (15%) active *C. trachomatis* infections diagnosed in 2020 vs. 182 (12%) in 2019, showing a 37% increase (IRR 1.37, 95% CI 1.13–1.66, $P < 0.001$). Supplementary Figure 2, http://links.lww.com/QAD/C436 shows the number of VDRL (Supplementary Fig. 2a, http://links.lww.com/QAD/C436), *T. pallidum* IgM (Supplementary Fig. 2b, http://links.lww.com/QAD/C436), and *T. pallidum* PCR (Supplementary Fig. 2c, http://links.lww.com/QAD/C436) tests done per month, and the proportion of active syphilis diagnoses per 100 syphilis tests performed per month (Fig. 2d); the number of *N. gonorrhoeae* PCR tests done per month (Supplementary Fig. 2e, http://links.lww.com/QAD/C436) and the proportion of active gonorrhoea diagnoses per 100 gonorrhoea tests performed per month (Supplementary Fig. 2f, http://links.lww.com/QAD/C436); the number of *C. trachomatis* PCR tests done per month (Supplementary Fig. 2g, http://links.lww.com/QAD/C436) and the proportion of active chlamydia diagnoses per 100 chlamydia tests performed per month (Supplementary Fig. 2h, http://links.lww.com/QAD/C436).

Discussion

As expected [3,4], prescheduled in-person activities such as HIV preexposure or postexposure prophylaxis visits or outpatient visits in persons with HIV decreased. Of note, a substantial proportion (39%) of outpatient visits during the COVID-19 epidemic were done virtually, which prevented a much higher negative impact on HIV care. Despite the decrease in prescheduled activities, the number of HIV diagnostic tests performed in persons not known to be HIV-infected and the number of plasma HIV RNA-monitoring tests in persons with HIV on routine care remained stable in 2020 relative to 2019 suggesting specific efforts to maintain a minimum of HIV testing and care. Although the number of de novo HIV diagnosis in 2020 decreased, persons newly diagnosed showed significantly less $CD4^+$ cell counts and more advanced disease suggesting a delay and a probable underestimation in the diagnosis. Furthermore, people with HIV showed worse nonvirologic healthcare outcomes and higher mortality in 2020 than in 2019.

We detected a significant decrease in the changes of antiretroviral regimens. As the rates of persons with unsuppressed HIV viremia between both periods remained stable, we presume that this decrease might have preferentially affected persons with suppressed HIV viremia suggesting that therapy optimization was likely moved into the background.

Total cholesterol, LDL cholesterol, and tryglycerides increased whereas HDL cholesterol decreased suggesting

a worse metabolic status. Although weight was not available in the cohort, the profile of lipid changes may be consistent with weight gain [14,15]. COVID-19 lockdown promoted unhealthy dietary changes and increases in body weight at the population level [16,17]. Dyslipidaemia promotes low-level inflammation and chronic immune activation [18]. As a consequence, the lipid changes observed if they persist over time could further contribute to increase the risk of cardiovascular disease in the cohort of people with HIV.

The number of deaths in the cohort of people with HIV was almost three times higher in 2020 relative to 2019. Paradoxically, the number of hospital admissions tended to decrease. The lower number of hospital admissions in the HIV cohort could be due at least in part to the competing skyrocketing number of admissions because of COVID-19 in the general population. Of note, nearly 40% of deaths in the HIV cohort in 2020 had laboratory-confirmed COVID-19 at the time of death. COVID-19 explains in part the excess of deaths in the HIV cohort in 2020 relative to 2019, although the number of non-COVID-19 deaths (particularly, cardiovascular complications) in 2020 was still higher than that in 2019. COVID-19 may be associated with a higher mortality in people with HIV than in the general population [19]. The increase in mortality because of non-COVID-19 causes may have been promoted at least in part by disruptions in society that diminished or delayed access to healthcare and the social determinants of health (e.g. jobs, income, food security) [20–22]. Our findings further support that general and non-COVID-19 mortality in people with HIV may have increased during COVID-19 pandemics as well.

The number of hepatitis B tests and number of de novo hepatitis B diagnosis remained stable. The incidence of hepatitis B in Spain is very low [23]. In contrast, the number of hepatitis C tests decreased but the number of de novo hepatitis C diagnoses among those tested also decreased. These results are in contrast with those from models predicting increased nondiagnosed cases of hepatitis C in Spain during the COVID-19 epidemics [24] but they are in accordance with recent real data from the USA [25]. De novo hepatitis C diagnosis in our setting has been more commonly linked to high-risk sexual practices and sexualized substance use [26]. It is possible that these practices may have been more affected by the epidemic than other sexual encounters.

Treponema pallidum tests most commonly performed were VDRL tests, followed by IgM, and finally PCR. The number of tests done decreased for VDRL, kept stable for IgM, and increased for PCR. Although the total number of active syphilis diagnoses remained unchanged, positivity of PCR diagnosis almost doubled from 2019 to 2020. *N. gonorrhoeae* and *C. trachomatis* testing were exclusively performed with PCR. Similar to *T. pallidum* PCR testing, *N. gonorrhoeae* and *C. trachomatis* PCR testing increased in 2020 relative to 2019. The cases of active gonorrhoea and active chlamydia infection diagnoses increased in 2020, as well as the cases of active syphilis as diagnosed by PCR. PCR tests have been increasingly used for testing of sexually transmitted infections [27]. They are more rapid and may have been better available than standard tests during the pandemic period. The increased PCR diagnosis of sexually transmitted infections in 2020 relative to 2019 is worrisome and suggests that overall transmission was not reduced despite pandemic restrictions. This fact further suggests that the real risk of HIV transmission could have been also higher and a proportion of de novo HIV diagnosis may remain undetected evolving to a more advanced stage. During the early months of the COVID-19 pandemic testing for sexually transmitted infections decreased likely because of disruptions to healthcare and sexually transmitted infections testing services [28,29]. Reduced access to testing and diagnoses in the first months of the pandemics may have led some people to unwittingly spread infection as shown by the higher rates of sexually transmittted infections in the last months of 2020 [30–32].

This study has limitations. We used 2019 as a convenient recent reference for comparisons with 2020 but incidence of HIV and other sexually transmitted infections in the city of Barcelona has been changing over time [33]. It is possible that the reduction in new HIV diagnosis may have not been only impacted by the epidemics but also by the initiation of the HIV preexposure prophylaxis program. By using an anonymized administrative database, some patients may have contributed multiple datapoints because of possibly repeated high-risk exposures or easier access to a clinical setting, biasing findings. We were unable to provide data on other sexually transmitted infections that are mainly diagnosed clinically, such as genital warts or herpes. An unknown proportion of HIV and hepatitis B and C tests were routinely performed in hospitalized COVID-19 patients with pneumonia as part of the management protocol of the Spanish Ministry of Health [34]; although this might have contributed to the diagnosis of some de novo infections, it increased artificially the number of screening tests performed. We have not included information on antimicrobial resistance and therapeutic management of HIV and other sexually transmitted infections.

In summary, we detected less HIV and hepatitis C infections and more gonorrhoea and chlamydia infections during the SARS-CoV-2 epidemics than in the previous year despite overall similar or even higher testing. However, de novo HIV infections showed more advanced disease. It is possible that the number of de novo HIV infections may be larger than detected. There were less scheduled visits for HIV care but this did not result in worse virological control. However, people with HIV had less antiretroviral prescription changes, worse plasma lipids, and more importantly an excess of mortality due in great part not only to COVID-19 but also to other non-COVID-19

causes. Our findings suggest that, in the years to come, healthcare services must be prepared to respond to the impact of COVID-19 on HIV and sexually transmitted infections testing and care. Providers and facilities should build on the lessons learned so far to further improve mitigation strategies and establish care priorities for both the pandemic and the postpandemic periods.

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Authors' contribution: M.A.M. and E.M. designed the study. E.d.L. undertook the statistical analyses. All authors were involved in the interpretation of data. E.d.L., A.M.-M., M.A.M., and E.M. drafted the manuscript. All authors critically reviewed and subsequently approved the final version.

Conflicts of interest

A.G.-C., M.L., J.L.B., A.I., B.T., M.M.-R., J.A., J.M., and E.M. have received honoraria for lectures or advisory boards and their institution has received research grants from Gilead, Janssen, MSD, and ViiV. J.M.M. has received honoraria for lectures or advisory boards and their institution has received research grants from Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Lysovant, Medtronic, MSD, Novartis, Pfizer, and ViiV. E.d.L., A.M.-M., I. C., M.M.M., J.C., J.B., M.A.-M., A.U., L.d.l.M., E.F, J.C.H., and M.A.M.: none to declare.

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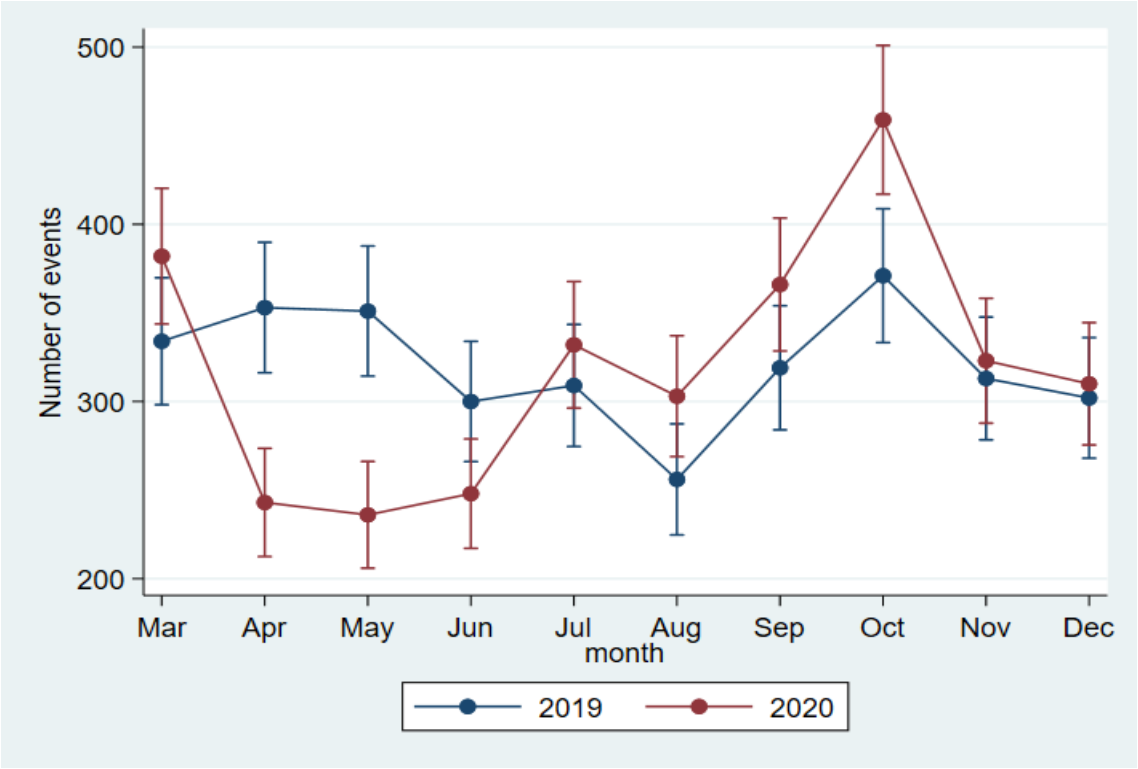
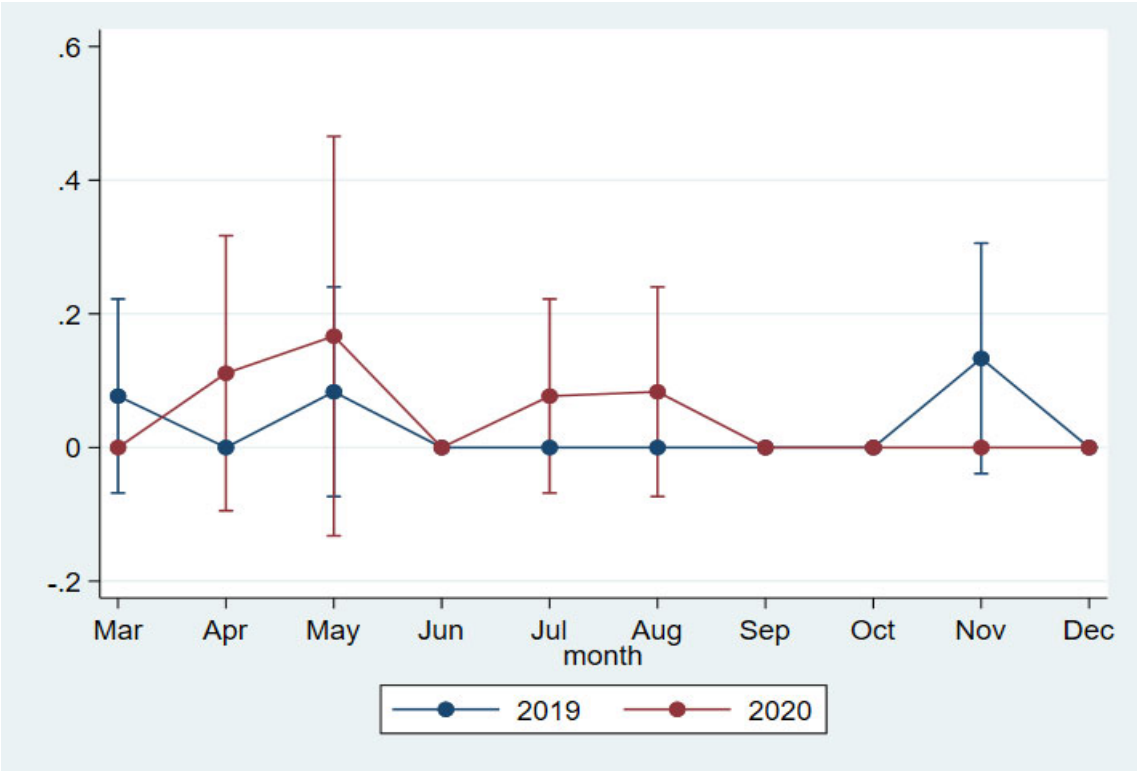
Supplementary Figure 1A. Number and 95% confidence intervals of hepatitis B surface antigen tests done per month.

Relative to the corresponding months of 2019, the number of HBsAg tests tests done per month in 2020 was significantly lower in April, May, and June and higher in August and November



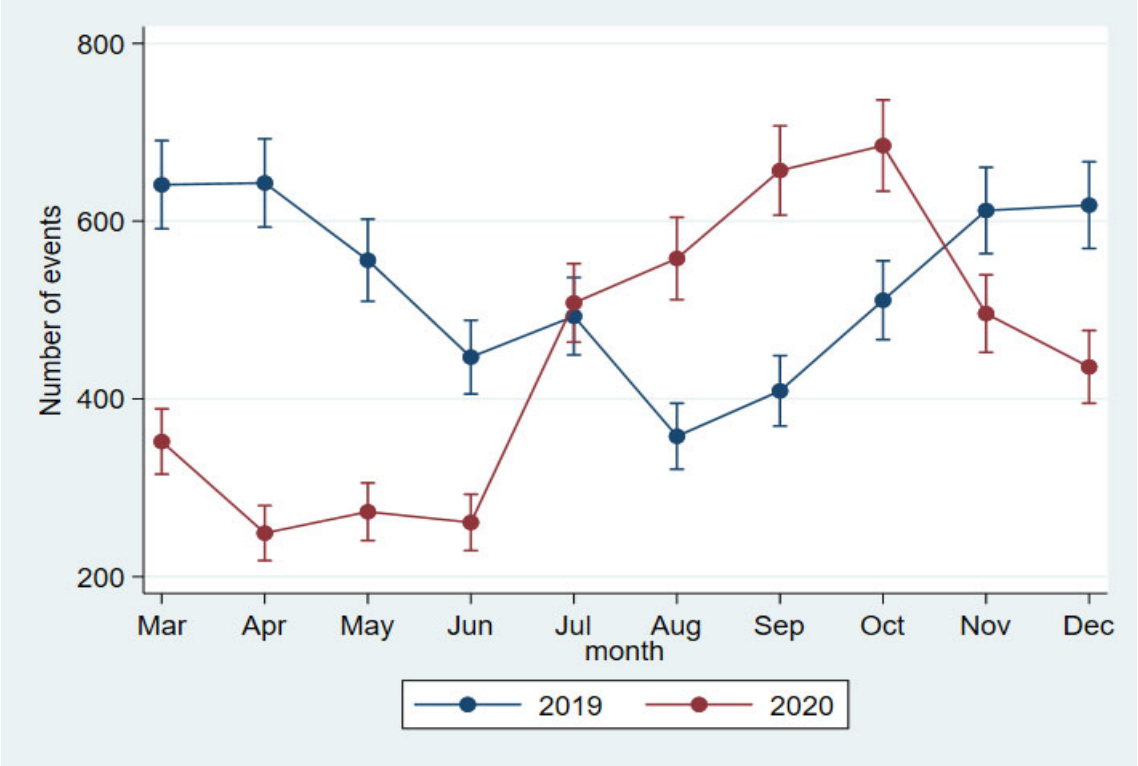
Supplementary Figure 1B. Proportion and 95% confidence intervals of *de novo* hepatitis B diagnoses per 100 hepatitis B surface antigen tests performed month.

Relative to the corresponding months of 2019, the proportion of *de novo* positive hepatitis B tests in 2020 was not significantly different in any month.



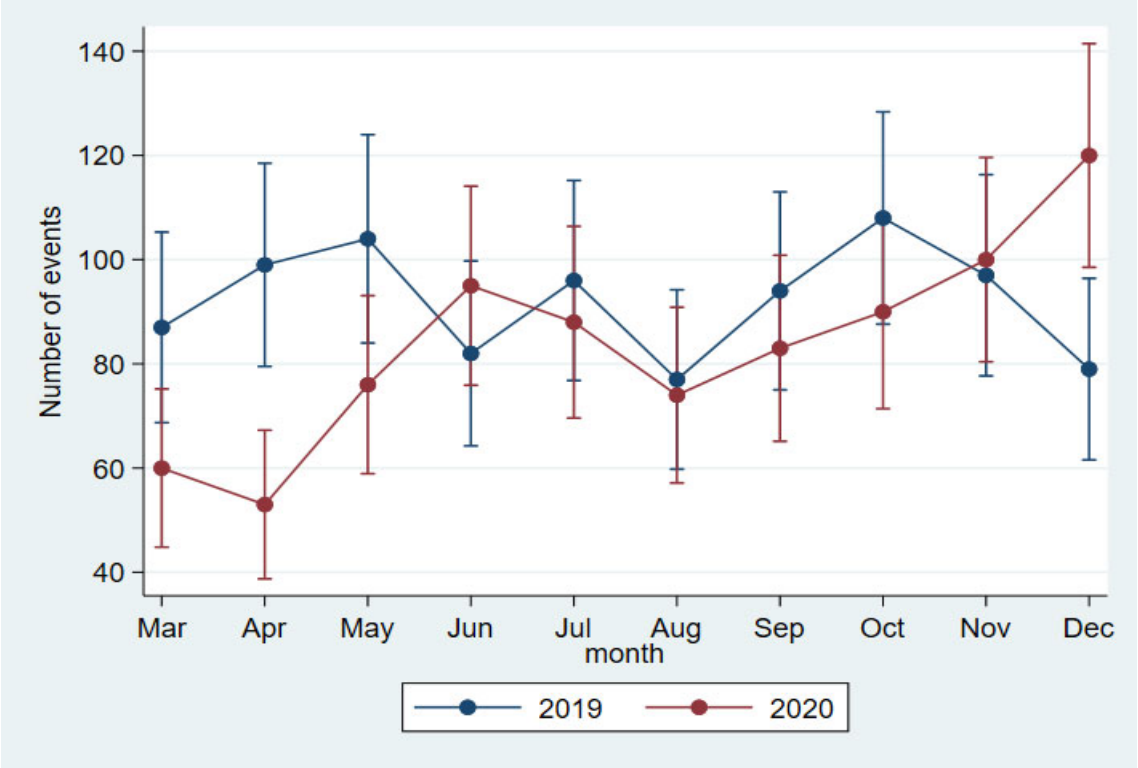
Supplementary Figure 1C. Number and 95% confidence intervals of hepatitis C antibody tests done per month.

Relative to the corresponding months of 2019, the number of hepatitis C antibodies done per month in 2020 was significantly lower in March, April, May, June, and November 2020.



