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Nuevas estrategias para mejorar la tolerabilidad del tratamiento antirretroviral y disminuir su impacto sobre las comorbilidades

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Nuevas estrategias para mejorar la tolerabilidad del tratamiento antirretroviral y disminuir su impacto sobre las comorbilidades

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Para optar al grado de Doctor por la Universidad de Barcelona

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Lista de abreviaturas

ABC: Abacavir.

ADN: Ácido desoxirribonucleico

ARN: Ácido ribonucleico

ARNm: ARN mensajero

Atripla: Comprimido a dosis fija de EFV/FTC/TDF

ATV: Atazanavir

AZT: Zidovudina

CoRIS: Cohorte de la Red Española de Investigación en sida

CV: Carga viral

d4T: Estavudina

DMO: Densidad mineral ósea

DTG: Dolutegravir

DXA: Absorciometría dual

EFV: Efavirenz

EMA: Agencia Europea de Medicamentos

ETR: Etravirina

EVG: Elvitegravir

FDA: Food and Drug Administration

FMR: Índice de masa grasa

FV: Fracaso virológico

HDL: Lipoproteínas de alta densidad

ICONA: Cohorte Italiana de pacientes Naive al TAR

IMC: Índice de masa corporal

INI: Inhibidor de la integrasa

IP/r: Inhibidores de la proteasa potenciados con ritonavir

ITIAN: Inhibidor de transcriptasa inversa análogo de nucleósido/nucleótido

ITINAN: Inhibidor de transcriptasa inversa no análogo de nucleósido

ITT: Análisis por intención de tratar

KVX: Abacavir/lamivudina

LDL: Lipoproteínas de baja densidad

LPV/r: Lopinavir/ritonavir

MRV: Maraviroc

NVP: Nevirapina

OMS: Organización mundial de la salud

ONUSIDA: Programa Conjunto de las Naciones Unidas sobre el VIH/Sida

RAL: Raltegravir

RPV: Rilpivirina

SAT: Tejido adiposo subcutáneo

SIDA: Síndrome de la inmunodeficiencia adquirida

SINIVIH: Sistema de información sobre nuevos diagnósticos de VIH

SNC: Sistema nervioso central

STR: Single Tablet Regimen

TAF: Tenofovir alafenamida

TAR: Tratamiento antirretroviral

TARGA: Tratamiento antirretroviral de alta eficacia

TC: Tomografía computarizada

TDF: Tenofovir disoproxil fumarato

TDF/FTC: Tenofovir/emtricitabina

VAT: Tejido adiposo visceral

VIH: Virus de la Inmunodeficiencia Adquirida

ZOL: Ácido zoledrónico

3TC: Lamivudina

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PREFACIO

La presente tesis, presentada para obtener el grado de Doctor por la Universidad de Barcelona es el resultado de ocho estudios llevados a cabo en el Servicio de Infecciones del Hospital Clínico de Barcelona, algunos de ellos en colaboración con otros hospitales.

Los ocho estudios se realizaron durante el contrato por parte de Fundació Clínic per a la Recerca Biomèdica

A continuación, se mencionan los artículos incluidos en dicha tesis, entre los que hay un póster publicado en una revista médica:

Artículo 1: ***"Improvement of lipoatrophy by switching from efavirenz to lopinavir/ritonavir".*** J. Rojas, M. Lonca, A. Imaz, V. Estrada, V. Asensi, C. Miralles, et al. HIV Medicine 2016; 17: 340-9. FI: 2,932. Q:

Artículo 2: ***"Effectiveness and safety of an abacavir/lamivudine1rilpivirine regimen for the treatment of HIV-1 infection in naive patients".*** A. Curran, J. Rojas, A. Cabello, J. Troya, A. Imaz, P. Domingo, et al. J Antimicrob Chemother 2016; 71: 3510–4. FI: 5,217.

Póster: ***"Effectiveness and tolerability of abacavir-lamivudine-nevirapine (ABC/3TC/NVP) in a multicentre cohort of HIV-infected, ARV-naive patients".*** D. Podzamczer, J. Rojas, I. Neves, E. Ferrer, J. Llibre, J.M. Leal, et al. Abstracts of the HIV

Drug Therapy Glasgow Congress 2014 Podzamczer D et al. Journal of the International AIDS Society 2014, 17(Suppl 3): 19773. FI: 5,131.

Artículo 3: ***"Zoledronic acid is superior to tenofovir disoproxil fumarate-switching for low bone mineral density in adults with HIV".*** J.F. Hoy, R. Richardson, P.R. Ebeling, J. Rojas, N. Pocock, S.J. Kerr, et al. AIDS 2018; 32: 1967-75. FI: 4,914.

Artículo 4: "Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression". J. Rojas, J.L. Blanco, M.A. Marcos, M. Lonca, A. Tricas, L. Moreno, et al. J Antimicrob Chemother 2016; 71: 1975–81. FI: FI: 5,217.

Artículo 5: "Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24-week analysis of the DOLAM randomized clinical trial". J.L. Blanco, J. Rojas, R. Paredes, E. Negredo, J. Mallolas, M. Casadella, et al. J Antimicrob Chemother 2018; 73: 1965–71. FI: FI: 5,217.

Artículo 6: "Tolerability of integrase inhibitors in a real-life setting". J. Peñafiel, E. de Lazzari, M. Padilla, J. Rojas, A. González-Cordon, J.L. Blanco et al. J Antimicrob Chemother 2017; 72 (6): 1752–9. FI: FI: 5,217.

Artículo 7: "A maintenance 3-day-per-week schedule with the single tablet regimen efavirenz/emtricitabine/tenofovir disproxil fumarate is effective and decreases sub-clinical toxicity" J. Rojas, J.L. Blanco, S. Sánchez-Palomino, M.A. Marcos, A.C. Guardo, A. González-Cordon, et al. AIDS 2018; 32: 1633-41. FI: 4,914.

1. INTRODUCCIÓN

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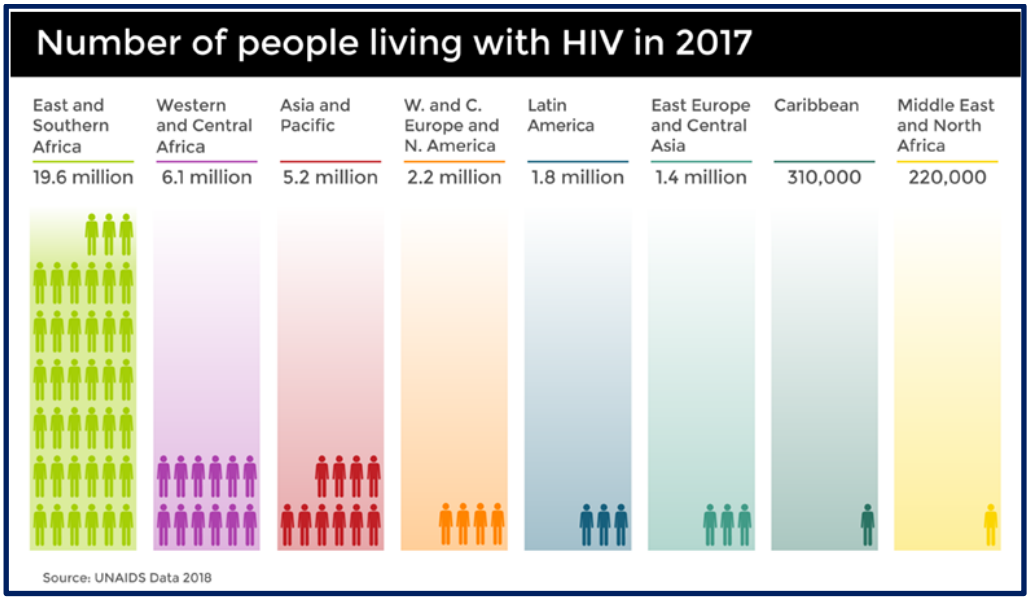
1.1- Epidemiología

La infección por el virus de la inmunodeficiencia humana (VIH) continúa siendo un problema importante de salud pública mundial. En 2017 aproximadamente 36,9 millones de eran portadoras del VIH (incluidos 1,8 millones de niños), con una prevalencia global del virus del 0,8% entre los adultos.