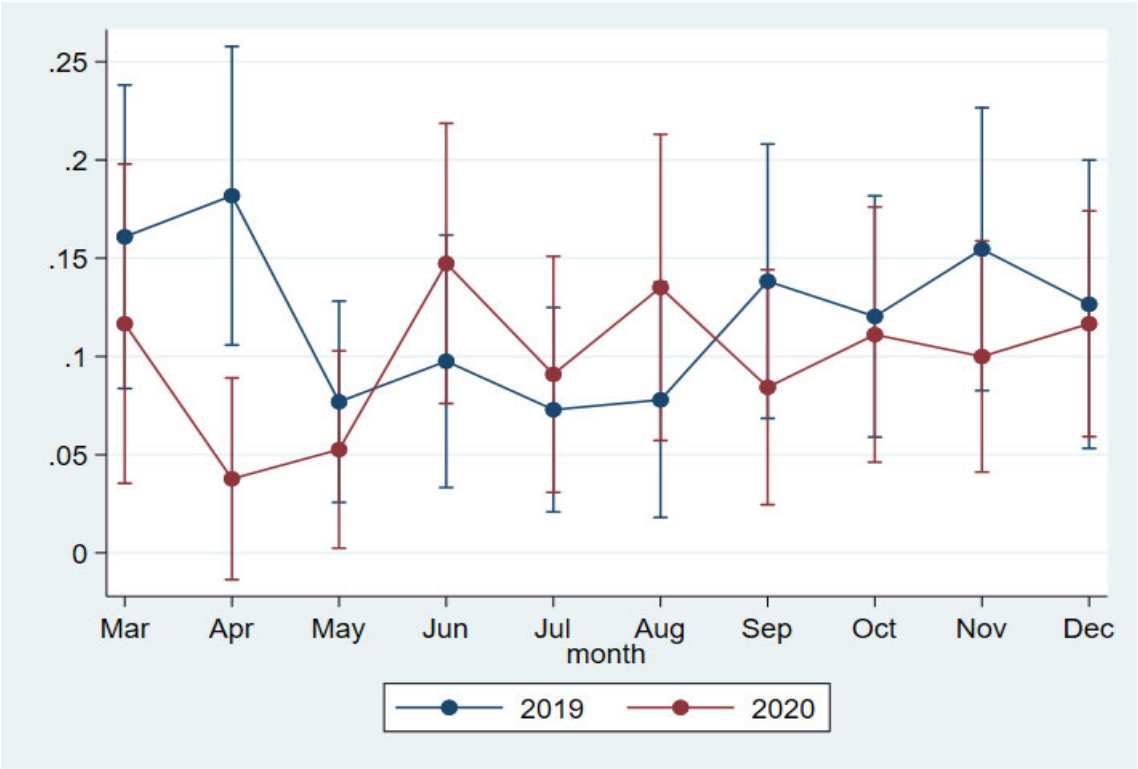
Supplementary Figure 1D. Number (and 95% confidence intervals) of hepatitis C RNA tests done per month.

Relative to the corresponding months of 2019, the number of hepatitis C RNA tests done per month in 2020 was significantly lower in March, April, and May, but it was significantly higher in December.



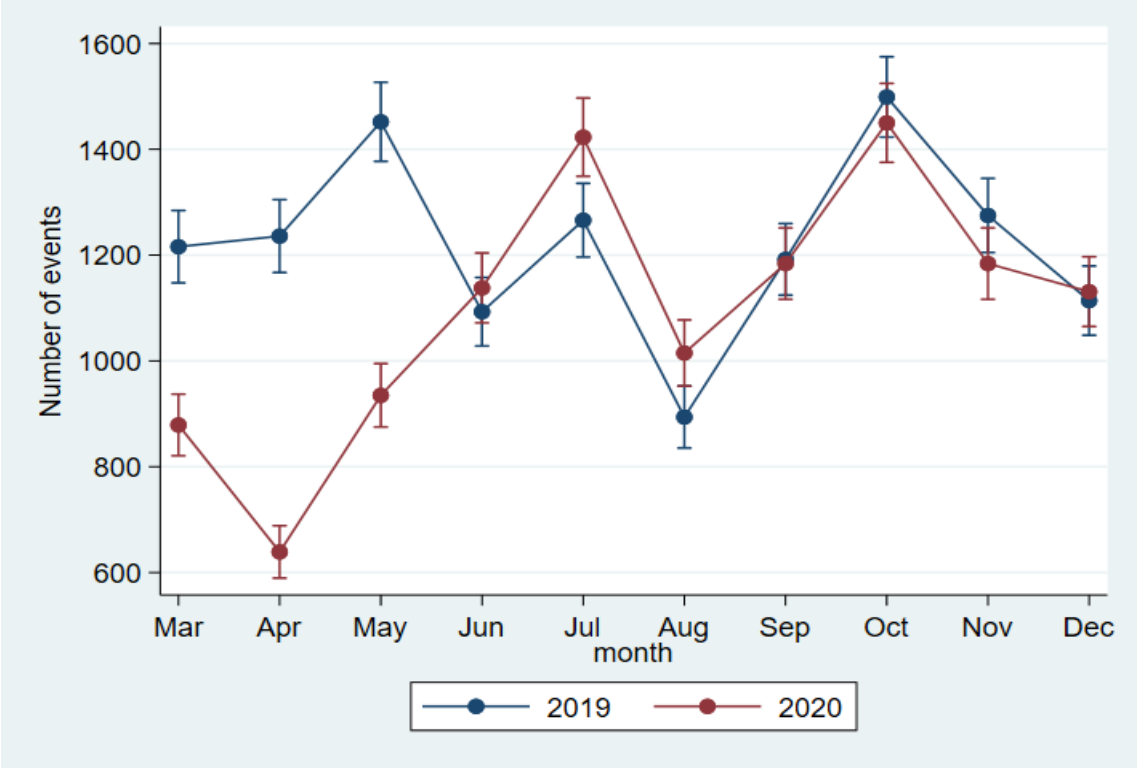
Supplementary Figure 1E. Proportion and 95% confidence intervals of *de novo* hepatitis C diagnoses per 100 hepatitis RNA tests performed month.

Relative to the corresponding months of 2019, the proportion of *de novo* hepatitis C diagnosed in 2020 was significantly lower in April 2020.



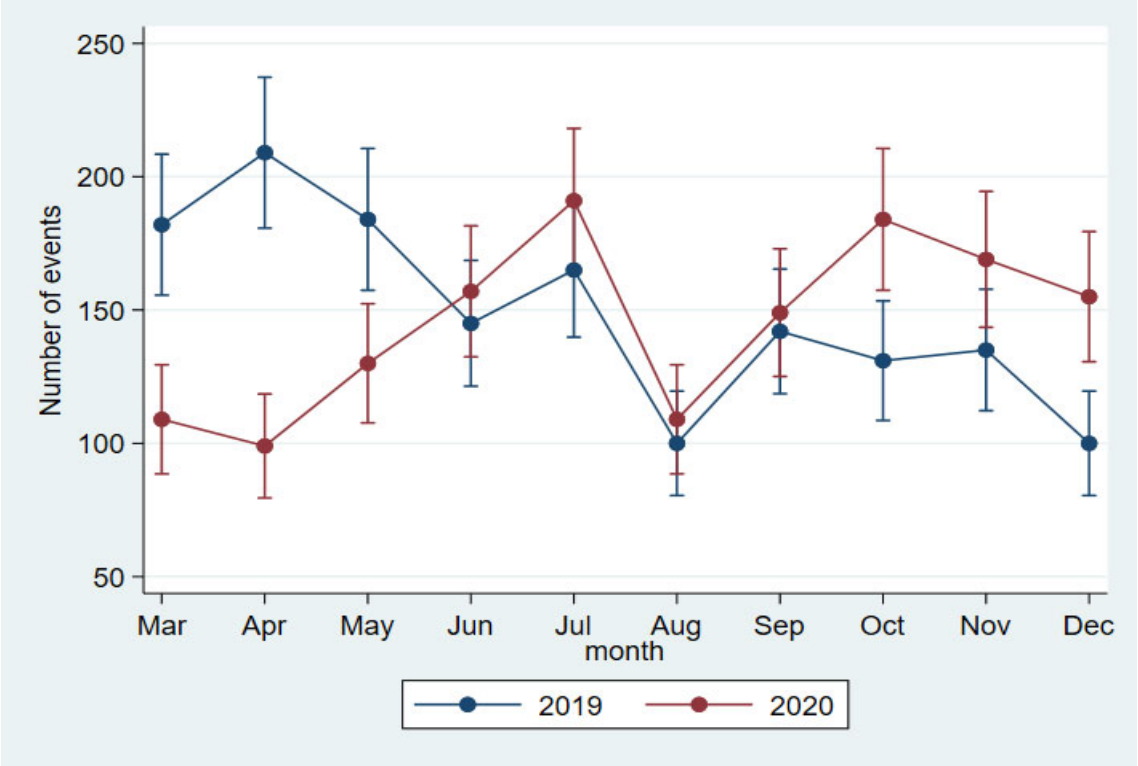
Supplementary Figure 2A. Number and 95% confidence intervals of VDRL tests done per month.

Relative to the corresponding months of 2019, the number of VDRL tests done per month in 2020 was significantly lower in March, April, and May, and significantly higher in July and August.



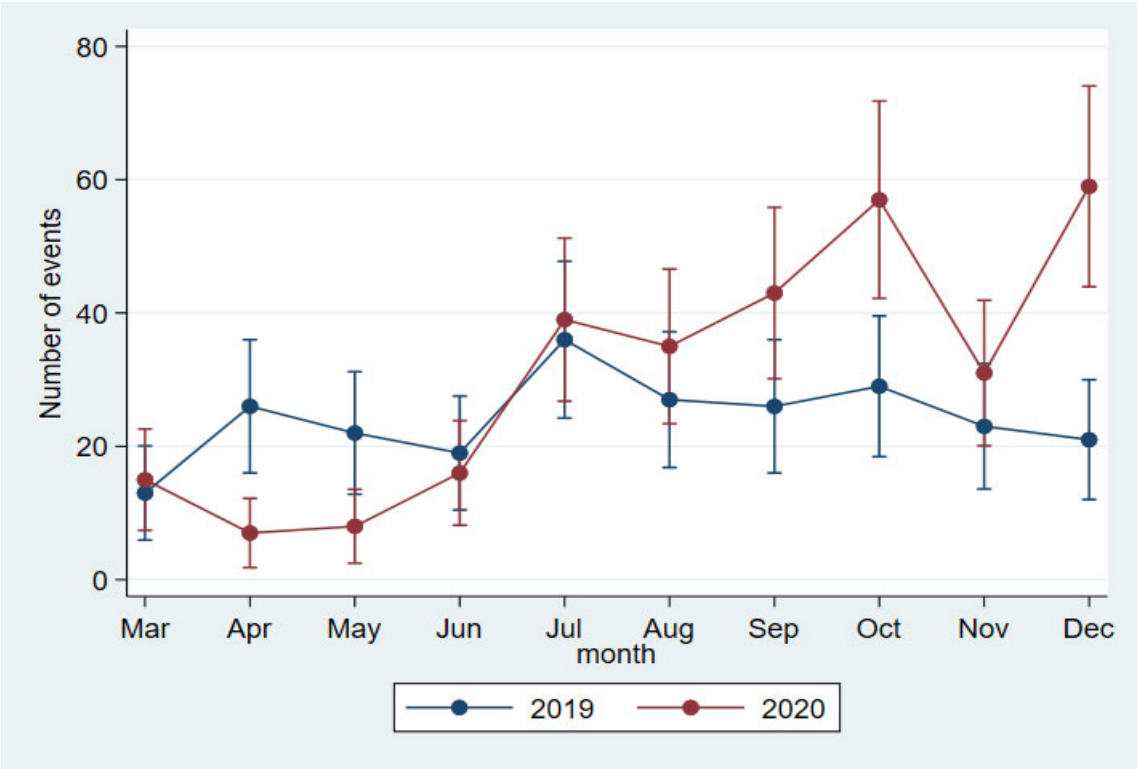
Supplementary Figure 2B. Number and 95% confidence intervals of *Treponema pallidum* IgM tests done per month.

Relative to the corresponding months of 2019, the number of IgM tests done per month in 2020 was significantly lower in March, April, and May, and significantly higher in October, November, and December.



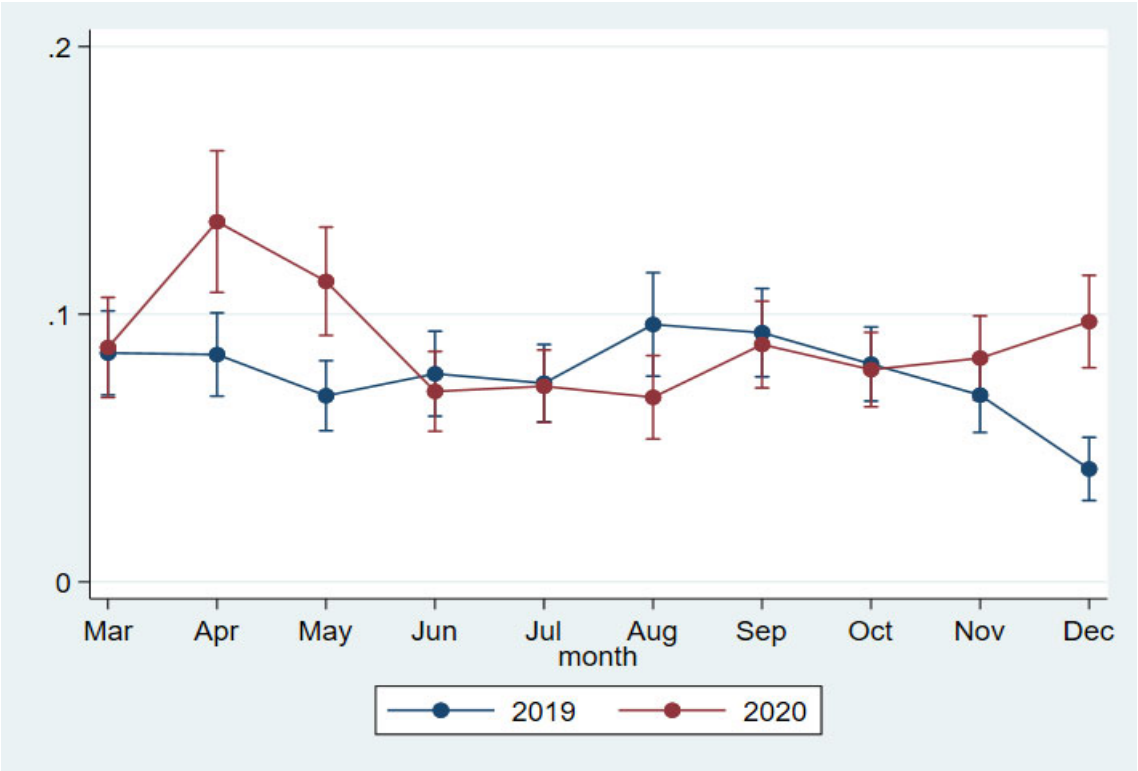
Supplementary Figure 2C. Number and 95% confidence intervals of *Treponema pallidum* PCR tests done per month.

Relative to the corresponding months of 2019, the number of *Treponema pallidum* PCR tests done per month in 2020 was significantly lower in April and May, and significantly higher in September, October, November, and December.



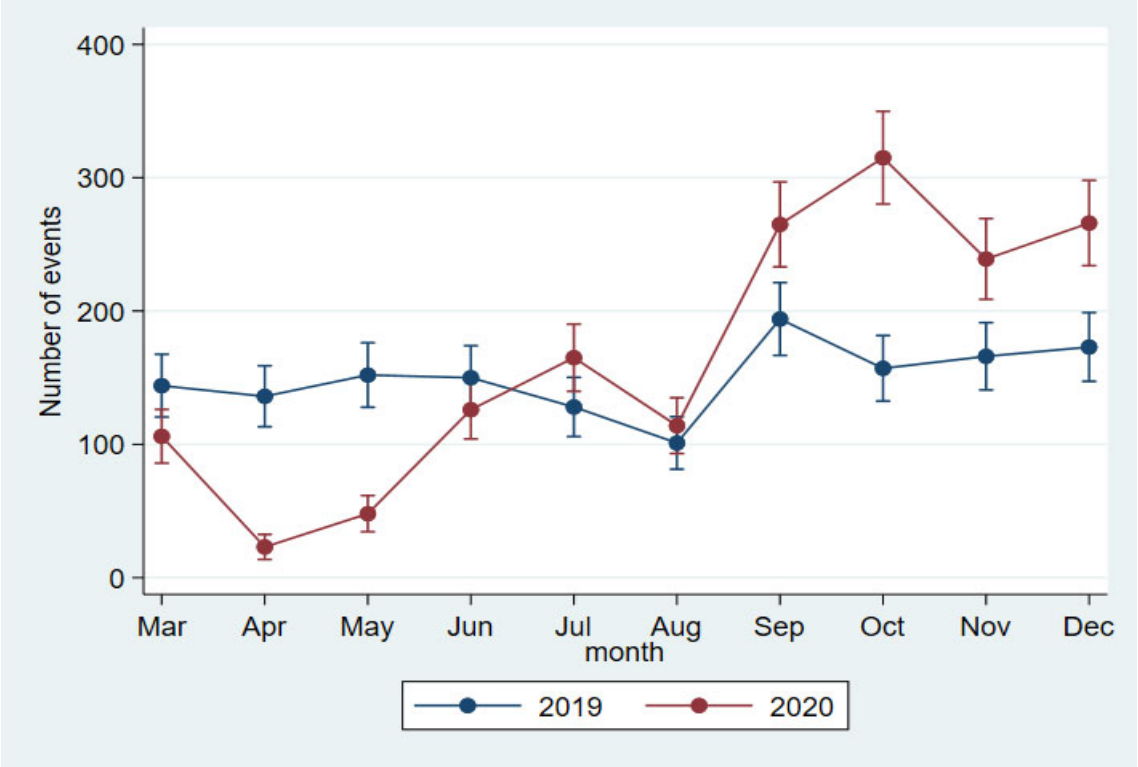
Supplementary Figure 2D. Proportion and 95% confidence intervals of *de novo* syphilis diagnoses per 100 syphilis tests performed month.

Relative to the corresponding months of 2019, the proportion of *de novo* syphilis diagnosed in 2020 was significantly higher in April, May, and December



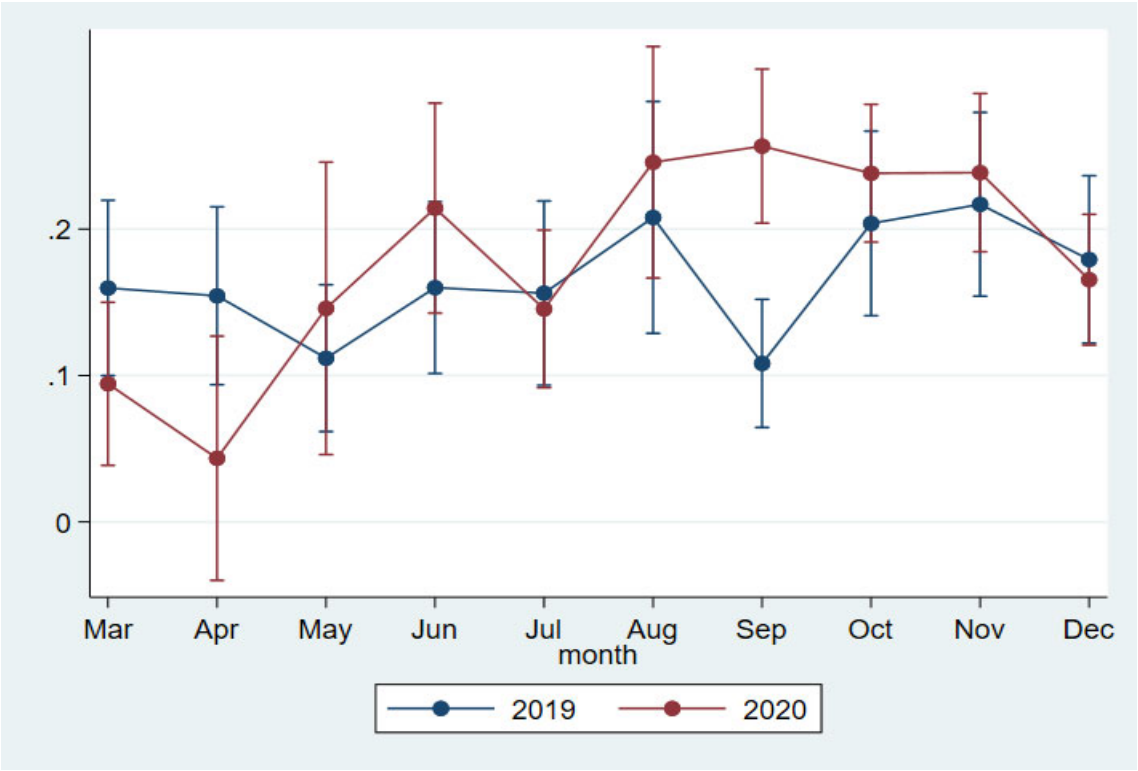
Supplementary Figure 2E. Number and 95% confidence intervals of *Neisseria gohorrhoeae* PCR tests done per month.

Relative to the corresponding months of 2019, the number of *Neisseria gohorrhoeae* PCR tests done per month in 2020 was significantly lower in March, April, and May, and significantly higher in July, August, September, October, November, and December.



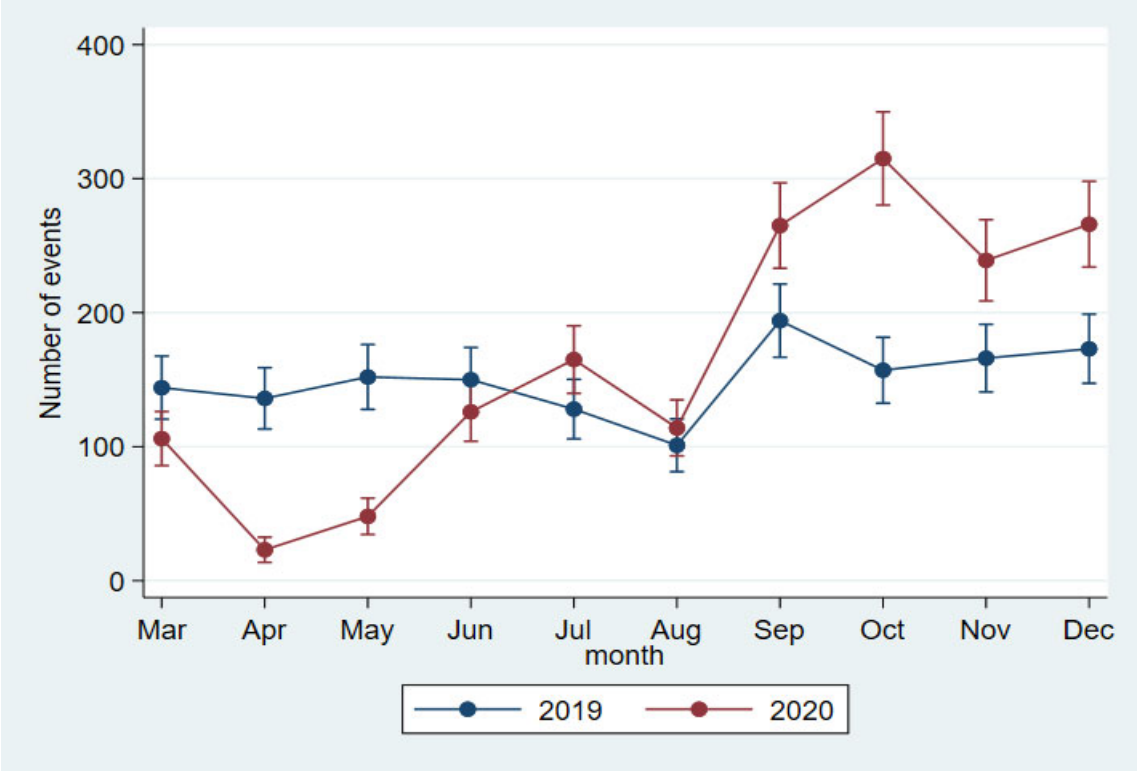
Supplementary Figure 2F. Proportion and 95% confidence intervals of *de novo* gonorrhoea diagnoses per 100 gonorrhoea tests performed month.

Relative to the corresponding months of 2019, the proportion of *de novo* gonorrhoea diagnosed in 2020 was significantly higher in September.



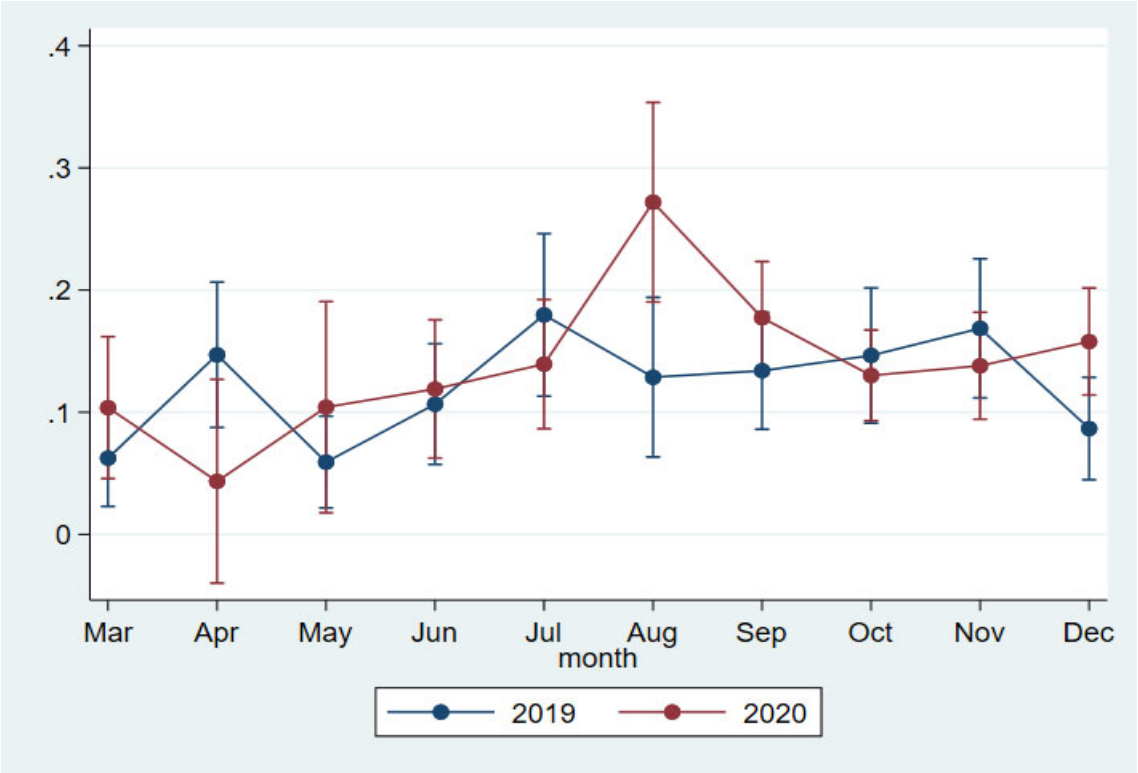
Supplementary Figure 2G. Number and 95% confidence intervals of *Chlamydia trachomatis* PCR tests done per month.

Relative to the corresponding months of 2019, the number of *Chlamydia trachomatis* PCR tests done per month in 2020 was significantly lower in March, April, and May, and significantly higher in July, August, September, October, November, and December.



Supplementary Figure 2H. Proportion and 95% confidence intervals of *de novo* chlamydia diagnoses per 100 chlamydia tests performed month.

Relative to the corresponding months of 2019, the proportion of *de novo Chlamydia trachomatis* infections diagnosed in 2020 was significantly higher in August and December.



Trabajo 7

Perception of quality of care using patient reported experience measures (PREMs) in a cohort of adults with HIV: A cross-sectional study.

Elisa de Lazzari, Leire Berrocal, Emma Fernández, Montserrat Laguno, Iván Chivite, Berta Torres, Ana González-Cordón, Lorena de la Mora, Juan Ambrosioni, Alexy Iniciarte, José Luis Blanco, José María Miró, Esteban Martínez, María Martínez-Rebollar, Josep Mallolas.
Medicine 2023. *102*(14), e33442.

Resumen

Objetivos: La infección por el virus de inmunodeficiencia humana (VIH) se considera una enfermedad crónica. La terapia antirretroviral ha permitido a las personas con VIH alcanzar los objetivos 90-90-90 propuestos por la Organización Mundial de la Salud para 2020; pero un desafío adicional es conseguir una calidad de vida adecuada relacionada con la salud. Un factor determinante en la calidad de vida del PLWHIV relacionada con la salud es la atención que perciben recibir. En este sentido, nuestro objetivo fue el de evaluar la percepción de la atención ambulatoria brindada e identificar posibles áreas de mejora.

Métodos: Estudio unicéntrico transversal realizado en la unidad de VIH del Hospital Clínic de Barcelona. Recogimos mediciones de la experiencia reportada por los pacientes (PREMs) mediante una encuesta electrónica anónima con 11 items basados en una escala de respuesta Likert de 1 a 6, y una pregunta final que mide la satisfacción y lealtad del usuario a través del Net Promoter Score (NPS). Todas las personas con VIH que realizaron al menos una visita clínica entre el 1 de enero de 2020 y el 14 de octubre de 2021 fueron invitadas a participar.

Resultados: De las 5493 personas contactas por correo electrónico, 1633 (30%) respondieron a la encuesta. La evaluación general de la atención clínica fue muy favorable. La evaluación del entorno físico y de las instalaciones, así como el tiempo

pasado en la sala de espera, recibieron las puntuaciones más bajas. Según los resultados del Net Promoter Score, el 66% de las personas encuestadas estaban dispuestas a recomendar este servicio, y el 11% no.

Conclusiones: La monitorización de las medidas de experiencia de las personas con VIH que reciben activamente atención ambulatoria en nuestro hospital permitió identificar la percepción de los usuarios sobre la calidad de la atención recibida, determinar la tasa de satisfacción con la atención e identificar áreas de mejora.

Observational Study

Medicine

OPEN

Perception of quality of care using patient reported experience measures (PREMs) in a cohort of adults with HIV

A cross-sectional study

Elisa de Lazzari, MSc[a,b], Leire Berrocal, MSc[b], Emma Fernández, MSc, APN[b], Montserrat Laguno, PhD, MD[a,b,*], Iván Chivite, MD[b], Berta Torres, PhD, MD[b], Ana González-Cordón, PhD, MD[b], Lorena de la Mora, PhD, MD[b], Juan Ambrosioni, PhD, MD[a,b], Alexy Iniciarte, MD[b], José Luís Blanco, PhD, MD[a,b], Josep Maria Miró, PhD, MD[a,b], Esteban Martínez, PhD, MD[a,b], Maria Martínez-Rebollar, PhD, MD[b], Josep Mallolas, PhD, MD[a,b]

Abstract

Human immunodeficiency virus (HIV) infection is considered a chronic disease. Antiretroviral therapy has allowed persons with HIV (PLWHIV) to achieve the 90-90-90 objectives proposed by the World Health Organization for 2020; but an additional challenge is getting an adequate health-related quality of life. A determining factor in the health-related quality of life of PLWHIV is the health care they perceive to receive. In this sense, we aimed to assess the perception of the outpatient care provided and to identify possible areas for improvement in a single-center, cross-sectional study at the HIV unit of Hospital Clínic, Barcelona. We sought patient reported experience measures by an anonymous e-survey with 11 statements based on a 1 to 6 Likert scale, and a final question measuring user satisfaction and loyalty through the Net Promoter Score (NPS). All PLWHIV with at least a clinical visit between January 1, 2020 and October 14, 2021 were invited. Of 5493 PLWHIV e-mailed, 1633 (30%) responded to the survey. The overall evaluation of clinical care was very favorable. The evaluation of the physical environment and facilities and the time spent in the waiting room received the lowest scores. According to the Net Promoter Score test results, 66% of respondents were willing to recommend this service, and 11% were not. Thus, monitoring patient reported experience measures in PLWHIV actively receiving outpatient care in our hospital allowed to identify the users' perception on quality of the care received, to determine the rate of satisfaction with the care, and to identify areas for improvement.

Abbreviations: HIV = human immunodeficiency virus, HRQoL = health-related quality of life, MCA = multiple/joint correspondence analysis, NPS = net promoter score, PLWHIV = persons living with HIV, PREMs = patient reported experience measures, SD = standard deviation.

Keywords: HIV, HRQoL, PREMS

1. Introduction

"Health-related quality of life"[1] (HRQoL) is defined as the perception that a patient has regarding the effects of a disease or the application of a certain treatment in areas of his or her life, especially on his or her physical, emotional and social well-being.

In the last century, the substantial development of new pharmacological products and health technology has increased the interest on the measurement of quality of life in health care.

Traditional medical outcome variables such as clinical symptoms, survival rate, and safety and clinical efficacy of a drug are no longer sufficient to adequately reflect the effect of

This work is part of a study that evaluates the optimal model of care for HIV patients (VIIV V02–2020 grant). "Programa coordinado de intervención intersectorial e interdisciplina enfocado a la prevención combinada del VIH y a la atención a la cronicidad en las personas con VIH, con el fin de potenciar el continuum de los cuidados a lo largo de todo el proceso asistencial (A coordinated program of intersectoral and interdisciplinary intervention focused on the combined prevention of HIV and care for chronicity in people with HIV to enhance the continuum of care throughout the entire care process." JMM received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–23.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was approved by the HCB Ethics Committee. Before starting the survey an explanation and "Data policy" was included in the email as an informed consent. Patients who agreed with these terms completed the e-survey.

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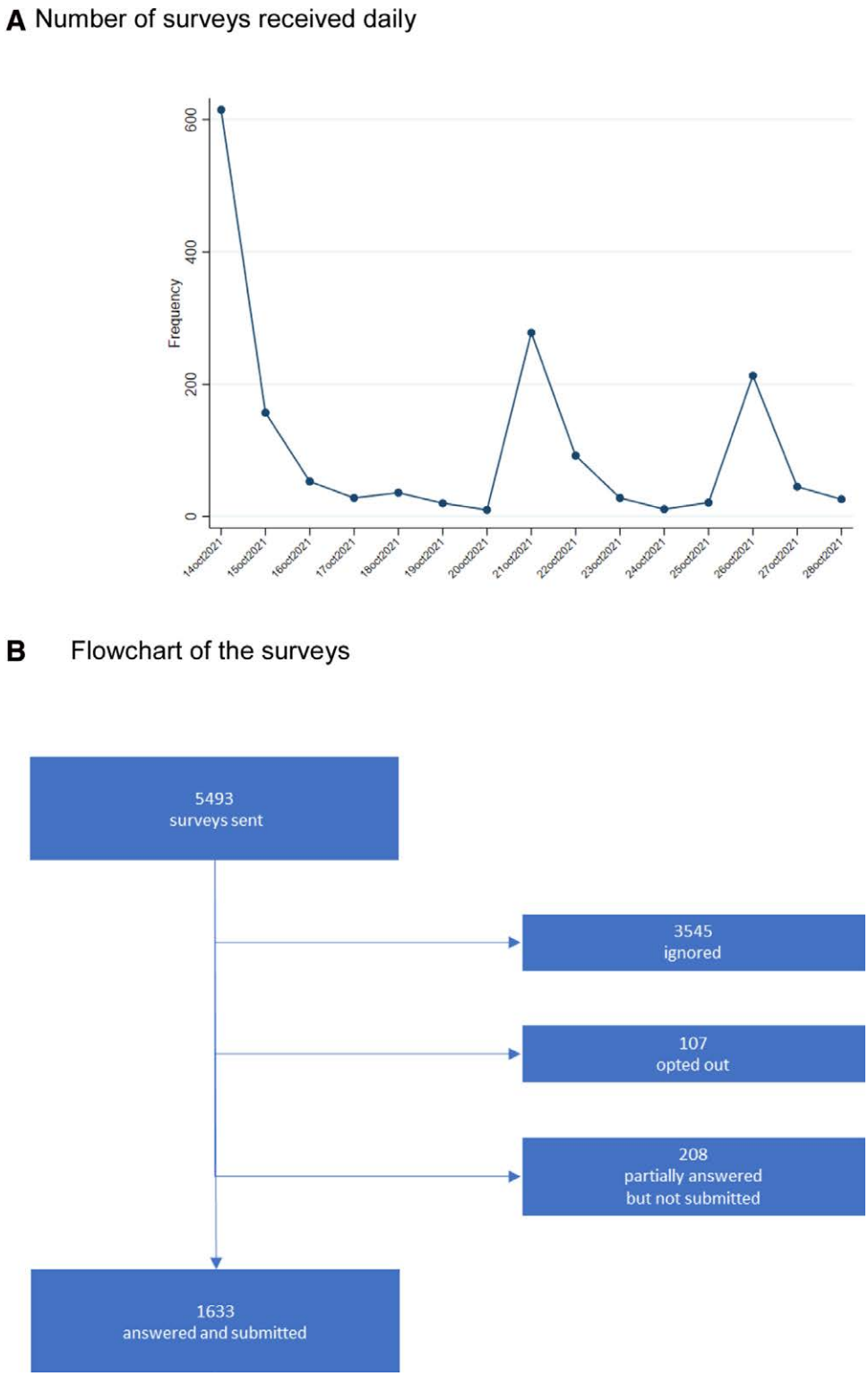


Figure 1. Surveys: (A) Number of surveys received daily. (B) Flowchart of the surveys.

health care and interventions, and it is considered necessary to analyze the perspective of the person with a disease too. What matters is how the person with a disease feels rather than how health professionals believe they should feel based on clinical measures.[2] In that way, whether therapy can achieve a life worthy of being lived, both from the social and psychological perspective as well as the physical perspective, should be assessed.

HRQoL has become an important measure of the impact of medical care. Currently, the focus is on the quality, rather than the quantity, of life. Gradually, the patient experience has been incorporated into analyses of care processes to evaluate quality from the perspective of the person receiving the service[3] to improve it. For this, new assessment tools have been introduced: PROMs (*patient-reported outcome measures)*, related to treatment objectives, and PREMs (*patient-reported*

Table 1

Characteristics of the population who responded to the survey.

Variable	Summary statistics
Age*	
Under 35 yr	164 (10%)
36–45 yr	441 (27%)
46–55 yr	513 (31%)
Over 55 yr	513 (31%)
Total	*1631 (100%)*
Education level*	
Primary	134 (8%)
Secondary	551 (34%)
University	943 (58%)
Total	*1628 (100%)*
Origin*	
Spain	1074 (66%)
Europe	155 (10%)
Latin America	348 (21%)
North Africa	1 (0%)
Sub-Saharan Africa	6 (0%)
Asia	10 (1%)
USA/Canada	16 (1%)
Other	18 (1%)
Total	*1626 (100%)*
Year of diagnosis*	
1980–1989	104 (7%)
1990–1999	327 (22%)
2000–2009	470 (31%)
2010–2021	600 (40%)
Total	*1501 (100%)*
Residence*	
Barcelona	1397 (94%)
Girona	22 (1%)
Tarragona	40 (3%)
Lleida	13 (1%)
Rest of Spain	14 (1%)
Total	*1484 (100%)*

*n (column percentage).

experience measures), related to the experience of a treatment or intervention.[4–6]

The management of human immunodeficiency virus (HIV) infection has been changing over the last decades, adapting to the needs of persons living with HIV (PLWHIV) and, above all, influenced by the available therapeutic arsenal. Currently, the high efficacy of antiretrovirals, with the consequent sustained viral suppression and disappearance of opportunistic diseases, has drastically reduced the mortality associated with HIV[7–9] in way such that PLWHIV show a life expectancy similar to that of the general population, turning HIV infection into a chronic disease.[10]

In addition to the goals outlined by the World Health Organization to control HIV infection for 2020,[11] that is, 90% of PLWHIV diagnosed, 90% treated and 90% have undetectable viral load, a fourth objective focused to achieve a correct quality of life in 90% of these patients has been also raised in recent years.[12]

The current challenge of the outpatient units caring for PLWHIV is to redefine what the optimal model of care should be, how to adapt resources according to the needs of each patient and how to incorporate this fourth 90% goal related to quality of life.

In recent years, tools have been introduced for the collection of patient-reported outcome measures in PLWHIV within clinical trials and controlled studies[13–17] to assess the possible benefits and risks of an intervention more accurately; however, the information reported in the literature on PREMs in PLWHIV is scarce.[18,19]

In the HIV Unit of the Hospital Clinic of Barcelona, nearly 6000 PLWHIV are currently receiving outpatient care, and health workers at the Unit have been committed for years to updating and improving the approach and care of them. In addition to assess the quality of care with well-established indicators of safety and efficacy,[20] we aimed to know about the experience of PLWHIV, which some authors consider the third pillar in the evaluation of quality of care and a key element for improving health care in the context of person-centered care.[21]

The objective of this study was to assess the user perception on quality of the care received, to determine the rate of satisfaction with the care and to identify potential areas for improvement.

2. Methods

This was a cross-sectional study that evaluated through an anonymous electronic survey (e-survey) the perceived satisfaction of PLWHIV with the care received in the HIV Unit of the Hospital Clinic of Barcelona. All patients for whom we had records for at least 1 visit between January 1, 2020 and October 14, 2021 were considered candidates to respond the survey. Two analysis instruments were used, a PREM assessment survey and the net promoter score (NPS).