Desde el inicio de la epidemia, se estima que 77,3 millones de personas se han infectado de VIH y que 35,4 millones de personas han muerto de enfermedades relacionadas con el síndrome de la inmunodeficiencia adquirida (SIDA). En 2017, 940.000 personas murieron de enfermedades relacionadas con el SIDA. Este número se ha reducido en más del 51% (1,9 millones) desde el pico en 2004 **(figura 1).**

Figura 1. Número de personas portadoras de VIH en 2017



El número anual de nuevas infecciones entre adultos se ha mantenido estable en los últimos años. En 2017, hubo aproximadamente 1,8 millones de nuevas infecciones por VIH (la misma cifra que en 2016). El número de contagios a nivel mundial ha disminuido sólo un 18% en los últimos siete años (de 2,2 millones en 2010 a 1,8 millones en 2017). Aunque se trata de casi la mitad del número de nuevas infecciones en comparación con el máximo alcanzado en 1996 (3,4 millones), la disminución no es lo suficientemente rápida como para alcanzar el objetivo de menos de 500.000 en 2020.

A pesar de los progresos a nivel de prevención y tratamiento del Programa Conjunto de las Naciones Unidas sobre el VIH/Sida (ONUSIDA) (90-90-90), estamos aún lejos de las metas y las tasas de progresión han descendido en los últimos años de manera que no se alcanzarán los objetivos antes de 2020.

1.2- Cambio en la expectativa de vida de los pacientes con infección VIH a lo largo de la historia de la enfermedad

En la actualidad el VIH es un problema persistente y creciente con un número cada vez mayor de personas que conviven con el VIH. Son factores contribuyentes a este fenómeno tanto los nuevos infectados, como la mayor supervivencia que se ha alcanzado gracias a medidas multidisciplinares destinadas a la lucha contra la erradicación de la infección.

Entre estas medidas destaca el desarrollo de fármacos antirretrovirales de uso más generalizado (para todos y desde el diagnóstico). Los nuevos antirretrovirales cada

vez son más eficaces, de mejor perfil farmacocinético y farmacodinámico, siendo posible la reducción en la frecuencia de las tomas. Además, aportan una mejor barrera genética, mayor robustez y menos interacciones. También es muy importante su uso en prevención.

Por tanto, podemos afirmar que el tratamiento antirretroviral (TAR) ha evolucionado de tal manera que permite el control eficaz de la infección. Además, según se ha podido confirmar recientemente en un estudio observacional llevado a cabo en 75 hospitales de 14 países europeos con la participación de 1166 parejas sero-discordantes (estudio PARTNER) se puede prevenir su trasmisión a otras personas que puedan tener contactos con ellos.

Además, es evidente que existe un cambio radical en la forma como el paciente ha convivido con la enfermedad en las últimas décadas.

En sus inicios la epidemia de la infección por el VIH afectó a la población más joven con efectos devastadores que en la mayoría de los casos tenía como común denominador un desenlace caracterizado por infecciones, tumores, síndrome constitucional y la muerte. Tras la aparición del tratamiento antirretroviral de alta eficacia (TARGA) en la década de los noventa cambió la historia natural de la infección por el VIH de manera que la tasa de mortalidad en hombres debida a VIH/SIDA a principios de los 90 pasó de casi 25 x 100.000 personas hasta 3.5 x 100.000 personas/año en 2010 [1]; **(figura 2).** Este descenso fue debido tanto a causas relacionadas con el SIDA como sin relación con el mismo **(figura 3).**

Figura 2. Tasas de mortalidad por VIH/SIDA en España (1981-2010)

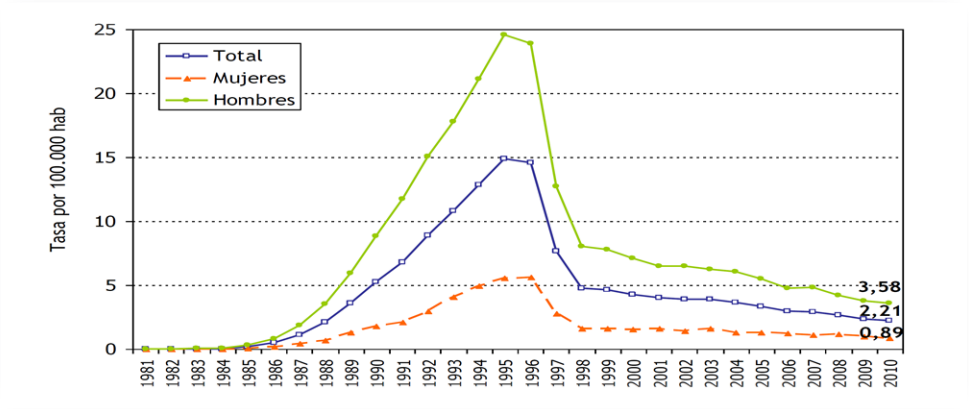
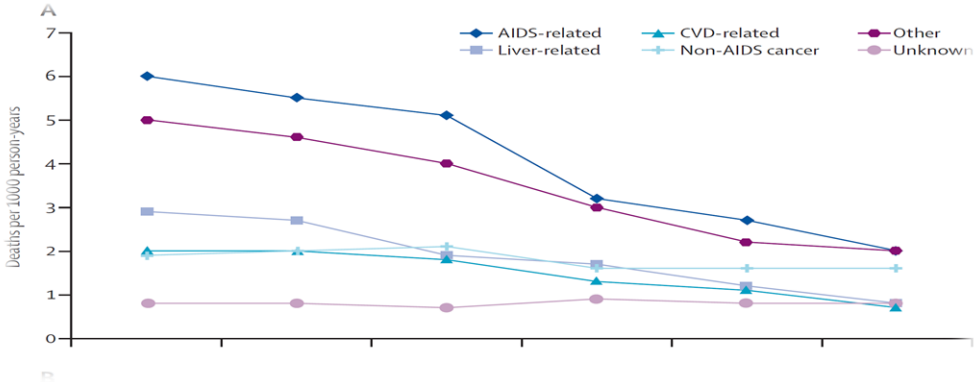
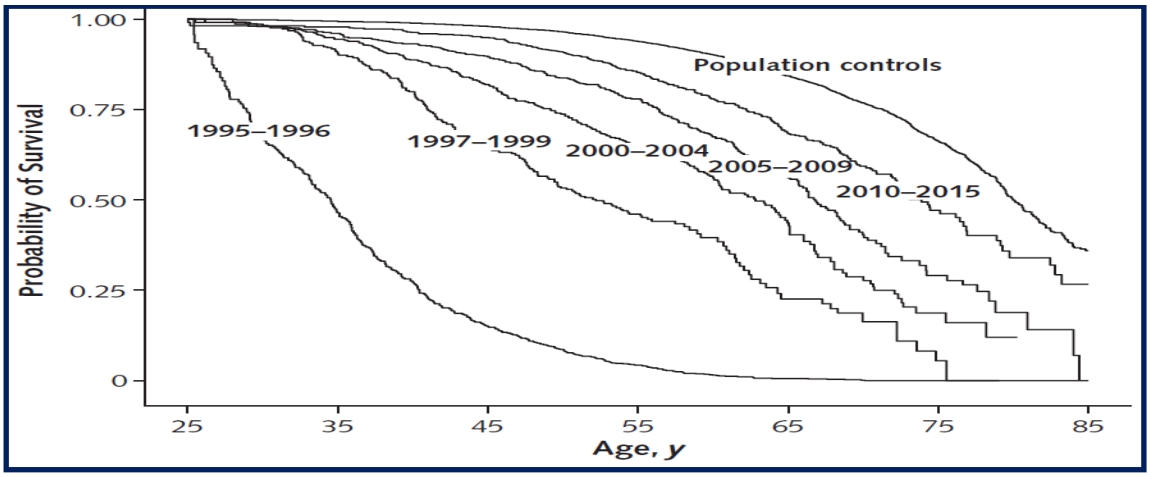