2.1. Instruments

The survey was prepared with the help of the Patient Care Research Team at our hospital, taking as a model similar surveys carried out in other areas of care for chronic patients of the Hospital Clinic of Barcelona and the recommendations of the Agency for Quality and Health Assessment of Catalonia.[22] The questionnaire includes 5 questions regarding demographic information to determine the profile of the respondent and 11 statements scored by the respondent based on the degree of disagreement or agreement using a Likert scale ranging from 1 to 6. These statements are as follows:

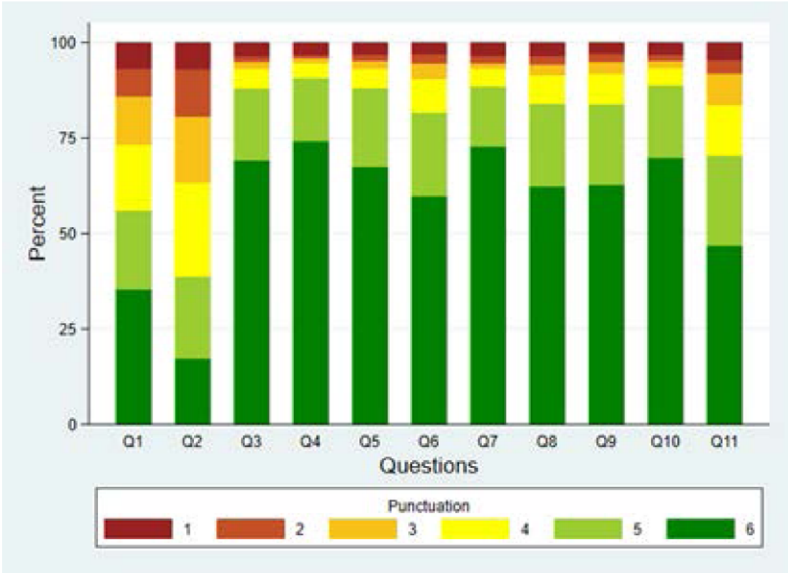
- Q1 The location where the consultation occurred was appropriate.
- Q2 The time spent in the waiting room was acceptable.
- Q3 The information received from the professionals who treated me was clear and concise.
- Q4 The vocabulary used was adequate.
- Q5 The information received during the visit responded to my needs.
- Q6 I believe my opinion mattered, and I felt like a participant in decision-making about my health.
- Q7 The visit was carried out in a climate of trust that allowed me to express my concerns.
- Q8 The time allocated to doubts and/or questions was sufficient.
- Q9 The total length of the consultation seemed to be the right amount.
- Q10 I feel that the attention received during the visit was adequate.
- Q11 The time spent in the consultation was worth it (considering travel, waiting time, etc).

In addition to the survey, a final question, "How likely is that you would recommend this Service to a friend or colleague?," based on a 0 to 10 scale was associated with measuring user satisfaction and loyalty with our service through the NPS indicator.[23]

The electronic questionnaire was implemented in 3 languages: English, Spanish and Catalan, using the online survey tool LimeSurvey hosted at Hospital Clinic of Barcelona.

The system was programmed to mass-send the survey to the registered email of all PLWHIV for whom there were

A Graph of the survey results



Q1. The location where the consultation occurred was appropriate.

Q2. The time spent in the waiting room was acceptable.

Q3. The information received from the professionals who treated me was clear and concise.

Q4. The vocabulary used was adequate.

Q5. The information received during the visit responded to my needs.

Q6. I believe my opinion mattered, and I felt like a participant in decision-making about my health.

Q7. The visit was carried out in a climate of trust that allowed me to express my concerns.

Q8. The time allocated to doubts and/or questions was sufficient.

Q9. The total length of the consultation seemed to be the right amount.

Q10. I feel that the attention received during the visit was adequate.

Q11. The time spent in the consultation was worth it (taking into account travel, waiting time, etc.).

Figure 2. Results: (A) Graph of the survey results. (B) Net promoter score results (How likely are you to recommend this service to a friend or family member?).

clinical records for at least 1 visit between the stablished period, January 1, 2020 and October 14, 2021. Seven and twelve days after the initial email on 10/14/2021, the system automatically sent 2 reminder emails to PLWHIV who had not yet responded.

2.2. Statistical analysis

Subjects were classified into 3 groups based on the scores obtained from the NPS question: those scoring 9 or 10 are considered *Promoters* (they would recommend this service to a friend or family member); those scoring 7 to 8, *Passives*, and those scoring 0 to 6 *Detractors*. The final NPS score was calculated as the difference between the percentage of *Promoters* and *Detractors*. Qualitative characteristics were described using absolute frequencies and percentages and were compared among the NPS groups with the chi-square test. Quantitative variables were summarized as the mean and standard deviation (SD), and comparisons among the NPS groups were conducted using analysis of variance. The pattern of relationships among the responses to the questionnaire was analyzed using the multiple/joint correspondence analysis (MCA) with 2 dimensions to capture the Guttman effect that affects preference data and occurs when higher order dimensions are polynomial functions of the first one. In our data the arch shaped form suggests a non-symmetric quadratic function. In the MCA graph the first dimension defines a scale of scores from worst to best, from left to right, and the second defines a contrast between extreme responses (positive part of the axis) and neutral/moderate responses (negative part of the axis). The NPS groups were used as a supplementary variable. All tests were 2-tailed with a 95% confidence level. Statistical analyses were performed with Stata (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC).

B Net promoter score results (How likely are you to recommend this service to a friend or family member?)

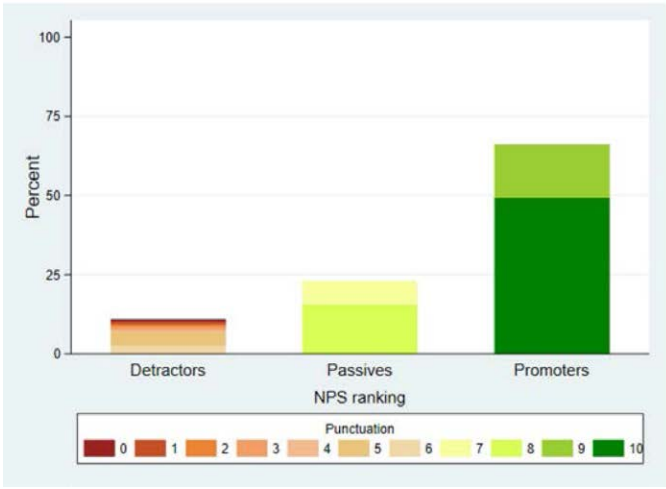


Figure 2. Continued

3. Results

The e-survey was submitted to 5493 PLWHIV. Figure 1A shows the number of surveys received daily. We collected 1633 (30%) correctly completed surveys, and 208 (4%) respondents only partially completed the questionnaire. One hundred and 7 (2%) PLWHIV accessed the e-survey invitation but did not participate. Figure 1B shows the flowchart of the surveys. Sixty-eight percent (n = 1250) of the surveys were answered in Catalan, 30% (n = 559) in Spanish and 2% in English (n = 32).

Most PLWHIV who responded were older than 35 years (90%) and the respondents were evenly distributed among the 3 age groups outlined in the questionnaire. Fifty-eight percent had received higher education, and only 8% reported primary education as their highest level. Two-thirds of the respondents were of Spanish origin, 10% were from other European countries and 21% were from Latin America. Sixty percent had a long-standing HIV infection diagnosed more than a decade ago. Baseline characteristics of the population are shown in Table 1. The age distribution for the cohort of responders was roughly similar to that of the whole cohort; the percentage older than 45 years was 63% and 54%, respectively. The percentage of PLWHIV with higher education (58% vs 46%) and of Spanish origin (66% vs 53%) was higher in the cohort of responders than in the whole cohort.

Overall, the average score for all the statements in the survey was above 4; that is, the responses were favorable, except that for question Q2 related to the time spent in the waiting room that was the worst-rated statement with an average score of 3.9 (SD 1.5) and viewed unfavorably (≤3) by 36% of the users (see Fig. 2A and Table 2). Question Q1, which assesses the physical environment and facilities, received an average score of 4.4 (SD 1.6), and 27% of users felt that the room for consultation was inadequate. Questions Q3, Q4, and Q5, which address how medical information is delivered and received, were very well rated, with average scores ≥ 5.4 (SD 1.2). The clarity of the information received from health care professionals as well as the language used were considered adequate (≥4) for more than 93% of respondents; in fact, Q4 was the highest scoring statement among those in the questionnaire. Finally, 93% of the respondents indicated that the information received responded to their needs. Question Q6, analyzes how the user perceived their involvement in decision making and 91% of the participants indicated that it was adequate. The following group of questions, from Q7 to Q10, delve into the assessment of the quality of the visit: Q7 assesses the development of a climate of trust in which concerns can be expressed, Q8 and Q9 assess time allocated for questions and total visit length and Q10 assess attention during the visit. All the responses in this area were very positive, with 90% of respondents agreeing with the survey statement. For the last question, Q11, which assesses overall experience, the average score was 4.9 (SD 1.4) and 84% of the users responded that the time spent in the consultation was worth it, taking into considering travel, time and waiting.

The average NPS was 8.7 (SD 1.9). Sixty-six percent of the users were classified as promoters. Only 11% scored below 7 and, therefore, were classified as detractors. Thus, the net value of the resulting NPS was 55 (see Fig. 2B). For the NPS results, we did not assess differences by age group or education level, but clearly, Spanish respondents were less likely than respondents of any other origin to be classified as promoters (P = .0005).

In the graph of the MCA (Fig. 3), respondents who were considered promoters were associated with the maximum score, 6, for most questions, given their closeness to these scores. Respondents who were considered passives differed slightly from the previous group, being closer to scores of 4 and 5. The detractors, are further from the center, in the negative part of the axis, because they represented the group who provided the lowest scores.

The groupings or clusters of scores indicated that there was a pattern in these responses: those who responded with a 1 to 1 of the statements tended to do the same to other statements (except for statements about the location of the consultation (Q1), waiting time (Q2) and time spent in total (Q11)), as indicated by the cluster at the top left. The same occurred with the cluster for the score of 6, for which there was a grouping for all statements. The other scores were more dispersed, indicating more variation in the responses.

4. Discussion

The availability and efficacy of antiretroviral treatment have allowed to achieve the goals proposed by the World Health Organization for controlling HIV infection by 2020[11] in our cohort. Specifically, of the 5493 PLWHIV followed in the HIV Unit of the Clinic Hospital of Barcelona, 99% were receiving antiretroviral treatment, and 94% had an undetectable viral load during the study period.

Table 2

Survey.

Variable	Summary statistics	
	n (Column percentage)	Arithmetic Mean (SD) [n]
The location where the consultation occurred was appropriate*		
1	113 (7%)	4.44 (1.57) [1629]
2	117 (7%)	
3	207 (13%)	
4	279 (17%)	
5	336 (21%)	
6	577 (35%)	
Total	*1629 (100%)*	
The time spent in the waiting room was acceptable*		
1	115 (7%)	3.93 (1.48) [1629]
2	201 (12%)	
3	283 (17%)	
4	398 (24%)	
5	351 (22%)	
6	281 (17%)	
Total	*1629 (100%)*	
The information received from the professionals who treated me was clear and concise*		
1	61 (4%)	5.41 (1.17) [1630]
2	21 (1%)	
3	31 (2%)	
4	83 (5%)	
5	308 (19%)	
6	1126 (69%)	
Total	*1630 (100%)*	
The vocabulary used was adequate*		
1	55 (3%)	5.52 (1.08) [1630]
2	11 (1%)	
3	23 (1%)	
4	63 (4%)	
5	270 (17%)	
6	1208 (74%)	
Total	*1630 (100%)*	
The information received during the visit responded to my needs*		
1	53 (3%)	5.41 (1.14) [1630]
2	26 (2%)	
3	33 (2%)	
4	82 (5%)	
5	336 (21%)	
6	1100 (67%)	
Total	*1630 (100%)*	
I believe my opinion mattered, and I felt like a participant in decision-making*		
1	51 (3%)	5.23 (1.23) [1627]
2	39 (2%)	
3	65 (4%)	
4	143 (9%)	
5	356 (22%)	
6	973 (60%)	
Total	*1627 (100%)*	
The visit was carried out in a climate of trust that allowed me to express my concerns*		
1	59 (4%)	5.45 (1.17) [1630]
2	30 (2%)	
3	23 (1%)	
4	75 (5%)	
5	257 (16%)	
6	1186 (73%)	
Total	*1630 (100%)*	
The time allocated to doubts and/or questions was sufficient*		
1	59 (4%)	5.28 (1.23) [1628]
2	35 (2%)	
3	46 (3%)	
4	120 (7%)	
5	354 (22%)	
6	1014 (62%)	
Total	*1628 (100%)*	
The total length of the consultation seemed to be the right amount*		

(*Continued*)

Table 2

(*Continued*)

Variable	Summary statistics	
	n (Column percentage)	Arithmetic Mean (SD) [n]
1	49 (3%)	5.30 (1.19) [1631]
2	34 (2%)	
3	51 (3%)	
4	129 (8%)	
5	344 (21%)	
6	1024 (63%)	
Total	*1631 (100%)*	
I feel that the attention received during the visit was adequate*		
1	53 (3%)	5.44 (1.14) [1629]
2	26 (2%)	
3	30 (2%)	
4	75 (5%)	
5	308 (19%)	
6	1137 (70%)	
Total	*1629 (100%)*	
The time spent in the consultation was worth it (taking into account travel, waiting time, etc)*		
1	76 (5%)	4.88 (1.41) [1620]
2	56 (3%)	
3	134 (8%)	
4	214 (13%)	
5	382 (24%)	
6	758 (47%)	
Total	*1620 (100%)*	

*n (column percentage).

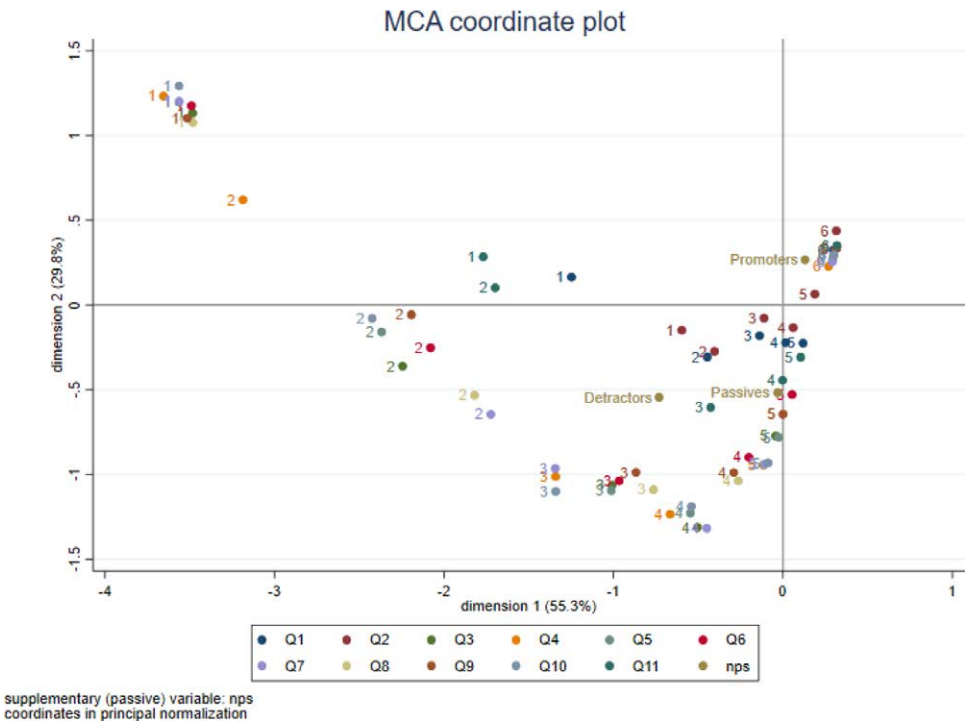


Figure 3. Multiple correspondence analysis.

In accordance with the redefinition of therapeutic success proposed by the scientific community,[12] which includes quality of life as a fourth goal to be achieved in 90% of PLHIV, we analyzed the quality of care we provide in our unit by reviewing the model of care offered to users and incorporating patient perception through an e-survey, with the ultimate goal of improving the service.

First, the response rate to the online invitation to participate in the study was remarkably high considering that PLWHIV had not been previously informed, nor the project was publicly advertised. One-third of the candidates answered our request, a percentage very similar to that obtained in an electronic format survey conducted in a different therapeutic area of the hospital.[24] These data suggest that PLWHIV are sensitive to collaborating in a project that can help improve their care.

The demographic profile of the people who responded to the survey differed slightly from the average profile of PLWHIV of the unit: higher percentage of people of Spanish origin and higher education among the survey respondents. These subtle

differences could indicate a selection bias about the persons included in the study. The digital divide existing in the population served in our unit may explain why some users did not feel comfortable with the electronic format and highlights the need to combine different strategies when presenting the survey that allows us to obtain responses from a greater number of users.

In general, we highlight the high percentage of positive responses to most of statements, with average scores >5, especially for those statements that evaluate the handling of information during the consultation and the perception of the quality of the visit. Thus, the overall assessment of the care received was 5.4 points out of 6. However, we must emphasize that there are issues related to space and time management worst rated and we must view this information as an opportunity to improve our service.

The waiting time prior to the consultation was reported as inadequate for almost half of the users, thus the corresponding statement was the lowest scored on the survey.

Similarly, 1-third of the users felt that the environment in which the consultation was carried out was inadequate. This result indicates the need to remodel this space, taking into consideration the opinion of the users to cocreate friendly environments where they feel comfortable and are guaranteed to have a good experience. Nine percent (9%) of respondents expressed disagreement with the role they have in decision-making. Although this is a small percentage, these data highlight the need to continue working on a patient-centered model where patients they perceive that their opinions are heard. There are few published data on satisfaction reported by PLHIV regarding the care they receive[18,19] in general, satisfaction is favorable, similar to our data, but the results are difficult to compare given that different PREMs were used.

In addition to the survey, we have used the NPS, a simple and validated tool that allows a quick and simple analysis of whether things are being done well in a job or service. Although this tool was developed 2 decades ago,[23] its use in the health field has been more recent and focuses on the benchmarking of private services. To date, there are no data in the literature on its use in the care of PLHIV. A NPS value above 50, such as that obtained in our study, is considered a high value and is synonymous with a positive score. Values similar to those obtained in this study, a NPS of 55, have been reported in studies conducted in the private health sector[25,26] of our setting. We are struck by the fact that Spanish respondents were more critical in their assessment and, therefore, significantly lowered the percentage of respondents classified as promoters. On the contrary, the responses of non-Spanish origin were more favorable.

We are aware that simply collecting data regarding the experience of patients is not sufficient, and that it is necessary to take action, as recommended by experts through PREMs.[27] The purpose of this study was to identify areas that need improvement, and we will evaluate NPS annually to verify whether any improvements impact the HRQoL perceived by the users.

This study has some limitations. Firstly, a bias for self-selection may have affected our results since only 1-third of the patients responded and their socio-demographic profile differed slightly from the average profile of the entire PLWHIV cohort who attended our hospital, as previously mentioned. Secondly, we don't have prior experience in large e-surveys sent to our patients with which compare the response rate. Finally, there is little published data on PREMS in PLWHIV to compare our findings to, and there is no data regarding NPS in the specific HIV infection field. We see this study as a starting point for further research in this area.

In conclusion, monitoring patient reported experience measures in PLWHIV actively receiving outpatient care in our hospital allowed to identify the users' perception on quality of the care received, to determine the rate of satisfaction with the care and to identify areas for improvement. The incorporation of the PREMs in the HIV units is essential to continue working on the improvement of the HRQoL of our patients. The periodic review of these tests will evaluate the effectiveness of the changes implemented after the needs detected have been addressed.

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Trabajo 8

Usability and user's satisfaction of an electronic case report data implemented in the REDCap system in the HIV clinical research context: the use case of DOLAM clinical trial.

Elisa de Lazzari, Montserrat Laguno, Josep Mallolas, Esteban Martínez.
En fase de redacción para enviar a una revista científica.

Resumen

Objetivos: La gestión de datos clínicos dentro de la investigación biomédica ha ganado importancia en la última década produciendo una creciente necesidad de una aplicación web que proporcione funciones de captura de datos electrónicos y gestión de datos clínicos para garantizar datos de alta calidad. Comparamos el sistema REDCap y OpenClinica (versión de distribución libre) y adoptamos el primero para diseñar e implementar el formulario electrónico de recogida de datos (CRFe) de nuestros proyectos de investigación, específicamente del ensayo clínico DOLAM fase-2.

Métodos: Se evaluó la usabilidad percibida del CRFe por los usuarios profesionales (enfermeros, investigadores, monitores de estudio y coordinadores) y su satisfacción mediante el cuestionario de la Escala de Usabilidad del Sistema (SUS) y el Net Promoter Score (NPS).

Resultados: Todos los respondedores (19 de 21) eran mujeres, con edad media de 35 años (DE 7), 11 eran coordinadores o monitores de estudio, 5 enfermeras y 3 clínicos/investigadores. La mediana de SUS fue de 72.5 (RIC 62.5; 80.0): los monitores/coordinadores del estudio tuvieron una mediana de puntuación de 77.5, los investigadores/clínicos, 72.5 y los enfermeros, 57.5. Los que se consideraron con menos conocimiento de informática puntuaron más alto 92.5 (57.5; 95.0) vs. Los más experimentados 71.3 (62.5; 78.8). El NPS total (% promotores - % detractores) fue de 21.1, 7 (37%) usuarios fueron considerados promotores, 9 (47%) pasivos y 3 (16%) detractores.

Conclusiones: Al adoptar un nuevo sistema, medir la usabilidad percibida y la satisfacción del usuario de manera cuantitativa y con medidas validadas es útil para identificar las necesidades de los usuarios no cubiertas y mejorar la interacción usuario-sistema que afectará positivamente a la calidad de los datos y, por ende, de la investigación.

USABILITY AND USER'S SATISFACTION OF AN ELECTRONIC CASE REPORT FORM IMPLEMENTED IN THE REDCap SYSTEM IN THE HIV CLINICAL RESEARCH CONTEXT: THE USE CASE OF DOLAM CLINICAL TRIAL.

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Key words: eCRF, REDCap, system usability, user's satisfaction, NPS, HIV, clinical trial.

Running title: Usability and user's satisfaction of a REDCap eCRF

Abstract

Background: The clinical data management within biomedical research has gained importance over the last decade producing an increasing need of a web-based software application providing electronic data capture and clinical data management functionalities to ensure high quality data. We chose REDCap system over OpenClinica (free-distribution) to design and implement the electronic case report form (eCRF) at our HIV Unit. We then evaluated eCRF usability and stakeholder satisfaction in an upcoming Phase 4 clinical trial.

Methods: We assessed the perceived usability of the eCRF by different professional users, including nurses, researchers, study monitors and coordinators of the phase-4 clinical trial, and their satisfaction using the System Usability Scale (SUS) questionnaire and the Net Promoter Score (NPS).

Results: Nineteen out of 21 persons involved agreed to participate. All were female, with mean age of 35 years (SD 7), 11 were study coordinators or monitors, 5 nurses and 3 clinicians/researchers. The median SUS was 72.5 (IQR 62.5; 80.0): monitors/study coordinators had median score of 77.5, researchers/clinicians, 72.5 and nurses, 57.5. Less Information Technology (IT) or computer-experienced scored higher 92.5 (57.5; 95.0) vs. more experienced 71.3 (62.5; 78.8). The overall NPS (% promoters - % detractors) was 21.1, 7 (37%) users were considered promoters, 9 (47%) passives and 3 (16%) detractors.

Conclusions: When adopting a new system, measuring user's perceived usability and satisfaction in a quantitative manner and with validated measures may be useful to identify users' uncovered needs and to improve future interaction user-system that will positively affect the quality of data managed in clinical research.

Introduction

The sentence “The quality of any trial is dependent on the quality of its data” (1) or the motto “Garbage in – garbage out” (GIGO) from the information technology field, epitomizes the importance of clinical data management (CDM) within clinical research. CDM encompasses the collection, cleaning, and management of subject data according to international standards and good practices, to ensure high quality data. The information needed in clinical studies often comes from a variety of data sources, some of them used in clinical practice (i.e. the health information system of the medical center, the electronic medical record, …) and other specifically designed for the research project (i.e. case report form (CRF), spreadsheets, …). The way they are designed, implemented and used has a direct effect on data completeness, accuracy and reliability.

Since the mid-1980s, the HIV Unit of the Hospital Clinic of Barcelona (Spain) has used a clinical data collection system specifically oriented for persons living with HIV (PLWHIV) data. During the first two decades, the system consisted of a user-friendly interface and a clinical data warehouse as a back-end hosted in the hospital server. This was the starting point to eventually implement an integral care telemedicine system for clinical care of PLWHIV trough standard-of-care and telemedicine (VIHrtual Hospital) (2)(3). The back-end was defined and implemented as a clinical data warehouse that allowed to retrieve basic clinical data for research purposes and to identify candidate patients for clinical trials recruitment; the front-end is a user-friendly interface. Nevertheless, VIHrtual Hospital is a system oriented to patient’s clinical care and has not the capabilities to capture and manage all the data generated by the research projects and clinical trials the Unit develops. Any modification of VIHrtual Hospital intended to adapt the system for this purpose would imply a number of resources in terms of time and money which is difficult to cover with project financing.

Hence, in our HIV Unit data from low-budget or not funded research projects were usually collected in carbon copy paper case report form (pCRF) and then manually entered into spread sheets (a very time-consuming process susceptible of multiple

errors) and stored locally in the clinician and/or data entry computer, without any formal control of access nor traceability of data and under the risk of ending up with different versions of the spreadsheet generated by the personnel involved in the project. Then, the data management step took place with the generation and resolution of the specific queries, involving the statistician, data entry personnel and the investigator. Thereafter, the statistical analysis could be adequately performed.

In 2016 we planned to move forward and to improve the quality of our research by means the adoption of a tool for research data planning, collection and management. We needed a clinical data management systems (CDMS), a web-based software application providing electronic data capture and clinical data management functionalities that responded to the common characteristics of the studies and also adapted to the specificities of each of them. In general terms, the capabilities of a CDMS includes the implementation of electronic case report form (eCRF) for data capture, management and monitoring through dynamic queries/reporting, distributed access, audit trail for user activity and data manipulation and export data procedure.

The collaborative nature of our projects implies that users with different backgrounds, roles and tasks (and sometimes, from different sites) interact with the eCRF in REDCap. For this reason, we decided to assess its usability and stakeholder's satisfaction. The usability consists in "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use" (8), it is an outcome generated by the human-system interaction rather than a property of the system itself.

One of the first eCRFs we implemented was for the DOLAM study: an open-label randomized controlled clinical trial to assess the safety, tolerability and efficacy of two dolutegravir-based simplification strategies in HIV-infected patients with prolonged virological suppression (9).

The aim of this work is to evaluate eCRF usability and user's satisfaction in the context of the DOLAM clinical trial as a use case.

Methods

A qualitative evaluation of different EDC systems reported by Franklin at al. (4) led us to evaluate the edition (free-distribution) of OpenClinica (5) and the REDCap system (6). In our opinion, OpenClinica had more powerful and flexible data validation and site/users roles and permissions modules but less flexibility in importing/exporting data, while REDCap presented a good ease of project structure definition, form design and check implementation. Randomization and surveys capabilities were offered only by REDCap. Both systems provided the possibility to implement visit schedules for data entry and to upload relevant documentation at project- and record- level. REDCap provided a wide and complete online training materials and documentation openly accessible, while for OpenClinica the open material was quite limited, so we considered that the learning process would be faster and easier in REDCap. In the light of the characteristics of both systems and the specific needs of our projects, we chose the REDCap system which was hosted at Eurecat (Technology Center of Catalonia) (7). Thereafter, we started a process of definition and implementation of the eCRF, primarily with clinical trials and later with other research studies at the VIH Unit.

eCRF

DOLAM (EudraCT 201500027435) is a phase 4, randomised, open-label, non-inferiority trial in which virologically suppressed persons with HIV treated with triple antiretroviral regimens were randomized 1:1:1 to maintain triple therapy (control arm), or to switch to dolutegravir/lamivudine, or to dolutegravir monotherapy stratifying by anchor drug for 48 weeks (9) (10). For this study we designed and implemented the CRF electronically using the REDCap system. The eCRF design was standardized to address the needs of all professionals participating in the trial (clinical investigators, study coordinators and monitors, data entry personnel and statistician), and also to produce a set of forms usable in future trials with the objective of reducing the variability between eCRF from different studies and the time of eCRF implementation. Standardized criteria involved variable names and coding assignment, the use of ontologies, generation of specific variables to check the completeness and correctness of the data entered and to avoid repeated information over the eCRF. A

collection of reports was generated into the same eCRF to ease the detection of potential errors and missingness in data and letting shorten the time to eCRF locking. Moreover, two short guides about how to start data entry, inform relevant fields/forms and manage queries were distributed to all users and uploaded in the File Repository of the eCRF, as a complement to the wide support material any user can find within the REDCap system.

Additionally, since the HIV-Unit VIHrtual Hospital system receives the laboratory parameters results from the hospital health information system (HIS) (SAP, Patient Management for Healthcare provides the administrative processes for registering and maintaining patient information) (11) by a web service integration, with the aim at reducing data entry errors and task completion time, the acquisition of laboratory data was integrated in the data management phase by the statistician who retrieved those results directly from the VIHrtual Hospital data base hosted on the hospital server and merged them with all trial data extracted from the eCRF in REDCap, including laboratory data from the other sites (Figure 1). In this way, at least for our hospital, the most repetitive, long and prone to errors task of data entry was substituted by traceable, repeatable and reusable scripts that retrieve data from the different sources, combine them, perform quality checks and prepare them for the final analysis.

Questionnaires

In order to assess the perceived usability of the new system, we administered a questionnaire to the professionals who used the eCRF in DOLAM trial to obtain a quantitative measure of usability and satisfaction, easy to interpret and with the possibility to be correlated with other user's characteristics and also with other metrics. We chose the System Usability Scale (SUS) (12) (table 1), a questionnaire with 10-items based on a 5-point Likert scale (from strong disagreement to strong agreement). Odds numbered questions were positively-worded while even numbered items were negatively-worded. Since the respondents in our context were Spanish speakers, to improve the understanding of the questionnaire, we adopted the modified version where the word "cumbersome" was substituted by "awkward", in

question 8 wording (12) (13) (14). Both adjectives can be translated into Spanish as *incómodo*, *poco manejable*, *difícil*. The final score, a composite measure of the overall usability, ranges from 0 to 100 with higher scores indicating better system usability. Scores above 68 points are considered acceptable and greater than 85 excellent indicating high level of usability (14).

It is a simple, low-cost and quick-response instrument, widely used to test products: websites, softwares, medical systems and mobile devices. It covers effectiveness, efficiency and satisfaction and its robustness and reliability has been consistently described (14) (15).

The SUS score was interpreted using the percentile ranks, grades and adjectives (16) (14).

To assess the user's experience and satisfaction, the Net Promoter Score (NPS) (17) was administered. It is a simple tool based on just one question "*How likely it is that you would recommend the system to a friend or colleague*?", in our case the REDCap system, whose answer ranges from 0, "*not at all likely*", to 10, "*extremely likely*". Respondents scoring 9 or 10 are considered *Promoters*; those scoring 7 to 8, *Passives*, and those scoring 0 to 6 *Detractors*. The final score is calculated as the difference between the percentage of *Promoters* and *Detractors* as represented in Figure 2a. Since in the Spanish school system grades range from 0 to 10 points, being 5 the threshold to pass a test, 6 and 7 a good result, 8 a very good result and 9 to 10 an excellent one (metric used also when our respondents were at school), our user's NPS answers may be biased toward that metric. Thus, additionally we adapted a modified categorization (Table 2b) where score 6 was assigned to the passive group and score 8 to the promoter group, ending up with the classification into detractor (0-5), passive (6-7) and promoter (8-9-10), similarly to the alternative NPS proposed by Krol et al. for their study carried out in the Netherlands (18).

The questionnaire was implemented in REDCap system as a survey and the link to access it was sent by email to each one of the respondents.

Statistical Methods

Responder characteristics were described using absolute (n) and relative (%) frequency and mean and standard deviation (SD) or median and interquartile range (IQR). SUS and NPS were reported with mean (SD), median (IQR) and range. Association between respondent's characteristics and SUS and NPS was based on Mann-Whitney test and Spearman's correlation coefficient. All tests were two-sided with a confidence level set at <0.05. The statistical analysis was performed using Stata version 18 (19).

Results

Out of 21 users invited, 19 undertook the survey. The two non-responders discontinued their contracts with institution at the time the survey invitation was sent and it was not possible to contact them. All respondents were female with a mean age of 35 years (SD 7). Eleven (58%) were study coordinators or monitors, 5 (26%) nurses and 3 (16%) clinicians/researchers. The majority considered themselves more experienced in IT/computer, only one nurse (20%) and two monitors/study coordinators (18%) chose the less experienced option. About half of the responders had already used the REDCap system in previous trials from other centres: 2 (67%) researcher/clinicians, 3 (60%) nurses and 5 (45%) monitors/study coordinators. The youngest responders were the nurses, followed by the researcher/clinicians and the monitor/study coordinators (table 2).

The System Usability Score

The SUS ranged from 45.0 to 95.0 with a mean value of 71.4 (SD 14.1) and median of 72.5 (IQR 62.5; 80.0). Highest scores were obtained by monitors and study coordinators (median (IQR): 77.5 (62.5; 92.5)), good scores by researchers/clinicians (72.5 (62.5; 75.0)) and the worst by nurses (57.5 (50.0; 70.0)) (p-value=0.1299). Self-perception of IT-experience was not associated with the usability score: less experienced 92.5 (57.5; 95.0) vs. more experienced 71.3 (62.5; 78.8); p-value=0.3398), neither previous experience with REDCap (never used: 75.0 (62.5; 80.0) vs. already used: 71.3 (60.0; 80.0); p-value=0.7429). There was no correlation between SUS and users age (Spearman's rho=-0.18; p-value=0.4836).

Considering the suggested ways of interpreting the SUS (15), the result found in our sample is just above the 60th percentile, a good result that can be graded as C+ according to school grade rate and corresponds to a passive result for NPS (Figure 3).

The Net Promoter Score

In our sample, the overall NPS (% promoters - % detractors) was 21.1. Individual scores ranged from 6 to 10, with a mean score of 7.8 (SD 1.5) and a median of 7 (IQR 7; 9).

Seven (37%) responders were considered promoters, 9 (47%) passives and 3 (16%) detractors. There were no statistically significant differences between NPS groups regarding users' characteristics (Table 3). Forty-five percent of the monitor/study coordinators were promoters and 45% were passive, 40% of nurses were promoters and 40% were passive, and none of researchers/clinicians were promoters, 67% were passive. Three (31%) less IT-literate users and 40% of already experienced in REDCap were promoters.

In our detractor group, mean SUS was 62.5, that correspond to a marginal acceptability and a D grade, the passive group also presented a marginal acceptability but with a C grade (mean SUS of 68.9), while the promoter group with the mean SUS of 78.9 demonstrated acceptability and A- grade.

As pointed out previously, in order to take into account the expected bias towards the Spanish school system grades our respondents could be affected by, we assigned those scoring 6 to the passive group instead of to detractor and those scoring 8 to promoter group instead of passive. The modified-NPS was 42.1, there were no detractor users, 11 (58%) were in the passive group and 8 (42%) in the promoter one. The median satisfaction score in modified-NPS groups was 80.8 (IQR: 60.0; 93.8) in promoter and 70.0 (IQR: 62.5; 75.0) in passive users (p-value=0.2810). With respect to this categorization, the less IT experienced responders were all promoters, while 69% of the more IT-literate were passive.

Discussion

Nowadays, data in biomedical research are considered of high value. As a result of improvements in information technology over the past 10 to 15 years, a number of systems exist that provide the electronic data capture capabilities necessary to preserve data integrity, accuracy, and reliability. In our HIV Unit we evaluated chose the REDCap system to implement the eCRF of our studies. This represented a step forward in innovation in the way we collect and manage data.

The results of this study showed how validated questionnaires about system usability and satisfaction perceived may be employed in the context of biomedical research studies and, specifically, of an eCRF from HIV field. Stakeholders asked to answer the tests were professionals from different backgrounds that typically collaborate in clinical trials and their characteristics would also be important to give a light on which profile would need more support to improve their interaction with the system and complete satisfactory their tasks.

Although the eCRF was designed and implemented to address the needs of all stakeholders participating in the trial, our results pointed out that the perceived usability varied across users' role, being data entry personnel (basically nurses) those who expressed the lowest usability and three out of 5 were detractors or passives. In our sample only 3 users (16%) considered themselves not very computer-literate and two of them showed very high satisfaction (SUS>90) and belonging to the promoter group. Nevertheless, almost half of the professionals had never used the system before the DOLAM study, the satisfaction was good in both experienced and non-experienced users, even with higher median value in non-experienced, indicating that maybe those with some experience expected better performance of the eCRF. Considering the modified-NPS, all clinicians and two nurses out of five were passive. User's age range was too narrow (from 25 to 45 years) to observe some difference in usability and satisfaction between younger and older user. Thus, the results of SUS and NPS showed the importance to pay more attention to the needs of certain professional's roles, in our case the data entry personnel, in the design and implementation of the eCRF. Some support strategies like training sessions directed to

different users' profiles and a closer support during user-system interaction over the study development may be required.

In order to take into account the different psychological boundaries of the 0-10 scale in Spain and avoid to underestimate the global NPS, we thought that it was more plausible to consider professionals answering 6 (a good mark) as passives than detractors and those scoring 8 (a very good mark) as promoters than passives. Thus, the modified-NPS rose from 21.1 up to 42.1. We agree with Krol et al. (18) that a way to obtain more consistent interpretation would be label all the response categories (not only the two at the extremes) instead of the distribution of detractors, passives and promoters applied a posteriori of data collection. In our opinion those labels would helpful, mostly in our context when in 10-point grading scale the pass result is 5.

The implementation of the electronic CRF in REDCap system, performed by the project statistician, represented a net benefit for the project budget as the total cost of the paper CRFs was saved as well as the time to fill them in manually. Moreover, the total cost of the project did not suffer significantly additional costs derived from the informatics system adopted since the REDCap system was available at no charge to non-profit organizations that join the REDCap consortium, having to assume only the server hosting and maintenance cost.

Limitations

Our sample size included few professionals and may fail to detect statistically differences between users' characteristics and the outcomes apart from providing imprecise estimates. Moreover, our respondents were all women limiting the generalizability of our results.

Conclusion

When adopting a new system, it is important to assess the perceived usability and user's satisfaction in a quantitative manner and with validated measures to identify users' uncovered needs and items that can be improved. Considering user experience will enhance future user-system interactions which positively affect the quality of data and, at the end, of the research.

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Figure 1: Architecture of systems involved in DOLAM data capture and management

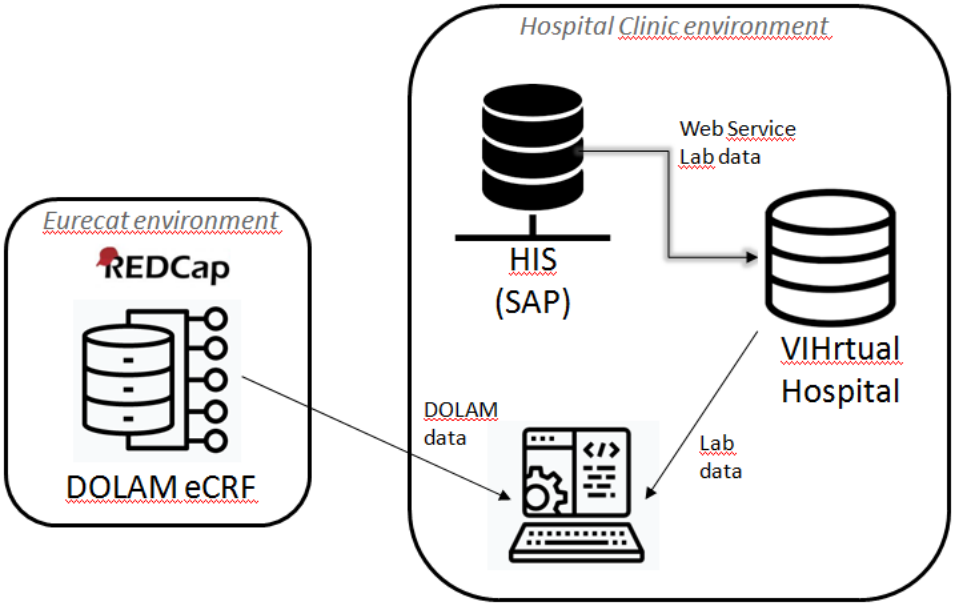

Figure 2 a) and b): Original (a) and adapted (b) Net Promoter Score (NPS) scale

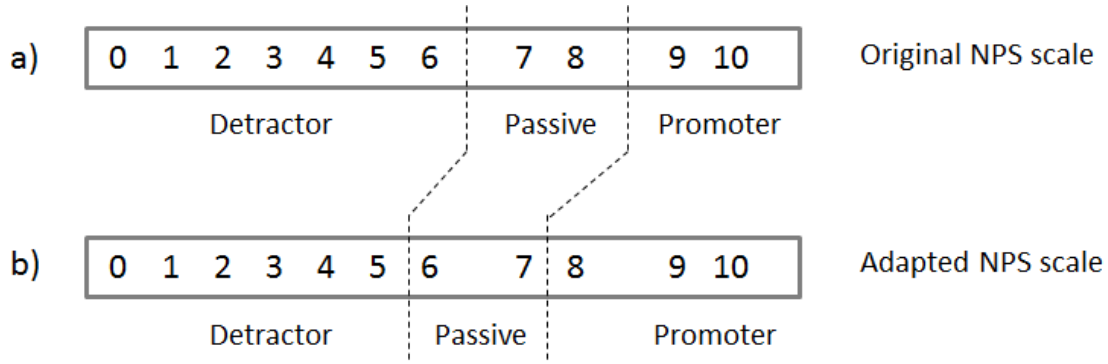

Figure 3: Results of System Usability Scale (SUS) in terms of different metrics and Net Promoter Score (NPS)

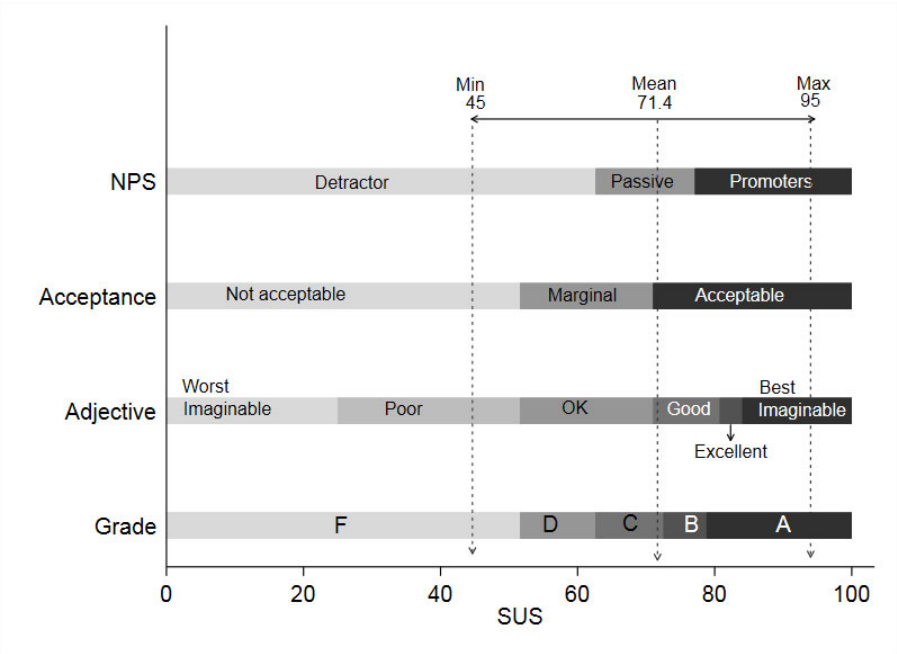

Table 1: System Usability Scale (SUS) questionnaire

Please, for each statement indicate whether you strongly desagree (1), desagree (2), are neutral (3), agree (4) or strongly agree (5) with it.