Figura 3. Tasa de incidencia de muerte (D:A:D study) [2]



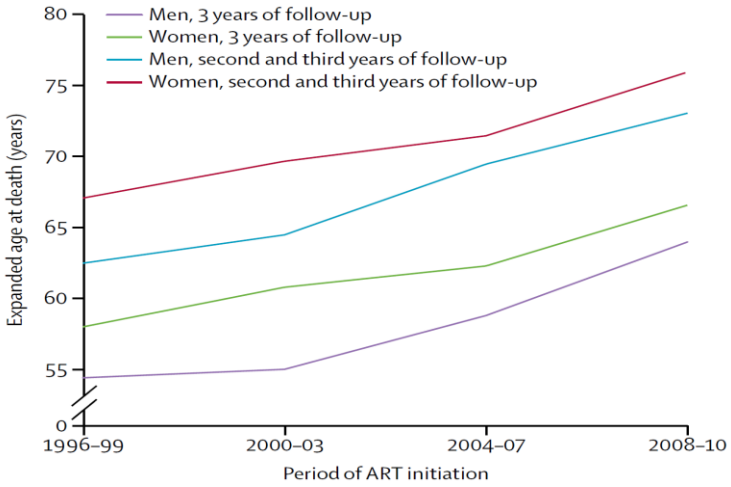
Esto conlleva una reducción absoluta en la tasa de muerte de forma remarcable [3] con mortalidad en algunos subgrupos cercana a la población no infectada por el VIH [4]. Por lo tanto, nos encontramos con número elevado de personas que viven con el VIH de forma crónica y mantienen niveles aceptables de calidad de vida siendo la esperanza de vida cercana a la de la población general **(figura 4).**

Figura 4. La esperanza de vida en pacientes con VIH versus población general [5].



En cuanto a edad de los infectados, según estimaciones aproximadamente 3,6 millones de todas las personas con infección por VIH tiene más de 50 años y esa tendencia aumenta progresivamente [6]. En EEUU en 2012 aproximadamente el 40% tenían más de 50 años y específicamente en San Francisco en 2010 la población que superaba los 50 años estaba por encima del 50% [7]. Además, en algunos sitios hasta un 18% de los nuevos infectados tiene más de 50 años [8]. Si a esto añadimos que incluso en la última era de la terapia antirretroviral, la supervivencia durante los primeros 3 años de tratamiento continúa mejorando [9], tenemos como resultado un claro aumento de la esperanza de vida **(figura 5)** de los infectados, que viene asociado sin embargo a complicaciones tales como un envejecimiento acelerado, mayor prevalencia de comorbilidades, así como síndromes geriátricos y de fragilidad que se presentan antes que la población no infectada por el VIH.

Figura 5. Aumento esperanza de vida en VIH

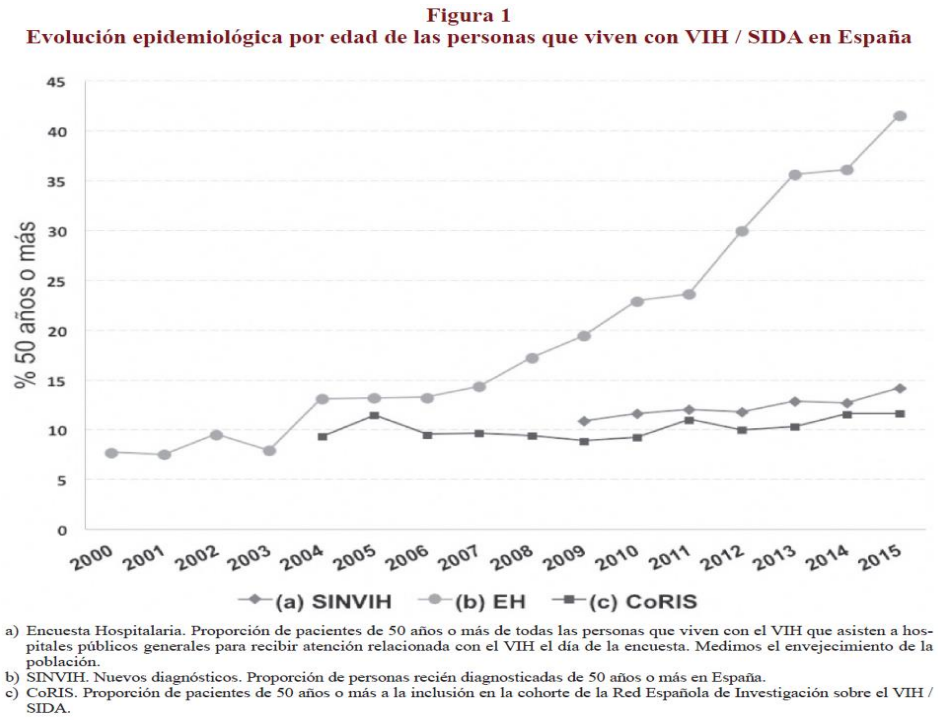


1.2.1- Cambio de paradigma: Envejecimiento de la población VIH, más allá del control virológico

Según diferentes fuentes de información nacional e internacional tanto de base poblacional *(Registro Nacional de casos de SIDA, y SINIVIH)* como no poblacional *(EH, CoRIS, PISCIS, VACH)* las personas que viven con VIH tienen una mayor esperanza de vida como ya comentamos anteriormente. Por tanto, hemos pasado de tener una enfermedad que afectaba principalmente a población joven y podía acompañarse de diversas infecciones oportunistas con altas tasas de mortalidad, a una enfermedad de población mayor (envejecida) acompañada de comorbilidades y polifarmacia.

Según SINIVIH, EH y CoRIS, en España la proporción de personas que viven con el VIH mayores de 50 años era del 8% en el año 2000, del 14% en el 2008 y era del 36% en el año 2014 **(figura 6)** [10].

Figura 6. Evolución epidemiológica por edad de las personas en España con VIH/SIDA



A pesar de este claro aumento de la supervivencia, la esperanza de vida sigue siendo menor con respecto a la población general debido a la mayor incidencia de comorbilidades que se presentan además a una edad más temprana [11].

La principal causa de comorbilidades es un envejecimiento prematuro del cual se desconoce su base fisiopatológica exacta pero que probablemente tiene una etiología multifactorial. En ella intervienen factores propios de la enfermedad como el envejecimiento del sistema inmunológico (“inmunosenescencia”), la situación pro-inflamatoria crónica que precede la aparición de diferentes comorbilidades (“inflamaging”), la toxicidad del tratamiento antirretroviral crónico, que además es mayor en los más veteranos, el efecto legado (“legacy”) de la infección no controlada,

la inmunodeficiencia, así como la mayor prevalencia en esta población de factores de riesgo clásicos como el abuso de sustancias tóxicas [12].