	StronglyDesagree1	Desagree2	Neutral3	Agree4	StronglyAgree5
1) I think that I would like to use this system frequently	○	○	○	○	○
2) I found the system unnecessarily complex	○	○	○	○	○
3) I thought the system was easy to use	○	○	○	○	○
4) I think that I would need the support of a technical person to be able to use this system	○	○	○	○	○
5) I found the various functions in this system were well integrated	○	○	○	○	○
6) I thought there was too much inconsistency in this system	○	○	○	○	○
7) I would imagine that most people would learn to use this system very quickly	○	○	○	○	○
8) I found the system very awkward to use	○	○	○	○	○
9) I felt very confident using the system	○	○	○	○	○
10) I needed to learn a lot of things before I could get going with this system	○	○	○	○	○

Table 2: Characteristics of responders

		Position at work			Total (n=19)	p-value
		Researcher, Clinician (n=3)	Nurse (n=5)	Monitor, Study Coordinator (n=11)		
IT/Computer Experience	More (vs. less)	3 (19%)	4 (25%)	9 (56%)	16 (100%)	1.000[1]
Previous usage of REDCap	Yes (vs. no)	2 (20%)	3 (30%)	5 (50%)	10 (100%)	1.000[1]
Age (years)	Median (IQR)	33 (32 ; 33)	29 (28 ; 33)	41 (28 ; 43)	33 (28 ; 42)	0.2493[2]

1: p-value from Fisher's exact test

2: p-value from Kruskal-Wallis test

Table 3: Characteristics of responders and Net Promoter Score (NPS) groups

		Classification by NPS				
		Detractor (n=3)	**Passive (n=9)**	**Promoter (n=7)**	**Total (n=19)**	**p-value**
NPS	mean (SD)	6 (0)	7.1 (0.3)	9.6 (0.5)	7.8 (1.5)	
Age	median (IQR)	32.0 (28.0; 35.0)	33.0 (33.0; 43.0)	34.5 (27.0; 42.0)	33.0 (28.0; 42.0)	0.5704[1]
Position at work	Researcher, Clinician	1 (33%)	2 (67%)	0 (0%)	3 (100%)	0.5949[2]
	Nurse	1 (20%)	2 (40%)	2 (40%)	5 (100%)	
	Monitor, Study Coordinator	1 (9%)	5 (45%)	5 (45%)	11 (100%)	
IT/Computer Experience	Less	0 (0%)	1 (33%)	2 (67%)	3 (100%)	0.7399[2]
	More	3 (19%)	8 (50%)	5 (31%)	16 (100%)	
Previous usage of REDCap	No	3 (33%)	3 (33%)	3 (33%)	9 (100%)	0.2266[2]
	Yes	0 (0%)	6 (60%)	4 (40%)	10 (100%)	

1: p-value from Wilcoxon rank sum test

2: p-value from Fisher's exact test

Discusión

Katherine Johnson *(Matemática, 1918-2020). Mujer afroamericana que calculó la trayectoria del vuelo del Apolo 11 que llevó por primera vez el hombre a la Luna.*

"Ninguna investigación humana puede ser denominada ciencia si no pasa a través de pruebas matemáticas." *Leonardo Da Vinci (Polimata, 1452-1519)*

"Las computadoras son increíblemente rápidas, precisas y estúpidas. Los hombres son increíblemente lentos, inexactos e inteligentes. El conjunto de los dos constituye una fuerza incalculable." *Albert Einstein (Físico, 1879-1955)*

"La medicina es la ciencia de la incertidumbre y el arte de la probabilidad." *William Osler (médico, 1849-1919)*

Con esta tesis he investigado, en las personas que viven con una infección por VIH, nuevas estrategias para la simplificación del tratamiento antirretroviral oral tanto en contexto de ensayos clínicos como en vida real, cómo ha impactado la inesperada epidemia de COVID-19 en la prevención y atención del VIH y otras infecciones de transmisión sexual, y he valorado la experiencia de las personas que viven con VIH con respecto a la atención sanitaria recibida como estrategias de mejora de su calidad de vida relacionada con la salud. Además, he valorado la usabilidad de la tecnología en investigación y satisfacción de los profesionales utilizando como caso de uso el ensayo clínico DOLAM reportado en el trabajo 4.

A continuación, dentro de cada bloque temático, se reporta la discusión de la investigación realizada en relación a cada objetivo, indicando además los trabajos asociados.

Acerca de la simplificación del tratamiento antirretroviral.

OBJETIVO 1: En una gran cohorte de personas con VIH: evaluar las características clínicas asociadas con el uso de 2DR y los factores asociados con antirretrovirales específicos en 2DR; evaluar la efectividad y seguridad del tratamiento 2DR con dolutegravir/lamivudina y la tasa de discontinuación.

Trabajo 1: Factors associated with the use and composition of two-drug regimens in a large single-centre HIV cohort.
Trabajo 2: Clinical use and effectiveness of Dolutegravir and lamivudine: a long-term, real-world, retrospective study.

En el primer trabajo pudimos comprobar que en la cohorte de personas que viven con una infección por VIH atendidas en nuestra Unidad, una de cada diez personas que recibían tratamiento antirretroviral combinado tenía 2DR. En relación con los 3DR, las personas en 2DR eran mayores y más suprimidas virológicamente, con un historial más largo de infección por VIH y exposición a tratamiento antirretroviral, SIDA previo, fallo

virológico previo y mutaciones genotípica de resistencia, lípidos plasmáticos más altos y hemoglobina más baja. Estos hallazgos concuerdan con resultados previos que indican que los 2DR se han dirigido de manera preferencial a las personas con VIH con mayor edad y con un buen estado de VIH pero opciones terapéuticas limitadas debido a la resistencia, la toxicidad antirretroviral acumulada o las comorbilidades concomitantes (68–71). La gran mayoría de los 2DR de nuestra cohorte incluían un inhibidor de la integrasa, un inhibidor de la proteasa o ambos. Identificamos diferentes perfiles de factores asociados con tener en el tratamiento doble un inhibidor de la integrasa o un IP. El colesterol HDL basal más bajo y la duración más prolongada con 2DR fueron factores independientes asociados a tener un inhibidor de la integrasa en el tratamiento con 2DR. El SIDA previo, las mutaciones de resistencia genotípica previas, la ratio CD4/CD8 más baja y la duración más corta fueron factores independientes asociados con tener un 2DR con inhibidor de la proteasa. Las diferencias en la duración de la prescripción 2DR pueden estar relacionadas, al menos en parte, con la mejor tolerabilidad y el menor riesgo de interacciones farmacológicas de los inhibidores de la integrasa en comparación con los IP. El uso de IP se asoció con un peor estado del VIH y mutaciones de resistencia previas. El uso de inhibidores de la integrasa se asoció con un colesterol HDL basal más bajo. El colesterol HDL bajo es un criterio de síndrome metabólico y un marcador de resistencia a la insulina y riesgo cardiovascular (72). También exploramos los factores asociados con 2DR basados tanto en IP como en inhibidores de la integrasa, que incluían tener mutaciones previas, fallo virológico previo y eventos de SIDA. Por lo tanto, fue la presencia de fracaso virológico previo con mutaciones de resistencia lo que se relacionó con la inclusión de IP con o sin inhibidores de la integrasa. En esta gran cohorte unicéntrica de personas que viven con el VIH pudimos comprobar que los 2DR se habían adaptado a las características clínicas de las personas con VIH y generalmente contenían IPs y/o inhibidores de la integrasa. Un peor estado cardiometabólico o una mayor resistencia archivada fueron factores clave asociados con la inclusión de inhibidores de la integrasa o IP, respectivamente, en los 2DR. Estos datos se vieron confirmados por los de otros estudios de múltiples cohortes europeas publicados posteriormente (73).

En el segundo trabajo, investigué el uso en vida real de una pauta 2DR con inhibidor de la integrasa, en concreto con dolutegravir más lamivudina. Según los resultados de ensayos clínicos aleatorizados, este régimen es preferido en personas tanto con experiencia previa al tratamiento antirretroviral (TE) como sin ella (TN), y otros estudios (74–77) también fortalecen los datos en vida real sobre su uso en ambos entornos (78–85). Nuestro estudio proporciona datos adicionales y sólidos para respaldar la efectividad de dolutegravir/lamivudina, con tasas de supresión virológica que alcanzan el 97% y el 98% después de 6 y 12 meses de seguimiento, respectivamente, en la población en tratamiento (OT). Nuestra cohorte es representativa de la epidemiología actual del VIH en Europa Occidental/Central, compuesta principalmente por HSH, edad media/mayor (el 42% de los pacientes tenía más de 50 años) y una prevalencia muy baja de usuarios de drogas inyectables (5%). Dado el bajo número de personas naïves al tratamiento, en nuestro estudio analizamos solo los experimentados. Este bajo número de naïves se explica por varias razones. En primer lugar, tanto los nuevos diagnósticos como las infecciones han ido disminuyendo en los últimos años, dada la expansión del tratamiento antirretroviral y la PrEP. En segundo lugar, la mayoría de las personas TN reciben prioridad para los ensayos clínicos, especialmente en la mayoría de los centros de referencia terciarios. En tercer lugar, la mayoría de los sujetos del estudio incluidos iniciaron dolutegravir/lamivudina durante la pandemia de COVID-19, y en estos períodos se priorizaron otras combinaciones recomendadas para el inicio rápido del tratamiento antirretroviral (activo frente al VHB y sin necesidad de esperar los resultados de laboratorio) (86). El alcance de la PrEP se ha ampliado considerablemente en nuestro medio; las personas que anteriormente tomaron PrEP o estuvieron en contacto con entornos de PrEP pueden tener una mayor prevalencia de sustitución de M184V (87), una situación en la que actualmente no se recomienda dolutegravir/lamivudina. Finalmente, la percepción de los médicos de los excelentes resultados obtenidos con la simplificación usando dolutegravir/lamivudina en varios escenarios clínicos puede conducir a un uso mucho más frecuente de esta línea de terapia en esta situación. Nuestra cohorte presentaba un buen estado inmunológico (el 80% tenía CD4/células/mm^3 ≥500) y tenía una mediana de tres esquemas previos de TAR en una mediana de 11.9 años desde el diagnóstico. El seguimiento más largo fue de 7.4 años.

La primera persona que comenzó con dolutegravir/lamivudina fue un hombre de 63 años que tomaba un régimen basado en tenofovir disoproxil fumarato (tenofovir disoproxil fumarato/lamivudina/rilpivirina) que desarrolló insuficiencia renal en 2014 y resultó positivo para HLA-B5701. Este sujeto comenzó a tomar dolutegravir/lamivudina en noviembre de 2014 (más de 5 años antes de la publicación de los resultados a la semana 48 del ensayo clínico TANGO). El uso temprano de esta combinación destaca el atractivo perfil de dolutegravir/lamivudina entre los médicos de nuestro centro, incluso antes de la publicación de los resultados de los ensayos pivotales de cambio de TAR (como los de la semana 48 del ensayo TANGO) (88). Sin embargo, como se esperaba, el número de personas que recibieron dolutegravir/lamivudina aumentó en gran medida en los últimos tiempos, siguiendo los resultados del ensayo TANGO y la disponibilidad de la formulación conjunta. El motivo principal de la suspensión de dolutegravir/lamivudina en nuestro estudio fue la toxicidad; sin embargo, dado que solo el 5% de nuestros pacientes tuvieron que cambiar su TAR por este motivo en particular, podemos asumir la seguridad general de este régimen. Nuestros datos de vida real también muestran el uso clínico del régimen de dolutegravir/lamivudina en situaciones más allá de las aprobadas por las agencias reguladoras, como el uso en personas con sustituciones de resistencia conocidas o un estado no detectable en el momento del cambio. Aunque detectamos la mutación M184V/I en 29 personas, el análisis estadístico demostró que no se asoció de forma independiente con menores probabilidades de supresión virológica. Estos hallazgos están en línea con estudios recientes que encontraron que 3 años después del cambio a dolutegravir/lamivudina en pacientes portadores de la mutación M184V/I, la probabilidad de fallo virológico y *blips* era muy baja (6.9%) (89). Esto era particularmente cierto si la carga viral de la persona permanecía indetectable durante largos períodos desde que se identificó la sustitución (90). Sin embargo, es necesario abordar varios puntos acerca de los hallazgos del análisis multivariable. La mediana de tiempo transcurrido entre la detección de M184V/I y el inicio de dolutegravir/lamivudina fue extremadamente larga (13.7 años). Esto destaca la menor relevancia otorgada por los médicos cuando se detectaron sustituciones en muestras antiguas y la carga viral de los individuos permaneció indetectable durante largos períodos. No obstante, hubo algunos casos que alcanzaron 6 y 12 meses de seguimiento. Dicho esto, el poder estadístico fue muy

bajo para concluir que la M184V/I no estaba relacionada con la falta de efectividad en el mes 12, y estos resultados deben interpretarse con precaución para evitar incurrir en el error estadístico de tipo II. Finalmente, en todos los casos excepto en uno se detectaron otras sustituciones en el GRT histórico, lo que indica un largo historial de exposición al tratamiento antirretroviral. De hecho, el uso previo de IP se asoció con la falta de efectividad en el modelo ajustado, lo que quizás ilustra este hecho, con una potencia más alta que la historia de sustitución de M184V/I en sí. Las mujeres y una carga viral detectable al inicio de dolutegravir/lamivudina también fueron factores asociados con la falta de eficacia en el mes 12. Se reporta con frecuencia que las mujeres tienen un éxito virológico más bajo en comparación con los hombres, especialmente con los hombres que tienen sexo con hombres. Esto puede estar relacionado con diferentes barreras para la adherencia al seguimiento y el tratamiento antirretroviral (91) (92) y no necesariamente específico del régimen. Esto puede resaltar la importancia de cambiar a este régimen solo en personas con supresión virológica; también puede indicar una menor adherencia, independientemente de la combinación antirretroviral utilizada. Estos resultados pueden sugerir que estos subgrupos de personas podrían beneficiarse de un seguimiento más estrecho y un refuerzo de la adherencia al cambiar a dolutegravir/lamivudina. La supresión virológica se evaluó a través de diferentes métodos (OT, ITT y mITT), mostrando en general altas tasas de supresión. Teniendo en cuenta que este es un estudio en vida real, el análisis en la población OT es probablemente el mejor enfoque para definir la efectividad, ya que los datos proporcionados reflejan mejor la realidad clínica cotidiana, es decir, es común que los pacientes se pierdan durante el seguimiento. Sin embargo, la proporción de individuos sin datos virológicos en ventana no fue especialmente elevada en nuestro estudio. Recientemente publicamos resultados sobre nuestra cohorte de personas con VIH que tomaban bictegravir/tenofovir alafenamida/emtricitabina (BIC/TAF/FTC) (93). Cabe mencionar algunas diferencias interesantes con la cohorte de los que reciben dolutegravir/lamivudina, lo que también muestra la percepción de los regímenes por parte de los médicos. En el estudio BIC/TAF/FTC, solo el 82% de los incluidos (en el grupo de cambio) tenían una carga viral indetectable al inicio de BIC/TAF/FTC, en comparación con el 97% que comenzó con dolutegravir/lamivudina. Aunque ambas combinaciones se recomiendan

para las estrategias de cambio, esta proporción variable destaca un uso diferente de tales regímenes: BIC/TAF/FTC se reserva para aquellos que se perciben como más difíciles de tratar, menos adherentes a la terapia o incluso que necesitan represión o rescate de la viremia o régimen de rescate. Por el contrario, dolutegravir/lamivudina parece utilizarse con más frecuencia en aquellos que se perciben como muy adherentes, en los que se desea una mejora de la combinación en términos de seguridad a largo plazo, sin perder eficacia virológica. Nuestro trabajo tiene varios puntos fuertes. Representa una gran cohorte de un solo centro con una población actual típica de personas con VIH. El número de sujetos del estudio es comparable al de las cohortes multicéntricas. También proporciona evidencia de la eficacia de este régimen, respaldada por múltiples análisis. La amplia cohorte actual también permite representar un número relevante de pacientes portadores de mutaciones; además, el período de seguimiento de los primeros casos fue extremadamente largo (en comparación con los estudios del mundo real publicados anteriormente). Sin embargo, el trabajo no está exento de algunas limitaciones importantes, como la ausencia de datos en nuestra base de datos sobre algunas comorbilidades relevantes (p. ej., riesgo cardiovascular). Debido al envejecimiento de la población de personas con VIH, estos datos son cada vez más importantes. Para otras comorbilidades como la enfermedad ósea, los datos solo estaban disponibles para un porcentaje de los pacientes. Este tipo de información habría resultado interesante para ilustrar el perfil de las personas a las que se les prescribió dolutegravir/lamivudina en nuestra cohorte. También proporciona datos de un solo hospital. Aunque nuestro centro es la unidad de referencia del área, puede no representar algunas características de las personas con VIH que residen en otras regiones. Como se trataba de un estudio de vida real, a un número no despreciable de personas les faltaban datos. Finalmente, muchos casos comenzaron este régimen recientemente, incluidos los que tenían sustituciones resistentes a los antirretrovirales, por lo que la cohorte experimentó una tasa de pérdidas significativa en el mes 6 y 12.

OBJETIVO 2: Evaluar la factibilidad, la eficacia virológica y tolerabilidad de la terapia dual con raltegravir/lamivudina en PVVIH con supresión viral sostenida en terapia antirretroviral combinada.

Trabajo 3: A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine.