1.2.2- Comorbilidades asociadas al envejecimiento

1.2.2.1- Enfermedad cardiovascular. El 45% de pacientes tienen riesgo moderado/elevado de enfermedad coronaria y el 87% presentan también riesgo medio/alto de progresión a enfermedad renal crónica lo cual se explica en gran parte por la mayor prevalencia de factores de riesgo [13].

1.2.2.2- Enfermedad renal. Más del 40% de los pacientes tiene una función renal alterada y un 73% presenta un riesgo moderado o elevado de progresión a enfermedad renal crónica [13].

1.2.2.3- Enfermedad ósea. Aunque en la población general existe una disminución media del 1% en la densidad mineral ósea (DMO) por cada año después de los 40 años, existe una mayor prevalencia de osteopenia/osteoporosis en la población VIH de la misma edad a la que contribuyen diversos factores como el tratamiento antirretroviral en particular el tenofovir disoproxil fumarato (TDF), la hipovitaminosis D, etcétera, que conllevan un mayor riesgo de fracturas que se percibe de forma significativa después de los 60 años.

1.2.2.4- Psiquiátrica. Como más prevalentes están la ansiedad, depresión, manía, psicosis, delirium, alteraciones del sueño y el suicidio.

1.2.2.5- Neoplasias. Cada vez son más frecuentes los tumores no definitorios de SIDA (pulmón, ano, linfoma de Hodgkin, hígado) debido a la alta prevalencia de factores de riesgo como la infección por virus oncogénicos o el tabaquismo, si bien los tumores

definitorios siguen teniendo una incidencia importante [14]. Aunque la tasa de mortalidad en la era post TARGA ha descendido en términos generales, la tasa de muerte por cáncer no definitorio de SIDA aumenta [15,16].

1.3- Ventajas y limitaciones del tratamiento antirretroviral actual

La eficacia del tratamiento antirretroviral se ha perfeccionado de tal manera que en la mayoría de pacientes infectados por VIH es posible conseguir un control sostenido de la replicación viral. En nuestro medio, más del 85% de los pacientes que reciben tratamiento antirretroviral mantienen una carga viral (CV) indetectable en plasma [17]. Además, cuanto más prolongada es la supresión virológica, menor es el riesgo de fracaso virológico (FV) [18].

Las recomendaciones del tratamiento de la infección por VIH se han basado generalmente en estudios realizados en pacientes naive al tratamiento antirretroviral. De esta forma, la triple terapia, que incluye dos inhibidores de la transcriptasa inversa análogos de los nucleósidos y un tercer fármaco de otra familia es el **tratamiento inicial estándar** [19,20]. Pero el seguimiento de los estudios de pacientes naive suele ser de unos pocos años, y una amplia proporción cada vez más numerosa de pacientes en las cohortes actuales han recibido tratamiento antirretroviral efectivo durante muchos años. A pesar de que el tratamiento antirretroviral es mejor tolerado y más simple que hace unos años, un 70% de discontinuaciones en la actualidad se debe a motivos de intolerancia/toxicidad o simplificación según un estudio reciente de la cohorte italiana de pacientes naive al TAR (ICONA) [21]. A medida que los pacientes envejecen, pueden

presentar comorbilidades que les harán necesitar tratamientos crónicos con fármacos que pueden tener interacciones significativas con algunos antirretrovirales (como inhibidores de la proteasa potenciados con ritonavir (IP/r) o inhibidores de la transcriptasa inversa no análogos de los nucleósidos (ITINAN)). Además, a pesar de la mejor tolerabilidad de los fármacos antirretrovirales actuales, algunos pacientes experimentan toxicidades directas con ellos o pueden ejercer efectos potencialmente negativos en la evolución de algunas comorbilidades (por ejemplo, efectos digestivos o metabólicos con IP/r, toxicidad o comorbilidades renales u óseas con tenofovir (TDF), enfermedad cardiovascular con abacavir (ABC), entre otros) y este riesgo aumenta con la edad.

En la actualidad, una proporción de pacientes (aproximadamente un 20%) en la cohorte del Hospital Clínic de Barcelona lleva tratamiento eficaz con menos de tres fármacos y los motivos son generalmente intolerancia/toxicidad y/o simplificación. Se han realizado numerosos estudios de modificación del tratamiento antirretroviral por intolerancia/toxicidad o por simplificación, particularmente en Europa y más concretamente en España. En consonancia con la información proporcionada por los estudios previos, las guías de tratamiento antirretroviral contemplan la posibilidad y orientan en la modificación del TAR por motivos de intolerancia/toxicidad o simplificación [19,20].

1.4- Evidencias de simplificación del tratamiento antirretroviral mediante la reducción del número de fármacos

Hasta ahora, las pautas antirretrovirales que contenían menos de 3 fármacos debían incluir un IP/r. Aunque la estrategia de monoterapia con IP/r tiene más riesgo de fracaso virológico que el tratamiento triple, la proporción de pacientes que consigue supresión virológica sostenida con monoterapia de IP/r en estrategias de simplificación es muy alta y el riesgo de resistencias en caso de fracaso virológico es muy escaso [22].

Más recientemente, dos ensayos clínicos españoles han demostrado que la bi-terapia con lopinavir (LPV) o atazanavir (ATV) potenciados con ritonavir más lamivudina (3TC) es no inferior a las pautas triples estándares que incluyen estos IP/r [23,24]. Otros estudios de biterapias con IP/r y bien un inhibidor de integrasa (INI), un ITINAN, o el inhibidor de la entrada maraviroc (MRV) han mostrado una eficacia y/o una tolerabilidad claramente inferior respecto a la biterapia de IP/r más 3TC [25]. Las estrategias previas permiten evitar la toxicidad asociada a los ITIAN, pero no evitan el riesgo de toxicidad o interacciones inherente a los IP/r. Aunque con menor calidad de evidencia que la biterapia de IP/r más 3TC, estudios recientes no controlados sugieren que combinaciones dobles que incluyen un ITINAN como etravirina (ETR) o nevirapina (NVP) más raltegravir (RAL) en pacientes con CV plasmática indetectable pueden mantener la eficacia virológica a la vez que mejorar la tolerabilidad [26-29]. Sin embargo, ETR y NVP pueden tener riesgo de toxicidad o interacciones. Hay estudios planeados o en desarrollo con dolutegravir (DTG) (ClinicalTrials.gov NCT02422797 y NCT02478632) o el

inhibidor de la integrasa (INI) GSK744 más rilpivirina (RPV) aunque no están aún finalizados.

1.5- Necesidad de nuevas estrategias manteniendo la eficacia

Tras lo expuesto en los párrafos anteriores es decir el cambio de la infección por VIH a una enfermedad crónica, que ha traído consigo mayor expectativa de vida y por tanto el envejecimiento asociado con las comorbilidades propias del paso de los años, todo ello gracias al adelanto en el TAR, entendemos sin embargo, que ante este nuevo paradigma la exigencia sobre el TAR debe ser mayor sabiendo sus limitaciones y por ello es necesaria la búsqueda de nuevas estrategias de TAR sin perder claro está la eficacia.

1.5.1- Nuevas estrategias que disminuyan o mejoren la toxicidad:

1.5.1.1- En lo relacionado con la lipodistrofia

La lipodistrofia asociada al VIH se caracteriza clínicamente por cambios en la grasa corporal, incluida la pérdida de grasa subcutánea (lipoatrofia) con o sin acumulación de grasa troncal (lipohipertrofia). La disfunción mitocondrial y la inflamación en el tejido adiposo subcutáneo son factores clave en la patogenia de la lipoatrofia asociada al VIH [30].

Los ITIAN con timidina, estavudina (d4T) y, en menor medida, la zidovudina (AZT) son los principales contribuyentes bien conocidos de la lipoatrofia [30].

El potencial diferencial de la implicación de otros fármacos antirretrovirales en los cambios de grasa corporal no fue evidente hasta hace poco. En 2007, dos ensayos clínicos aleatorizados independientes sugirieron por primera vez que la terapia que contiene efavirenz (EFV) puede conducir a una mayor pérdida de grasa en las extremidades en comparación con la terapia que contiene LPV/r en adultos infectados por el VIH- naive [31,32]. Estos estudios cuestionaron la opinión sostenida de que los inhibidores de la proteasa pueden contribuir al desarrollo de la lipodistrofia. Sin embargo, la presencia de los ITIAN con timidina en esos estudios hizo difícil determinar en qué medida LPV/r y EFV realmente diferían en sus efectos sobre la grasa corporal.

El cambio de los ITIAN con timidina es la única estrategia recomendada para restaurar la grasa subcutánea en pacientes con lipoatrofia asociada al VIH, pero la mejoría es lenta y limitada [33]. Se desconoce si los cambios en los medicamentos antirretrovirales distintos de los ITIAN con timidina tendrán un impacto adicional en la grasa corporal en pacientes infectados por el VIH con lipoatrofia que ya han suspendido los ITIAN con timidina.

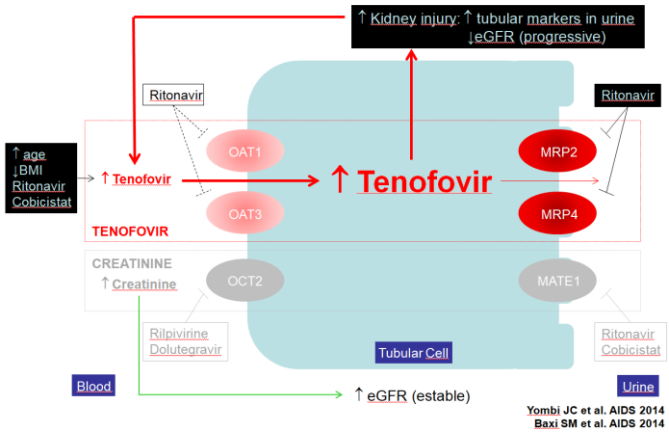
1.5.2- Nuevas estrategias que tengan un mejor impacto que los tratamientos previos sobre las comorbilidades

1.5.2.1- Tenofovir Disoproxil Fumarato (TDF): Toxicidad renal/ósea y su efecto negativo sobre la comorbilidad renal/ósea

Como lo hemos mencionado anteriormente dentro de las comorbilidades presentes en el paciente con infección por el VIH destacan por su frecuencia y sus implicaciones a corto y largo plazo la toxicidad renal y ósea.

La toxicidad por TDF es bien conocida y está documentado en diferentes estudios su efecto sobre las células del túbulo contorneado proximal con la consiguiente pérdida de fosfato y otros elementos que en casos severos se traduce en síndrome de Fanconi; así mismo provocaría un incremento en el metabolismo óseo con aumento en los marcadores de recambio óseo de forma más pronunciada en los dos primeros años de exposición **(figura 7).**

Figura 7. Efecto del tenofovir



1.5.1.2- Abacavir/lamivudina (ABC/3TC) como tratamiento alternativo

Una alternativa es ABC/3TC pero hay poca información con algunas pautas en combinación; entre estas son particularmente interesantes las pautas con ITINAN distintos a EFV por su simplicidad, tolerabilidad, y escasas interacciones.

Abacavir/lamivudina (ABC/3TC) ofrece algunas ventajas comparado con tenofovir/emtricitabina (TDF/FTC), evitando principalmente la potencial toxicidad renal y ósea [34,35]. Este también tiene una combinación de dosis fija, que permite regímenes

diarios con poca carga de comprimidos y un costo reducido en comparación con TDF/FTC.

RPV es un ITINAN de segunda generación aprobado para el tratamiento de pacientes infectados por VIH con VIH-ARN < 100000 copias / ml en combinación con otros antirretrovirales [36].

La eficacia y seguridad de la RPV en pacientes sin tratamiento previo se ha demostrado en ensayos clínicos aleatorios, combinados con dos ITIAN [37-39]. La mayoría de estos pacientes estaban recibiendo TDF/FTC como tratamiento de base [37]. Solo 35 pacientes (10%) en el estudio THRIVE recibieron ABC/3TC [38].

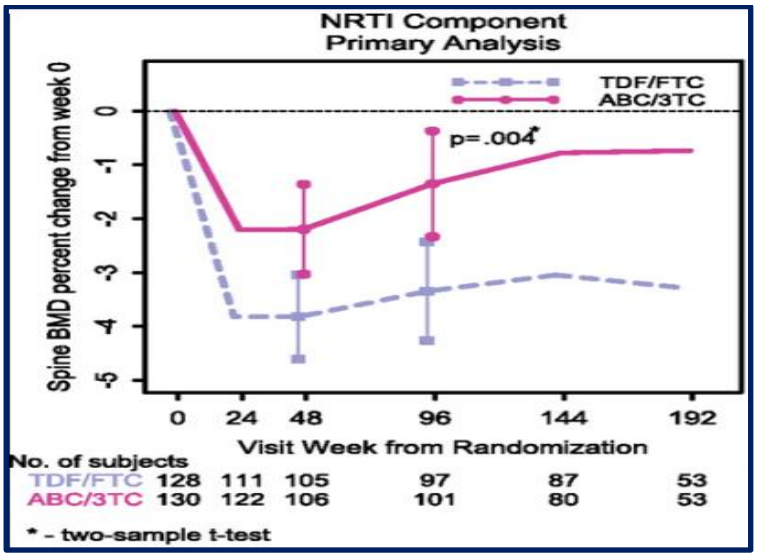
Sin embargo, ABC/3TC + RPV no se considera una opción preferida en pacientes naive en las guías [39-42], probablemente debido a la escasez de datos en los ensayos clínicos.

1.5.1.3- Bifosfonatos para osteopenia/osteoporosis en pacientes con VIH + en tratamiento con TDF.

Los adultos con infección VIH tienen una prevalencia más elevada de DMO baja (40-83%) con respecto a los adultos no infectados [43] y los adultos con infección VIH en TAR con respecto a los adultos infectados naive [44]. El inicio del TAR está asociado con pérdida de DMO [45]. La DMO disminuye un 3-5% en cadera y columna en el primer año de TAR con TDF y esta disminución es significativamente más alta (aproximadamente 2 veces) que con los regímenes de TAR que no incluyen TDF [46-48. En un subestudio del ACTG A5202 en la semana 96, el análisis ITT mostró que el brazo de ABC/3TC tuvo una

disminución significativamente menor en el porcentaje de cambio medio en la DMO de la cadera, en comparación con el brazo de TDF/FTC (−2,6% frente a −4,0%; Δ, 1,4%; IC 95%, 2% –2,5%; P = ,024) **(figura 8).**

Figura 8. DMO en pacientes naive versus pacientes que recibieron ABC/3TC o TDF/FTC (Subestudio ACTG A5202)