También este trabajo se focaliza en una pauta 2DR con un inhibidor de la integrasa, en concreto raltegravir más lamivudina, pero en un contexto de ensayo clínico y ya no en vida real como los dos trabajos vinculados al objetivo 1. Este ensayo clínico representa una prueba de concepto de que el cambio de la terapia antirretroviral combinada a raltegravir/lamivudina en pacientes con supresión viral sostenida mantiene la supresión viral a las 24 semanas y es bien tolerado. Los resultados respaldan que raltegravir puede comportarse de manera similar a dolutegravir para construir regímenes de mantenimiento dual junto con lamivudina (94) (74). No hubo fallos virológicos ni irregularidades en el brazo de raltegravir y lamivudina durante las 24 semanas. Sin embargo, estos resultados deben interpretarse con cautela debido al corto seguimiento. El rebote viral en los estudios de monoterapia con dolutegravir se observó con mayor frecuencia a las 24 semanas o después (53,95–97). Los eventos adversos no fueron graves y no difirieron entre los brazos. Esto es particularmente importante ya que el cambio a nuevos medicamentos en pacientes que ya toleran sus regímenes antirretrovirales generalmente produce un efecto de deserción debido a problemas de tolerabilidad con los nuevos medicamentos. No hubo más efectos adversos en el sistema nervioso central (SNC) en el brazo de raltegravir y lamivudina. Los efectos sobre el SNC se han notificado con mayor frecuencia con dolutegravir que con raltegravir o elvitegravir (98–100). En un meta-análisis de ensayos clínicos aleatorizados (101), dolutegravir (frente a otros agentes principales) se asoció con un mayor riesgo de insomnio. En nuestro estudio, la calidad del sueño medida por el PSQI no difirió entre brazos de tratamiento. Hubo un mayor aumento no significativo de peso y grasa corporal con raltegravir y lamivudina, pero el tamaño del cambio fue

pequeño y de relevancia clínica dudosa. Ha habido informes recientes que sugieren un mayor aumento de peso con los inhibidores de la integrasa que con otros agentes (102) (103). En el ensayo clínico aleatorizado NEAT022, los pacientes que cambiaron de inhibidores de la proteasa potenciados a dolutegravir ganaron aproximadamente 1kg en 48 semanas (104) y el aumento de peso se asoció con una disminución de la adiponectina (105), un marcador de resistencia a la insulina y obesidad. Se necesitan más datos para determinar si el aumento de peso es un efecto de clase de los inhibidores de la integrasa y cuál es su significado clínico. Nuestro estudio tuvo limitaciones. Hubo pocos pacientes y el seguimiento fue corto. Sin embargo, esta fue una forma conveniente de planificar un estudio piloto tan intensivo sobre una nueva estrategia terapéutica. Para compensar estas limitaciones, se planificaron estudios virológicos e inmunológicos intensivos, y actualmente está en curso una fase adicional de extensión de 48 semanas. A pesar de haber sido aprobado por la FDA y la AEMPS, la formulación de dosis fija utilizada, Dutrebis nunca ha estado disponible comercialmente debido a una decisión de la empresa fabricante, Merck, pero los productos individuales raltegravir y lamivudina están disponibles en una dosis diaria. En resumen, este estudio piloto sugiere que cambiar a raltegravir y lamivudina en pacientes con supresión viral mantiene la eficacia y es bien tolerado. Este régimen de mantenimiento podría ser una opción rentable para los pacientes con riesgo de interacciones farmacológicas o que necesiten evitar el impacto negativo sobre las comorbilidades o las toxicidades específicas de ciertos fármacos antirretrovirales.

OBJETIVO 3: En las PVVIH virológicamente suprimidas, evaluar la no-inferioridad de la terapia dual con dolutegravir/lamivudina con respecto a la terapia triple en cuanto a la eficacia virológica y seguridad.

Trabajo 4: Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial.

Además de la evaluación de la pauta 2DR con dolutegravir más lamivudina en vida real, he investigado su rendimiento en el contexto de un ensayo clínico (tercer objetivo de la tesis) donde, después de 48 semanas de seguimiento, el cambio a una terapia basada en dolutegravir más lamivudina resultó ser no inferior a mantener el régimen triple estándar, con un margen de no-inferioridad del 8%. Muy pocos participantes tuvieron fallo virológico y con un nivel de ARN del VIH bajo en el momento del fallo. El fracaso virológico se asoció con una adherencia sub-óptima en ambos grupos. No se detectaron mutaciones de resistencia a los fármacos del estudio en los participantes con fallo virológico definido por el protocolo en la terapia dual, lo que respalda la alta barrera genética de la combinación de fármacos (23). No encontramos diferencias en la eficacia según el tipo de tercer fármaco o ITIAN al inicio del estudio, recuento de células CD4, sexo o edad. La presencia de *blips* no se asoció a fallo virológico.

Los resultados del estudio DOLAM respaldan los resultados del estudio TANGO y otros estudios más pequeños (13–16). El estudio DOLAM incluyó sin restricciones a adultos con VIH en cualquier terapia triple y la terapia de combinación dual se administró como dos comprimidos separados, explorando así de manera más amplia la aplicabilidad de la estrategia de cambio. Aunque aproximadamente dos de cada tres participantes asignados a dolutegravir más lamivudina provenían de regímenes antirretrovirales de una sola pastilla, el cambio no afectó negativamente la adherencia ni los resultados virológicos. Se ha demostrado previamente que el cambio de la terapia triple a dolutegravir más emtricitabina conduce a una mejora en las puntuaciones de calidad de vida (16). El modelo matemático ha sugerido que el

régimen de terapia dual de dolutegravir más lamivudina sería rentable y económico en los EE. UU. (24).

La seguridad de dolutegravir más lamivudina en el estudio DOLAM fue consistente con el perfil de seguridad informado previamente en estudios de primera línea y estudios de cambio. La mayoría de los efectos adversos fueron leves o moderados. Hubo números casi idénticos de participantes con al menos un efecto adverso o efectos adversos generales en ambos grupos. Este hallazgo es sobresaliente como un estudio de cambio, en el que los participantes del grupo de estudio se exponen a un nuevo medicamento mientras que los del grupo de control continúan con un medicamento previamente tolerado (25).

Aunque no observamos cambios significativos en la glucosa y los lípidos en ayunas entre los grupos en general, los participantes en regímenes triples basados en tenofovir disoproxil fumarato o tenofovir alafenamida revelaron efectos opuestos significativos sobre el colesterol total y el colesterol LDL de acuerdo con informes anteriores (26). Hubo una reducción esperada en la tasa de filtración glomerular estimada en el grupo de dolutegravir más lamivudina, debido al menos en parte a la inhibición de la secreción de creatinina tubular por dolutegravir sin afectar la filtración glomerular en sí (27).

El peso de los participantes aumentó significativamente más en el grupo de terapia dual que en el grupo de terapia triple, de acuerdo con los resultados del estudio SIMPL'HIV (16). Cabe destacar que el aumento de peso fue significativo cuando los participantes estaban en regímenes triples que contenían tenofovir disoproxil fumarato o inhibidores de la integrasa. En adultos con VIH sin tratamiento previo con antirretrovirales, se ha asociado un mayor aumento de peso con los inhibidores de la integrasa en general, y más específicamente con dolutegravir y bictegravir, que con otros fármacos ancla, y con tenofovir alafenamida que con otros ITIAN (28). Aunque aún se desconocen las tendencias a largo plazo y las posibles implicaciones clínicas del aumento de peso a las 48 semanas detectado en pacientes que cambiaron a dolutegravir más lamivudina, no observamos ninguna correlación entre los cambios de peso y los cambios en los parámetros metabólicos.

No hubo diferencias entre los grupos en los cambios en la calidad del sueño. La puntuación del índice de calidad del sueño de Pittsburg se ha validado en adultos con

VIH y hemos mostrado resultados discriminatorios en estudios controlados aleatorios anteriores (27). El inicio de un tratamiento que contiene dolutegravir se ha asociado con un mayor riesgo de síntomas neuropsiquiátricos, siendo el más específico el insomnio (29). Los informes de insomnio en personas con VIH que recibían tratamiento con dolutegravir eran frecuentes cuando dolutegravir estuvo clínicamente disponible. Sin embargo, los principales ensayos clínicos (7,8,13,14,30–32) no han encontrado ningún efecto clínico sustancial de la terapia que contiene dolutegravir sobre el sueño.

Este estudio no es exento de limitaciones. El diseño de etiqueta abierta podría haber dado lugar a un sesgo de verificación; sin embargo, debido a que el resultado primario y muchos criterios de valoración secundarios se midieron de manera objetiva, era menos probable que ocurriera un sesgo de verificación que si hubieran sido medidas subjetivas. Justificamos y elegimos un margen de no inferioridad del 8%, que es más alto que el 4% recomendado por las principales agencias de salud, pero pudimos demostrar la no inferioridad del cambio de dolutegravir más lamivudina en relación con la terapia triple estándar usando este margen del 8%. El diseño en dos fases hizo que el ensayo durara más que si hubiéramos hecho el ensayo en una sola fase. Aunque los métodos fueron similares en ambas fases, el manejo real del fallo virológico en los participantes asignados a la terapia dual probablemente difirió del planeado originalmente debido a que el conocimiento clínico y la confianza en la combinación dual de dolutegravir más lamivudina aumentaron con el tiempo. Dolutegravir y lamivudina se tomaron como medicamentos separados porque la combinación fija no estuvo disponible durante el período de estudio; aunque la adherencia a la combinación dual fue alta durante todo el seguimiento, podría haber sido aún mejor con una combinación de dosis fija. Como la mayoría de los participantes eran hombres blancos o latinos, los resultados de este estudio deben interpretarse con precaución en mujeres o personas de otras razas o etnias. No evaluamos la dieta ni el ejercicio físico, aunque el diseño aleatorizado debería haber evitado cualquier posible desequilibrio entre los grupos. Los resultados del estudio DOLAM han sido confirmado en otro ensayo clínico de diseño similar, el estudio SALSA (106), aunque de carácter multicéntrico internacional y con un tamaño muestral doble que el del estudio DOLAM.

OBJETIVO 4:

Realizar una aproximación multi-ómica, que incluya proteómica, metabolómica y lipidómica, para tener una mejor comprensión de las vías metabólicas que podrían verse afectadas en la simplificación terapéutica a dolutegravir más lamivudina, en el contexto del estudio de los objetivos 3.

Trabajo 5: Multiomics plasma effects of switching from triple antiretroviral regimens to dolutegravir plus lamivudine

El estudio DOLAM (vinculado al objetivo 3), de forma similar a otros ensayos clínicos aleatorizados como TANGO o SALSA, mostró que cambiar de 3DR a 2DR en una selección de adultos con VIH con supresión virológica es virológicamente no inferior y tan seguro como continuar 3DR (75) (106). Sin embargo, el dolutegravir se ha asociado con aumento de peso en personas con VIH tanto naïves como experimentadas y hay preocupación de que también podría estar asociada con diabetes y enfermedad cardiovascular (107) (108). En el estudio DOLAM, las personas con pautas 2DR aumentaron significativamente de peso y se observaron más personas con sobrepeso u obesas a las 48 semanas en comparación con los que continuaban la pauta 3DR, pero no pudimos detectar cambios significativos en la grasa corporal, masa magra, o densidad mineral ósea (DMO) entre brazos (109). Aprovechando los enfoques ómicos para una mejor comprensión del metabolismo celular, intentamos explorar si había alguna alteración molecular plasmática afectada por el cambio de 3DR a 2DR.

La combinación de proteómica no dirigida, metabolómica (compuestos polares) y lipidómica evidenció que el cambio de 3DR a 2DR se relacionó con algunas perturbaciones metabolómicas circulantes. Específicamente, el enfoque multiómico identificó dos proteínas, un metabolito y un lípido expresado diferencialmente en el grupo 2DR en comparación con 3DR. Los análisis de correlación identificaron una asociación entre la regulación de estas cuatro moléculas en el grupo 2DR. La

combinación de proteómica no dirigida, metabolómica (compuestos polares) y lipidómica evidenció que el cambio de 3DR a 2DR se relacionó con algunas perturbaciones metabolómicas circulantes. Específicamente, el enfoque multiómico identificó dos proteínas, un metabolito y un lípido expresado diferencialmente en el grupo 2DR en comparación con 3DR. Los análisis de correlación identificaron una asociación entre la regulación de estas cuatro moléculas en el grupo 2DR. A las 48 semanas de seguimiento, los participantes que recibieron 2DR mostraron una mayor concentración plasmática de N-acetilmuramoil-L-alanina amidasa (Q96PD5) y proteína de unión al factor de crecimiento insulínico 3 (A6XND0) en comparación con 3DR. Q96PD5 es una proteína codificada por la proteína del reconocimiento del peptidoglycan (PGLYRP2), un gen de la familia de las proteínas del reconocimiento del peptidoglycan (PGLYRPs). PGLYRPs son proteínas que se conservan de insectos a mamíferos que actúan en la inflamación y las respuestas inmunes independientemente de sus actividades bactericidas y enzimáticas (110). Específicamente, PGLYRP2 ha mostrado propiedades antiinflamatorias y pro-inflamatorias, probablemente relacionado con su vínculo con el factor de transcripción familia factor nuclear κB (NF-κB) (111–114). El factor nuclear κB (NF-κB) representa una familia de factores de transcripción inducibles involucrados en la regulación de genes pertenecientes a vías inmunes e inflamatorias (incluyendo citoquinas, quimioquinas e inflamatorios) cuya expresión se ha relacionado con la vía de señalización p53 (114) (115). Nuestros resultados sugieren una posible asociación entre las proteínas expresadas diferencialmente asociadas con la simplificación de la terapia y la vía de señalización p53 (114) (115). Nuestros resultados sugieren una posible asociación entre las proteínas expresadas diferencialmente asociadas con la simplificación de la terapia y la vía de señalización p53. Un estudio reciente también mostró una correlación positiva entre PGLYRP2 y ApoB/A1 en pacientes con lupus eritematoso sistémico, lo que sugiere un papel potencial de PGLYRP2 en la dislipemia y los riesgos de enfermedad cardiovascular en pacientes con lupus eritematoso sistémico (116). En el presente estudio, no se encontró asociación entre Q96PD5 y las especies lipídicas identificadas diferencialmente entre grupos (TG48:0), pero Q96PD5 resultó estar significativamente relacionado con la proteína 3 (A6XND0), cuya expresión génica (IGFBP3) estaba relacionado previamente con el metabolismo lipídico

(117). En el suero, IGFBP-3 es la proteína más abundante de la familia IGFBP que funciona en un factor de crecimiento similar a la insulina (IGF)-dependiente (entrega de IGF y activación de IGF señalización aguas abajo), así como en un IGF independiente (interacción con proteínas) manera (118). Aunque algunos estudios revelaron su papel en la regulación metabólica, el papel exacto de IGFBP3 en la glucosa y el metabolismo de lípidos sigue siendo confuso, incluso en personas que viven con VIH (118) (119). Algunos estudios sugirieron que el IGFBP3 sérico podría estar involucrado en la progresión de la enfermedad del VIH y relacionado con la resistencia a la insulina, pero por otro lado, tres meses de tratamiento con IGF-I/IGFBP-3 mejoraron la tolerancia a la glucosa y triglicéridos en ayunas en hombres que viven con el VIH con exceso de adiposidad abdominal y resistencia a la insulina (120–122). Según nuestros resultados, la función de un aumento de la concentración plasmática de IGFBP3 en el grupo 2DR sigue siendo incierta, ya que no se observaron alteraciones metabólicas significativas entre los grupos 3DR y 2DR a las 48 semanas de aleatorización del tratamiento (109). Sin embargo, es importante destacar que nuestros resultados sugieren una relación positiva entre los niveles de A6XND0 y alanina plasmática, y entre los niveles de alanina plasmática y triglicéridos (48:0). A nivel molecular, los participantes del grupo 2DR mostraron un aumento de las concentraciones plasmáticas tanto en alanina plasmática circulante como en TG (48:0) en comparación con el grupo 3DR. El aumento de las concentraciones de alanina circulante podría indicar una alteración en el ciclo glucosa-alanina en el que la alanina se puede sintetizar a partir del piruvato derivado del músculo esquelético a través de la reacción enzimática de la alanina aminotransferasa (ALT) y luego transportado al hígado para ser utilizado para la gluconeogénesis. La alta concentración de alanina circulante se ha relacionado con el riesgo de diabetes tipo II incidente, mientras que las tasas reducidas de ciclo de glucosa-alanina se han asociado con la regulación de la oxidación mitocondrial hepática (123) (124). Con respecto al triglicérido monoácido TG (48:0), estudios previos han considerado el TG saturado (48:0) como una especie lipídica clave en los paneles de biomarcadores relacionados con el contenido de grasa hepática (125) (126). Este estudio tenía limitaciones. El análisis multiómico se realizó desde el inicio hasta 48 semanas después de la aleatorización, periodo en el que no se evidenciaron posibles consecuencias metabólicas del aumento de peso. La integración de datos

multiómico puede traer varios problemas y requerir varias atenciones para combinar datos de alto rendimiento obtenidos de diferentes capas moleculares. Reducir la heterogeneidad entre las tres tecnologías ómicas diferentes aplicadas y la dificultad de interpretar modelos de sistemas multicapa derivados de la combinación de datos ómicos y datos no ómicos (datos clínicos), se prefirió un análisis único para el presente trabajo centrado en la simplificación antirretroviral. Sería de gran interés realizar un análisis multiómico después de un seguimiento más largo. Como punto fuerte, este estudio proporciona información novedosa y valiosa, ya que no se ha publicado previamente ningún análisis multiómico que investigue cambios después de cambiar de 3DR a 2DR.

Acerca de la atención a las PVVIH y prevención del VIH y otras infecciones de trasmisión sexual.

En el transcurso de la investigación de mi tesis apareció en nuestras vidas de forma inesperada una nueva pandemia causada por un nuevo virus, el SARS-CoV-2. La afectación no fue solo en nuestras vidas como ciudadanos, sino que afectó el desarrollo y los objetivos de esta tesis doctoral. Esta situación de crisis representó también una oportunidad para investigar cómo afectaron las epidemias de COVID-19 la prevención y atención clínica de las personas que viven con VIH y la detección y el diagnóstico de la infección por el VIH y otras enfermedades de transmisión sexual en el ámbito del Hospital Clínic.

OBJETIVO 5: Evaluar el impacto de las epidemias de COVID-19 en la prevención y atención clínica de las PVVIH y en la detección y el diagnóstico de la infección por el VIH y otras enfermedades de transmisión sexual, en el ámbito del Hospital Clínic de Barcelona.

Trabajo 6: Impact of coronavirus disease 2019 epidemics on prevention and care for HIV and other sexually transmitted infections.

El trabajo se centró en comparar los parámetros de interés entre el período marzo-diciembre 2020 con respecto a los mismos meses de 2019 y como era de esperar (127) (128) observamos una disminución de las actividades presenciales pre-programadas, como las visitas de profilaxis antes o después de la exposición al VIH o las visitas ambulatorias en personas con VIH. Es de destacar que una proporción sustancial (39%) de las consultas ambulatorias durante la epidemia de COVID-19 se realizó de manera virtual, lo que evitó un impacto negativo mucho mayor en la atención del VIH.