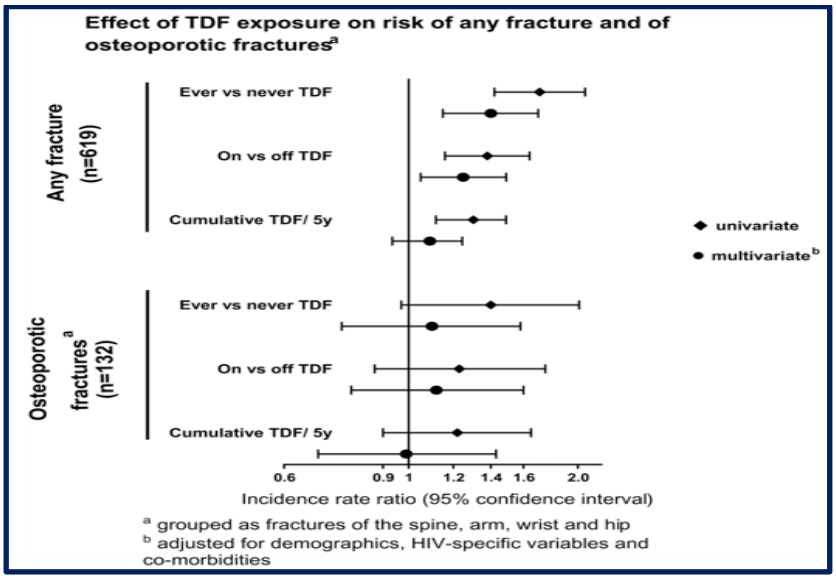


En algunos estudios, la DMO continua con una disminución aproximada del 1% por año, una tasa más alta que en los controles sanos [49,50]. El TDF es el componente más popular de los ITIAN como tratamiento de base en los países de bajos y medios ingresos por lo cual son deseables medidas para minimizar sus efectos adversos sobre el hueso.

Las fracturas por fragilidad son la consecuencia clínica de una baja DMO. Los estudios de cohorte prospectivos informan de un aumento significativo de las fracturas en los infectados por VIH en comparación con los hombres no infectados por VIH [51-

52]. El uso del TAR también se asocia con un aumento significativo de las fracturas [53], mientras que el uso pasado y actual de TDF se asoció con un aumento significativo de las fracturas en un gran estudio de cohorte europeo [54,55] **(figura 9).**

Figura 9. Efecto de la exposición al TDF sobre el riesgo de cualquier fractura y de las fracturas osteoporóticas.



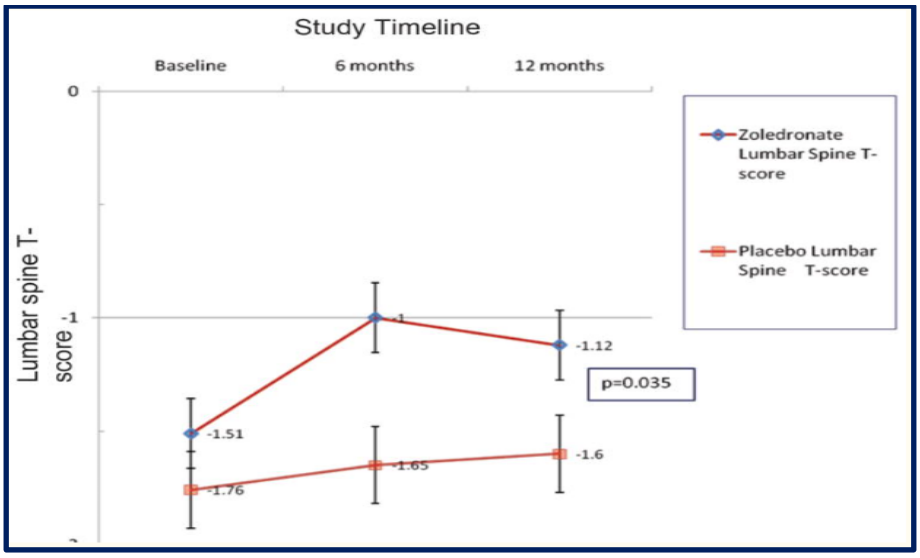
**** a) Agrupadas como fracturas de la columna vertebral, brazo, muñeca y cadera. b) Ajustado por las características demográficas, variables específicas del VIH y comorbilidades.**

La prevalencia de fracturas aumenta con la edad en mayor medida en pacientes con VIH [54-56], lo que tiene implicaciones para la población con VIH que envejece con éxito debido a un TAR eficaz.

Existen varias intervenciones comprobadas para la baja DMO en adultos con VIH: ya sea un **tratamiento antirresortivo** con un bifosfonato o el **cambio de TDF a otro**

fármaco antirretroviral activo. Los ensayos de terapia con bifosfonatos en adultos con VIH han reportado aumentos en la DMO con alendronato oral 70 mg por semana o 5 mg de ácido zoledrónico por vía intravenosa una vez al año [57-60] **(figura 10).**

Figura 10. Aumento de DMO en columna lumbar (3,7 ± 4,1% (media ± DS)) en comparación con los pacientes que recibieron placebo (0,7 ± 3,1%, p=0,04) a los 12 meses de tratamiento con zoledronato.



La DMO también aumenta después de cambiar TDF a ABC, RAL o tenofovir alafenamida (TAF) en adultos suprimidos virológicamente [61 - 64]. Las comparaciones entre estudios sugieren que los efectos de la terapia con bifosfonatos pueden ser mayores que el cambio de TDF a los 2 años, pero no ha habido un estudio comparativo para determinar qué estrategia es superior.

1.5.3- Nuevas estrategias que disminuyan la carga de tratamiento antirretroviral

1.5.3.1- Disminución de la carga de TAR mediante reducción del número de fármacos

1.5.3.1.1- Dolutegravir como anclaje para simplicaciones

Dolutegravir (DTG) ha causado una revolución en el campo del TAR por sus muchas características positivas y práctica ausencia de características negativas. Los IPs se han usado en monoterapia, pero han resultado ser inferiores a la terapia combinada; no así, la biterapia con IP + 3TC. DTG, a similitud de los IP, podría utilizarse con pauta de menos de tres fármacos. Hay muchos pacientes con dificultades para recibir distintos antirretrovirales que se podrían beneficiar de las pautas reducidas de DTG.

El Hospital Clínic de Barcelona es un centro de referencia que hasta finales de 2014 atendía una media de 4500 personas infectadas por el VIH. De éstas, el 10% se trataron con monoterapia con IP y el 20% con terapias duales, incluido un IP o un INI o ambos. Las razones de estos regímenes no estándar difirieron entre los pacientes, pero se debieron mayoritariamente a opciones terapéuticas limitadas debido a toxicidad, interacciones o problemas de resistencia.

La mayor preocupación de la monoterapia con IP potenciada es un riesgo de rebote viral más alta que con el tratamiento triple estándar, a pesar de la aparente ausencia de emergencia de resistencias [65, 66]. Además, la monoterapia con IP puede tener problemas de efectos digestivos, metabólicos u

otros efectos adversos relacionados con los IP y el riesgo de interacciones clínicamente significativas debido a la potenciación del IP [67, 68].

DTG tiene varias características favorables que se asemejan a aquellas de los IPs potenciados, incluyendo alta potencia, alto cociente inhibidor y alta barrera a la resistencia que le hacen atractivo para la monoterapia; además, DTG también tiene ausencia de interferencias con comorbilidades, un bajo riesgo de interacciones, una vida media más prolongada y es más fácil de tomar y mejor tolerado que los IPs [69].

El 3TC (fármaco antirretroviral más utilizado hasta la fecha) todavía se considera en las principales pautas, ya que no ha mostrado toxicidades relacionadas importantes, tiene baja probabilidad de interacciones y han surgido datos prometedores de terapias duales basadas en IPs [70-72].

La experiencia clínica de la terapia dual con DTG / 3TC en pacientes experimentados también ha sido prometedora.

1.5.3.1.2- Dolutegravir: tolerancia en la práctica clínica diaria

Aunque los INIs han tenido una mejor tolerabilidad que los IPs y los ITINAN, en los ensayos clínicos se ha descrito el riesgo de efectos adversos sobre el SNC con todos los INIs comercializados y más específicamente con DTG aunque los datos publicados son controvertidos. Los INI disponibles en la actualidad se han convertido en los medicamentos de compañía preferidos para los pacientes sin tratamiento antirretroviral en diferentes guías a nivel mundial [73-75],

debido a que se han comparado favorablemente con EFV [76-78] y con IPs potenciados [79-81], en ensayos clínicos aleatorizados.

La discontinuación de RAL, EVG o DTG debido a efectos adversos en ensayos clínicos ha sido usualmente más baja que el del comparador oscilando entre el 1% y el 4% de los pacientes a las 48 o 96 semanas [76-81]. En los ensayos clínicos no se identificó ninguna toxicidad específica en los órganos asociada con los INI. El RAL fue el primer INI aprobado (FDA de EUA, octubre de 2007; EMA, enero de 2008), pero su uso inicial se destinó de forma preferencial a la terapia antirretroviral de rescate. EVG (como una combinación de régimen de una sola tableta (STR) con TDF, FTC y cobicistat) se aprobó posteriormente (FDA, agosto de 2012; EMA, mayo de 2013) y DTG fue el primero que se aprobó más recientemente como un solo medicamento (FDA, agosto de 2013; EMA, noviembre de 2013) y más tarde como un STR en combinación con ABC más 3TC (FDA, agosto de 2014; EMA, septiembre de 2014). En contraste con el uso de RAL, EVG y DTG se dirigieron principalmente a pacientes sin tratamiento antirretroviral y a pacientes tratados que requerían un cambio de antirretroviral por razones distintas al fracaso virológico.

Las publicaciones iniciales sobre la tolerabilidad de los INI se centraron en la toxicidad muscular asociada con RAL, que generalmente consistió en aumentos transitorios leves o asintomáticos en las enzimas musculares y se informó de que se trataba de un evento grave en muy pocos pacientes [82-83]. Sin embargo, en 2017, un estudio observacional de una cohorte holandesa

reportó una tasa inesperadamente alta de discontinuación de DTG por toxicidad, principalmente efectos neuropsiquiátricos [84]. Otro estudio informó de tasas variables de discontinuación debida a efectos adversos. [85-93].

Datos preliminares a la semana 24 del estudio STRIVING (ensayo clínico aleatorizado abierto que evaluó la eficacia y seguridad del cambio de IPs a DTG en pacientes suprimidos virológicamente) también mostró que varios pacientes tuvieron que suspender DTG debido a los efectos neuropsiquiátricos en los primeros días de la terapia [94].

En contraste el cambio de EFV a DTG en pacientes suprimidos virológicamente con efectos neurológicos asociados al EFV fue asociado con una mejoría significativa en la toxicidad del sistema nervioso central (SNC), con una mejoría en la función cognitiva y en los síntomas depresivos, los mareos y la calidad del sueño sin afectar la eficacia antirretroviral [95,96]. Curiosamente el potencial efecto neuropsiquiátrico se reconoce en el resumen actual de las características del producto de la EMA de los tres inhibidores de la integrasa disponibles [97-99].

Si existen diferencias en las tasas de discontinuación debido a toxicidad entre los inhibidores de la integrasa actuales y si los efectos adversos neuropsiquiátricos que llevan a la discontinuación puede ser más común con DTG que con otros INI actualmente no está claro.

1.5.3.2- Disminución de la carga de TAR mediante reducción de la dosis de fármacos

1.5.3.2.1- ATRIPLA como anclaje para simplificación

Debido a la eficacia subóptima y el número limitado, los tratamientos antirretrovirales fueron aprobados usualmente en la dosis máxima tolerada más que en la dosis mínima efectiva [100]. Hay una clara relación entre los niveles plasmáticos de algunos antirretrovirales tales como EFV [101] o TDF [102] y su potencial desarrollo de toxicidad relacionada con los medicamentos **(figuras 11 y 12).**

Figura 11. La toxicidad en el SNC (sistema nervioso central) relacionada con EFV esta relacionda con los niveles plasmáticos de EFV en plasma

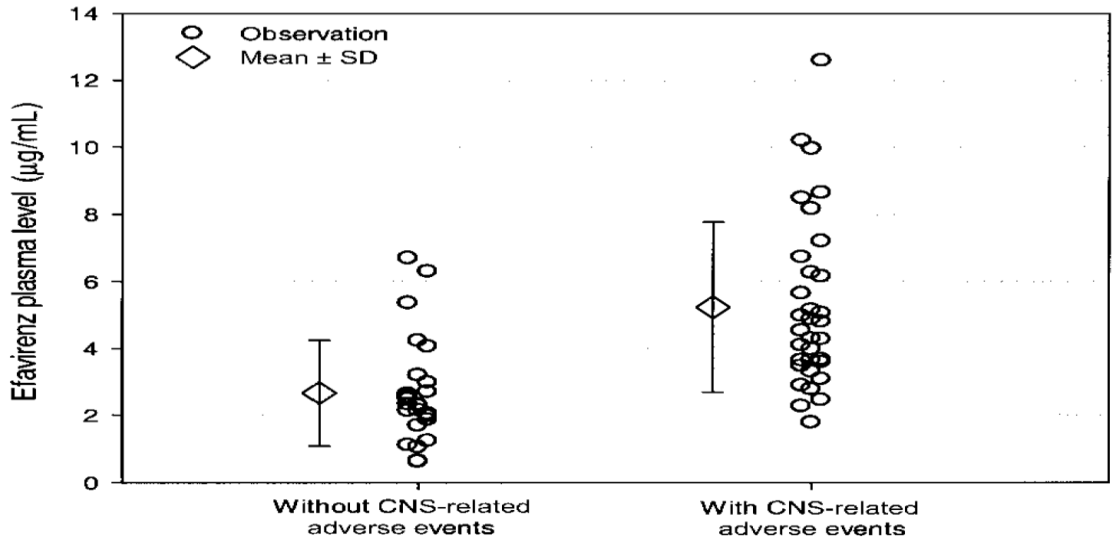
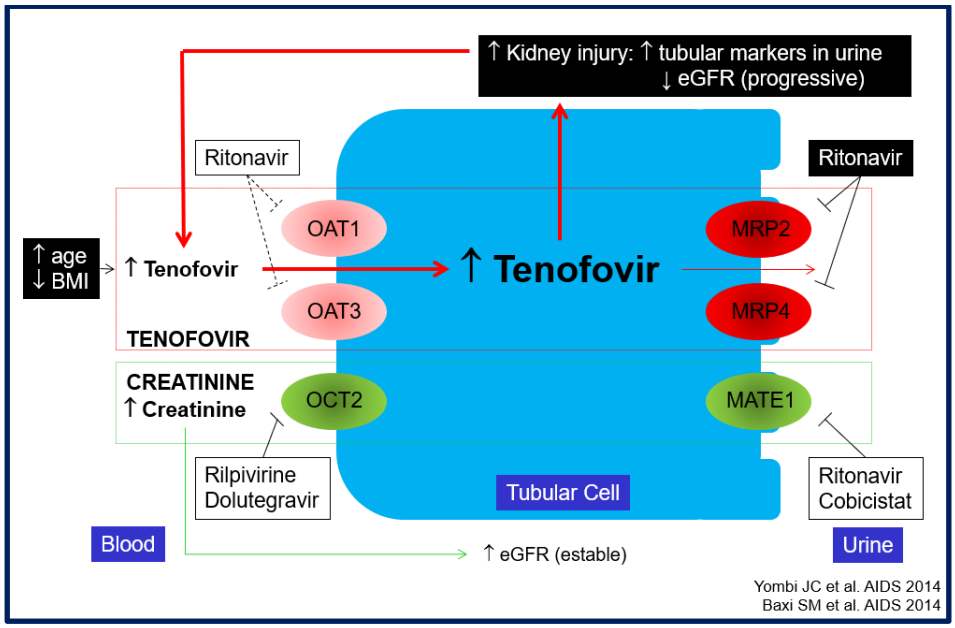