A pesar de la disminución de las actividades pre-programadas, la cantidad de pruebas diagnósticas del VIH realizadas y la cantidad de pruebas de monitoreo de ARN del VIH en plasma en personas con VIH en rutina asistencial se mantuvieron estables en 2020 en relación con 2019, lo que sugiere esfuerzos específicos en mantener un mínimo de pruebas y atención del VIH. Aunque el número de diagnósticos de VIH *de novo* en 2020 disminuyó, las personas recién diagnosticadas mostraron recuentos de células CD4+ significativamente menores y una enfermedad más avanzada, lo que sugiere un retraso y una probable subestimación en el diagnóstico. Además, las personas con VIH mostraron peores resultados de salud no virológica y una mayor mortalidad en 2020 que en 2019. Detectamos una disminución significativa en los cambios de los regímenes antirretrovirales. Dado que las tasas de personas con viremia del VIH no suprimida entre ambos períodos se mantuvieron estables, suponemos que esta disminución podría haber afectado preferentemente a las personas con viremia del VIH suprimida, lo que sugiere que la optimización de la terapia probablemente pasó a un segundo plano. El colesterol total, el colesterol LDL y los triglicéridos aumentaron, mientras que el colesterol HDL disminuyó, lo que sugiere un peor estado metabólico. Aunque el peso no estaba disponible en la cohorte, el perfil de cambios en los lípidos puede ser consistente con el aumento de peso (129) (130). El confinamiento por la COVID-19 promovió cambios dietéticos poco saludables y aumentos en el peso corporal a nivel poblacional (131) (132). La dislipidemia promueve la inflamación de bajo nivel y la activación inmunitaria crónica (133). Como consecuencia, los cambios observados en los lípidos, si persisten en el tiempo, podrían contribuir aún más a aumentar el riesgo de enfermedad cardiovascular en la cohorte de personas con VIH. El número de muertes en la cohorte de personas con VIH fue casi tres veces mayor en 2020 con respecto a 2019. Paradójicamente, el número de ingresos hospitalarios

tendió a disminuir. El menor número de admisiones hospitalarias en la cohorte de VIH podría deberse, al menos en parte, al número disparado de admisiones debido a COVID-19 en la población general. Cabe destacar que casi el 40% de las muertes en la cohorte de VIH en 2020 tenía una prueba de laboratorio confirmatoria de COVID-19 en el momento de la muerte. La COVID-19 explica en parte el exceso de muertes en la cohorte de VIH en 2020 en relación con 2019, aunque el número de muertes no relacionadas con la COVID-19 (en particular, complicaciones cardiovasculares) en 2020 aún fue mayor que en 2019. La COVID-19 puede asociarse con una mayor mortalidad en personas con VIH que en la población general (134). El aumento de la mortalidad por causas ajenas a la COVID-19 puede haber sido promovido, al menos en parte, por trastornos en la sociedad que redujeron o retrasaron el acceso a la atención médica y los determinantes sociales de la salud (p. ej., empleos, ingresos, seguridad alimentaria) (135–137). Nuestros hallazgos respaldan aún más que la mortalidad general y no relacionada con COVID-19 en personas con VIH puede haber aumentado durante las pandemias de COVID-19 también. El número de pruebas de hepatitis B y el número de diagnósticos de hepatitis B *de novo* se mantuvieron estables. La incidencia de la hepatitis B en España es muy baja (138). Por el contrario, el número de pruebas de hepatitis C disminuyó, pero también disminuyó el número de diagnósticos de hepatitis C *de novo* entre los examinados. Estos resultados contrastan con los de los modelos que predicen un aumento de casos no diagnosticados de hepatitis C en España durante la epidemia de COVID-19 (139), pero están de acuerdo con datos reales recientes de EE. UU. (140). El diagnóstico de hepatitis C *de novo* en nuestro medio se ha relacionado más comúnmente con prácticas sexuales de alto riesgo y consumo sexualizado de sustancias (141). Es posible que estas prácticas se hayan visto más afectadas por la epidemia que otros encuentros sexuales. Las pruebas de *Treponema pallidum* más comúnmente realizadas fueron las pruebas VDRL, seguidas de IgM y finalmente PCR. El número de pruebas realizadas disminuyó para VDRL, se mantuvo estable para IgM y aumentó para PCR. Aunque el número total de diagnósticos de sífilis activa se mantuvo sin cambios, la positividad del diagnóstico de PCR casi se duplicó entre 2019 y 2020. Las pruebas de *Neisseria gonorrhoeae* y *Chlamydia trachomatis* se realizaron exclusivamente con PCR. De manera similar a las pruebas de PCR para *Treponema pallidum*, las pruebas de PCR para *Neisseria gonorrhoeae* y

Chlamydia trachomatis aumentaron en 2020 en relación con 2019. Los casos de gonorrea activa y los diagnósticos de infección activa por clamidia aumentaron en 2020, así como los casos de sífilis activa diagnosticados por PCR. Las pruebas de PCR se han utilizado cada vez más para detectar infecciones de transmisión sexual (142). Son más rápidas y puede que su disponibilidad fuera mayor que las pruebas estándar durante el período de la pandemia. El aumento del diagnóstico por PCR de infecciones de transmisión sexual en 2020 en relación con 2019 es preocupante y sugiere que la transmisión general no se redujo a pesar de las restricciones pandémicas. Este hecho sugiere además que el riesgo real de transmisión del VIH también podría haber sido mayor y que una proporción de diagnósticos de VIH *de novo* pueden pasar desapercibidos y evolucionar a una etapa más avanzada. Durante los primeros meses de la pandemia de COVID-19, las pruebas para infecciones de transmisión sexual disminuyeron probablemente debido a las interrupciones en los servicios de atención médica y pruebas de infecciones de transmisión sexual (143) (144). El acceso reducido a pruebas y diagnósticos en los primeros meses de las pandemias puede haber llevado a algunas personas a propagar la infección sin saberlo, como lo demuestran las tasas más altas de infecciones de transmisión sexual en los últimos meses de 2020 (145–147).

Este estudio tiene limitaciones. Usamos 2019 como una referencia reciente conveniente para las comparaciones con 2020, pero la incidencia del VIH y otras infecciones de transmisión sexual en la ciudad de Barcelona ha ido cambiando con el tiempo (148). Es posible que la reducción de nuevos diagnósticos de VIH no solo se haya visto afectada por las epidemias, sino también por el inicio del programa de profilaxis previa a la exposición al VIH. Al utilizar una base de datos administrativa anonimizada, algunos pacientes pueden haber contribuido con múltiples puntos de datos debido a posibles exposiciones repetidas de alto riesgo o un acceso más fácil a un entorno clínico, lo que sesga los hallazgos. No pudimos proporcionar datos sobre otras infecciones de transmisión sexual que se diagnostican principalmente clínicamente, como las verrugas genitales o el herpes. Una proporción desconocida de pruebas de VIH y hepatitis B y C se realizaron de forma rutinaria en pacientes hospitalizados con neumonía por COVID-19 como parte del protocolo de manejo del Ministerio de Salud de España (149); aunque esto podría haber contribuido al

diagnóstico de algunas infecciones *de novo*, aumentó artificialmente el número de pruebas de detección realizado. No hemos incluido información sobre resistencia antimicrobiana y manejo terapéutico del VIH y otras infecciones de transmisión sexual. En resumen, detectamos menos infecciones por VIH y hepatitis C y más infecciones por gonorrea y clamidia durante las epidemias de SARS-CoV-2 que en el año anterior a pesar de que las pruebas en general fueron similares o incluso más altas. Sin embargo, las infecciones por VIH *de novo* mostraron una enfermedad más avanzada. Es posible que el número de infecciones por VIH *de novo* sea mayor de lo detectado. Hubo menos visitas programadas para la atención del VIH, pero esto no se tradujo en un peor control virológico. Sin embargo, las personas con VIH tuvieron menos cambios en la prescripción de antirretrovirales, peores lípidos plasmáticos y, lo que es más importante, un exceso de mortalidad debido en gran parte a no solo a COVID-19 sino también a otras causas no relacionadas con COVID-19. Nuestros hallazgos sugieren que, en los próximos años, los servicios de atención médica deben estar preparados para responder al impacto de la COVID-19 en las pruebas y la atención del VIH y las infecciones de transmisión sexual.

OBJETIVO 6: Evaluar la calidad percibida por los usuarios de la atención recibida en la Unidad de VIH del Hospital Clínic, conocer el grado de satisfacción de los usuarios con el cuidado que se les presta e identificar posibles áreas de mejora.

Trabajo 7: Perception of quality of care using patient reported experience measures (PREMs) in a cohort of adults with HIV: A cross-sectional study.

La disponibilidad y eficacia del tratamiento antirretroviral ha permitido alcanzar las metas propuestas por la Organización Mundial de la Salud para el control de la infección por VIH para el año 2020 (150) en nuestra cohorte. En concreto, de las 5493 personas que viven con una infección por VIH seguidas en la Unidad de VIH del Hospital Clínico de Barcelona, el 99% estaba recibiendo tratamiento antirretroviral, y el 94% presentaba carga viral indetectable durante el periodo de estudio. De acuerdo con la redefinición de éxito terapéutico propuesta por la comunidad científica (59),

que incluye la calidad de vida como cuarta meta a alcanzar en el 90% de las personas que viven con VIH, analizamos la calidad de atención que brindamos en nuestra unidad revisando el modelo de atención que se ofrece a los usuarios e incorporando la percepción de los pacientes a través de una encuesta electrónica, con el objetivo final de mejorar el servicio. Primero, la tasa de respuesta a la invitación en línea para participar en el estudio fue notablemente alta considerando que las personas no habían sido informadas previamente, ni el proyecto fue anunciado públicamente. Un tercio de los candidatos respondieron a nuestra solicitud, porcentaje muy similar al obtenido en una encuesta en formato electrónico realizada en otra área terapéutica del hospital (151). Estos datos sugieren que las PVVIH son sensibles a colaborar en un proyecto que pueda ayudar a mejorar su atención.

El perfil demográfico de las personas que respondieron a la encuesta difería ligeramente del perfil medio de las personas con VIH de la unidad: mayor porcentaje de personas de origen español y estudios superiores entre los encuestados. Estas sutiles diferencias podrían indicar un sesgo de selección sobre las personas incluidas en el estudio. La brecha digital existente en la población atendida en nuestra unidad puede explicar que algunos usuarios no se sintieran cómodos con el formato electrónico y pone de manifiesto la necesidad de combinar diferentes estrategias a la hora de presentar la encuesta que nos permita obtener respuestas de un mayor número de usuarios. En general, destacamos el alto porcentaje de respuestas positivas a la mayoría de afirmaciones, con puntuaciones medias mayores de 5, especialmente para aquellas afirmaciones que evalúan el manejo de la información durante la consulta y la percepción de la calidad de la visita. Así, la valoración global de la atención recibida ha sido de 5.4 puntos sobre 6. Sin embargo, debemos destacar que hay cuestiones relacionadas con la gestión del espacio y el tiempo peor valoradas y debemos ver esta información como una oportunidad para mejorar nuestro servicio. El tiempo de espera previo a la consulta fue reportado como inadecuado por casi la mitad de los usuarios, por lo que la afirmación correspondiente fue la de menor puntaje en la encuesta. Del mismo modo, un tercio de los usuarios consideró que el entorno en el que se llevó a cabo la consulta fue inadecuado. Este resultado indica la necesidad de remodelar este espacio, tomando en consideración la opinión de los usuarios para co-crear ambientes amigables donde se sientan cómodos y se garanticen

una buena experiencia. El nueve por ciento (9%) de los encuestados expresó su desacuerdo con el rol que tienen en la toma de decisiones. Aunque se trata de un porcentaje pequeño, estos datos ponen de manifiesto la necesidad de seguir trabajando en un modelo centrado en el paciente donde los pacientes perciban que sus opiniones son escuchadas. Hay pocos datos publicados sobre la satisfacción reportada por las PVVIH con respecto a la atención que reciben (152) (153) en general, la satisfacción es favorable, similar a nuestros datos, pero los resultados son difíciles de comparar dado que se utilizaron diferentes PREM. Además de la encuesta, hemos utilizado el Net Promoter Score (NPS), una herramienta sencilla y validada que permite un análisis rápido y sencillo de si se están haciendo bien las cosas en un trabajo o servicio. Si bien esta herramienta fue desarrollada hace 2 décadas (154), su uso en el campo de la salud ha sido más reciente y se enfoca en el benchmarking de servicios privados. Hasta la fecha, no existen datos en la literatura sobre su uso en el cuidado de las personas con VIH. Un valor de Net Promoter Score superior a 50, como el obtenido en nuestro estudio, se considera un valor alto y es sinónimo de una puntuación positiva. Valores similares a los obtenidos en este estudio, un NPS de 55, han sido reportados en estudios realizados en el sector privado de la salud (155) (156) de nuestro medio. Nos llama la atención que los encuestados españoles fueran más críticos en su valoración y, por tanto, bajaran significativamente el porcentaje de encuestados clasificados como promotores. Por el contrario, las respuestas de origen no español fueron más favorables. Somos conscientes de que la simple recopilación de datos sobre la experiencia de los pacientes no es suficiente, y que es necesario tomar medidas, como lo recomiendan los expertos a través de PREM (157). El propósito de este estudio fue identificar áreas que necesitan mejorar, y evaluaremos NPS anualmente para verificar si alguna mejora impacta en la calidad de vida relacionada con la salud percibida por los usuarios. Este estudio tiene algunas limitaciones. En primer lugar, un sesgo de autoselección puede haber afectado nuestros resultados, ya que solo un tercio de los pacientes respondieron y su perfil sociodemográfico difería ligeramente del perfil promedio de toda la cohorte de PVVIH que acudió a nuestro hospital, como se mencionó anteriormente. En segundo lugar, no tenemos experiencia previa en grandes encuestas electrónicas enviadas a nuestros pacientes con las que comparar la tasa de respuesta. Finalmente, hay pocos datos publicados sobre PREM en

personas que viven con VIH para comparar nuestros hallazgos, y no hay datos sobre NPS en el campo específico de la infección por VIH. Vemos este estudio como un punto de partida para futuras investigaciones en esta área.

Relacionados con el uso de la tecnología y la satisfacción de los profesionales de la investigación en VIH.

Toda investigación cuantitativa requiere recopilar datos, procesarlos y analizarlos. La colección y manejo de datos durante un estudio de investigación es una fase importante que frecuentemente se apoya en algún sistema informatizado, herramienta tecnológica que facilita las tareas a desempeñar y donde intervienen distintos profesionales que actúan como usuarios de ese sistema. Por tanto, obtener datos de valor depende, entre otros factores, de la interacción entre ese sistema informatizado y los profesionales usuarios del sistema mismo.

OBJETIVO 7: Evaluar la usabilidad del cuaderno electrónico de recogida de datos (CRDe) que se implementará en el sistema REDCap y la satisfacción de los profesionales usuarios e identificar posibles áreas de mejora.

Trabajo 8: Usability and user's satisfaction of an electronic case report data implemented in the REDCap system in the HIV clinical research context: the use case of DOLAM clinical trial.

En la actualidad, los datos en la investigación biomédica se consideran de alto valor. Como resultado de las mejoras en tecnología de la información durante los últimos 10-15 años, existen varios sistemas que proporcionan las capacidades de captura electrónica de datos necesarias para preservar la integridad, precisión y confiabilidad de los datos. En nuestra Unidad de VIH, evaluamos y elegimos el sistema REDCap para implementar el cuaderno electrónico de recogida de datos (CRDe) de nuestros estudios. Esto representó un avance en innovación en la forma en que recopilamos y gestionamos los datos. Los resultados de este estudio mostraron cómo cuestionarios validados sobre la usabilidad del sistema y la satisfacción percibida pueden emplearse

en el contexto de estudios de investigación biomédica y, específicamente, de un CRDe del campo del VIH. Los involucrados en responder a los cuestionarios fueron profesionales de diferentes ámbitos que típicamente colaboran en ensayos clínicos, y sus características también pueden ser relevantes para arrojar luz sobre qué perfil podría necesitar más apoyo para mejorar su interacción con el sistema y completar satisfactoriamente sus tareas.

Aunque el CRDe fue diseñado e implementado para satisfacer las necesidades de todas las partes interesadas que participaban en el ensayo, nuestros resultados señalaron que la usabilidad percibida variaba según el rol de los usuarios, siendo el personal de entrada de datos (principalmente enfermeras) aquellos que expresaron la menor usabilidad y tres de cada cinco fueron detractores o pasivos. En nuestra muestra, solo 3 usuarios (16%) se consideraron poco familiarizados con la informática y dos de ellos mostraron una satisfacción muy alta (SUS>90) y pertenecían al grupo promotor. Sin embargo, casi la mitad de los profesionales nunca habían utilizado el sistema antes del estudio DOLAM, la satisfacción fue buena tanto en usuarios experimentados como no experimentados, incluso con un valor medio más alto en no experimentados, lo que indica que quizás aquellos con algo de experiencia esperaban un mejor rendimiento del CRDe. Considerando el NPS modificado, todos los médicos y dos enfermeras de cada cinco fueron pasivos. El rango de edad de los usuarios fue demasiado estrecho (de 25 a 45 años) para observar alguna diferencia en usabilidad y satisfacción entre usuarios más jóvenes y mayores. Por lo tanto, los resultados del *System Usability Scale* (SUS) y *Net Promoter Score* (NPS) mostraron la importancia de prestar más atención a las necesidades de ciertos roles profesionales, en nuestro caso, el personal de entrada de datos, en el diseño e implementación del CRDe. Es posible que se requieran algunas estrategias de apoyo, como sesiones de formación dirigidas a diferentes perfiles de usuarios y un apoyo más cercano en la interacción usuario-sistema durante el desarrollo del estudio.

Para tener en cuenta las diferentes barreras psicológicas de la escala del 0 al 10 en España y evitar subestimar el NPS global, consideramos más plausible considerar a los profesionales que respondieran con 6 (una buena calificación) como pasivos en lugar de detractores, y a aquellos que obtuvieran una puntuación de 8 (una calificación muy buena) como promotores en lugar de pasivos. Así, el NPS modificado aumentó de 21.1

a 42.1. Estamos de acuerdo con Krol et al. (158) en que una forma de obtener una interpretación más consistente sería etiquetar todas las categorías de respuesta (no solo las dos en los extremos) en lugar de la distribución de detractores, pasivos y promotores aplicada después de la recolección de datos. En nuestra opinión, esas etiquetas serían útiles, sobre todo en nuestro contexto, cuando en una escala de calificación de 10 puntos, el resultado de aprobación es 5.

La implementación del CRDe electrónico en el sistema REDCap, realizada por la estadística del proyecto, representó un beneficio neto para el presupuesto del proyecto, ya que se ahorró el costo total de los CRD en papel, así como el tiempo necesario para completarlos manualmente. Además, el costo total del proyecto no sufrió costos adicionales significativos derivados del sistema informático adoptado, ya que el sistema REDCap estaba disponible sin cargo para organizaciones sin fines de lucro que se unen al consorcio REDCap, teniendo que asumir solo el costo de alojamiento y mantenimiento del servidor.

Nuestro estudio presenta algunas limitaciones: el tamaño muestral incluyó a pocos profesionales y puede no ser capaz de detectar diferencias estadísticas entre las características de los usuarios y los resultados, aparte de proporcionar estimaciones imprecisas. Además, todos nuestros encuestados fueron mujeres, lo que limita la generalización de los resultados.

El propósito de esta tesis fue investigar desde distintas vertientes la mejora de la calidad de vida de las personas que viven con una infección por VIH. Evaluamos estrategias de simplificación del tratamiento antirretroviral tanto en una gran cohorte de PVVIH como en el contexto de ensayos clínicos, centrándonos en las características clínicas asociadas con el uso de 2DR, en la efectividad y seguridad del tratamiento con dolutegravir/lamivudina, y también en la viabilidad, eficacia virológica y tolerabilidad de terapias duales como raltegravir/lamivudina. Según nuestros hallazgos, los regímenes 2DR son efectivos, seguros y presentan tasas de discontinuación comparables a las terapias triple estándar. Además, los análisis multi-ómicos proporcionaron una mejor comprensión de las vías metabólicas afectadas por estos tratamientos. La pandemia mundial de COVID-19 ocurrida en el decurso de la tesis, brindó la oportunidad de investigar cómo afectó a la prevención y atención del VIH,

poniendo de manifiesto una disminución en el diagnóstico y atención de infecciones de transmisión sexual debido a la inevitable reducción de recursos y modificación de protocolos sanitarios. También se investigó la calidad percibida de la atención sanitaria por parte de las personas que viven con VIH, identificando áreas de mejora como la comunicación y accesibilidad de los servicios, lo que es fundamental para incrementar la satisfacción del paciente y mejorar los resultados de salud. Finalmente, la tesis evaluó la usabilidad y satisfacción de los profesionales de la salud con el cuaderno electrónico de recogida de datos (CRDe) implementado en el sistema REDCap, destacando su efectividad y facilidad de uso, aspectos que son la base de una buena gestión de datos y que revierten directamente en la calidad de la investigación.

Conclusiones

Ada Byron Lovelace *(Matemática, 1815-1852). Desarrolló el primer algoritmo apto a ser procesado por una máquina (la máquina analítica), gracias a unas secuencias numéricas aplicadas a unas tarjetas perforadas. Por ello es considerada la primera persona programadora de ordenadores.*

"La perseverancia es la virtud por la cual todas las otras virtudes dan su fruto." *Arturo Graf* *(Escritor, 1848-1913)*

"Con frecuencia he sido cuestionada, especialmente por las mujeres, sobre cómo podría conciliar la vida familiar con una carrera científica. Bueno, no ha sido fácil." *Maria Skłodowska-Curie* *(Física y química, 1867-1934)*

1.

En nuestro centro, un peor estado cardiometabólico o una mayor resistencia archivada fueron factores asociados con la inclusión de inhibidores de la integrasa o de la proteasa, respectivamente, en las pautas 2DR cuando aún no era de uso habitual.

2.

Un ensayo clínico piloto de 24 semanas sugirió que el cambio a raltegravir junto con lamivudina en personas con VIH con supresión viral mantiene la eficacia y es bien tolerado. Se requiere un estudio más amplio y de mayor duración para confirmar estos hallazgos.

3.

La pauta 2DR dolutegravir más lamivudina resultó ser una opción de simplificación eficaz y segura en personas seleccionados con VIH con supresión virológica en tratamiento antirretroviral triple.

4.

El cambio de un tratamiento antirretroviral triple a dolutegravir más lamivudina en personas con VIH virológicamente suprimidas se asoció a cambios moleculares potencialmente asociados con la inflamación e inmunoactivación y con el metabolismo de los lípidos y la glucosa, aunque su significación clínica es incierta.

5.

El impacto de la COVID-19 en las pruebas y la atención del VIH y las infecciones de transmisión sexual sugieren que los proveedores y las instalaciones deben aprovechar las lecciones aprendidas hasta ahora para mejorar aún más las estrategias de mitigación y establecer prioridades de atención tanto para la pandemia como para los períodos posteriores a la pandemia.

6.

El seguimiento de las medidas de experiencia reportadas (PREMs) por las personas con VIH que reciben atención ambulatoria activa en nuestro hospital permitió identificar la

percepción de los usuarios sobre la calidad de la atención recibida, determinar la tasa de satisfacción con la atención e identificar áreas de mejora.

7.

La evaluación de la usabilidad percibida y la satisfacción del usuario identificó áreas de mejora en la interacción usuario-sistema informático que es necesario abordar de manera dirigida según el tipo de usuario.

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