Figura 12. La toxicidad renal relacionada con Tenofovir está relacionada con las concentraciones en plasma y a nivel intracelular



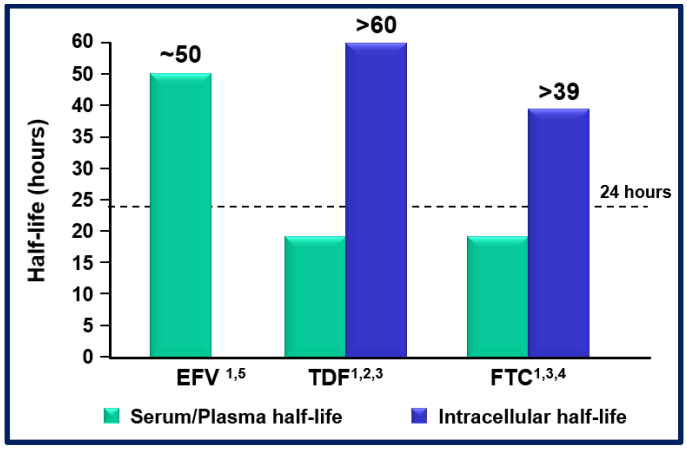
Reducir la dosis diaria de EFV de 600 a 400mgs en pacientes naive [103,104] y usar TAF en lugar de TDF [105, 106] son estrategias que disminuyen la exposición a EFV y tenofovir, respectivamente que han mostrado no inferioridad en eficacia y mejor perfil de seguridad.

La terapia antirretroviral ha evolucionado con un gran número de familias disponibles y medicamentos con esquemas de dosificación conveniente y mejor tolerabilidad en general. La construcción de combinaciones a dosis fija con vidas medias prolongadas que permitan dosis una vez al día establece el régimen antirretroviral básico preferido en la última década.

Atripla una combinación a dosis fija de EFV 600mgs/FTC 200mgs/TDF 300 mgs, fue la primera combinación a dosis fija una vez al día, aprobada hace más de 10 años.

Los medicamentos contenidos en el comprimido de Atripla se encuentran entre los que tienen vidas medias más largas **(figura 13),** lo que permita una supresión viral sostenida a pesar de una adherencia subóptima [107-110].

Figura 13. Vida media Atripla



Aunque los regímenes triples basados en INI están actualmente recomendados como primeras opciones en la mayoría de los países desarrollados, la combinación de EFV con 3TC o FTC y TDF persiste como el régimen de primera línea preferido de acuerdo con la organización mundial de la salud (OMS) [111] y se espera que un número sustancial de pacientes lo utilicen en los países de ingresos bajos y medios en los próximos años [112,113].

Ensayos clínicos previos pequeños aleatorizados controlados han mostrado que un ciclo corto de 5 días de toma con 2 días de descanso como

tratamiento intermitente, con EFV/FTC/TDF [114] o una combinación de terapia triple que incluye EFV con 2 ITIAN [115, 116], resultaron no inferiores en eficacia y con mejoría en el perfil de seguridad relativo al TAR continuo estándar. Estos estudios sin embargo no se desarrollaron con el comprimido de Atripla, estuvieron basados en toma de 5 días con 2 de descanso en lugar de 3 veces por semana y no evaluaron los beneficios potenciales a nivel subclínico o en cambios más profundos como parámetros inmunológicos ó virológicos.

1.6- Necesidad de nuevos métodos para evaluar la eficacia de nuevas estrategias de simplificación del TAR

La monitorización de la eficacia del tratamiento antirretroviral tanto en la asistencia médica como en la investigación clínica se ha realizado clásicamente con la CV estándar en plasma y las poblaciones linfocitarias CD4 y CD8 en sangre.

En la mayoría de los pacientes estables (que tienen una cv plasmática indetectable de forma sostenida y un recuento de células CD4 y CD8 relativamente estable), la CV estándar en plasma y las poblaciones linfocitarias CD4 y CD8 no permiten una mayor discriminación con finalidad pronóstica.

Nuevas herramientas virológicas no estándares como la determinación de la CV plasmática ultrasensible y la medición del reservorio celular de VIH-1 en células CD4 pueden proporcionar una mejor discriminación del pronóstico de los pacientes con CV plasmática estándar indetectable que simplifican el TAR de la forma que se plantea en el presente proyecto.

De la misma manera, técnicas inmunológicas más refinadas como los cambios en las células T naive efectoras y en biomarcadores de inflamación (PCR de alta sensibilidad, IL-6) y de activación mononuclear (sCD14, sCD163) pueden proporcionar una información útil sobre potenciales diferencias en la eficacia de las pautas de simplificación estudiadas.

Nuestro grupo ha evaluado algunas de estas técnicas en un proyecto de simplificación del tratamiento antirretroviral completado recientemente que recibió financiación en una Convocatoria de Ayudas de Proyectos de Investigación en Salud *("Seguridad virológica e inmunológica de una estrategia de reducción de dosis con la pauta antirretroviral efavirenz/tenofovir/emtricitabina", expediente PI12/01217).*

2. HIPÓTESIS

2. HIPÓTESIS

2.1 *Es posible diseñar nuevas estrategias de TAR que disminuyan o mejoren la toxicidad*

2.1.1 En lo relacionado con la lipodistrofia

El cambio de los ITIAN con timidina es la única estrategia recomendada para restaurar la grasa subcutánea en pacientes con lipoatrofia asociada al VIH, pero la mejoría es lenta y limitada [33].

Otros cambios de tratamiento antirretroviral diferentes de los ITIAN con timidina podrían mejorar aún más la distribución de la grasa corporal en pacientes con infección VIH con lipoatrofia persistente a pesar de haber suspendido los ITIAN con timidina.

2.2 Es posible diseñar nuevas estrategias de TAR que tengan un mejor impacto sobre las comorbilidades

2.2.1 En lo relativo al impacto del TDF

2.2.1.1 KVX puede ser una alternativa en pacientes VIH + sin tratamiento previo.

2.2.1.2 La terapia antirresortiva con ácido zoledrónico (ZOL) aumentará la DMO de forma más efectiva a 2 años que el cambio de TDF a otro fármaco antirretroviral en pacientes VIH + con osteopenia/osteoporosis y tratamiento con TDF.

2.3 Es posible diseñar nuevas estrategias de TAR que disminuyan la carga del TAR

2.3.1 Disminución mediante reducción del número de fármacos

El tratamiento dual con dolutegravir/lamivudina o la monoterapia con dolutegravir tendrían una eficacia similar a la del tratamiento antirretroviral triple en pacientes con supresión viral persistente.

2.3.2 Disminución mediante reducción de la dosis de fármacos

La simplificación del comprimido a dosis fija de EFV/FTC/TDF (Atripla) de la dosis estándar 1 vez al día a 3 días por semana sería factible, capaz de mantener la supresión viral y menos tóxica.

3.OBJETIVOS

3. Objetivos

3.1 Evaluar el impacto del cambio de efavirenz por lopinavir/ritonavir sobre la grasa corporal en adultos infectados por VIH con lipoatrofia persistente a pesar de estar libres de ITIAN timidínicos.

3.2 Evaluar la eficacia y seguridad de abacavir/lamivudina con los ITINAN rilpivirina o nevirapina en pacientes infectados por VIH sin tratamiento previo.

3.3 Evaluar el impacto del uso de bifosfonatos (ácido zolendrónico) vs el cambio del tratamiento con tenofovir a otros regímenes en la densidad mineral ósea de adultos infectados por el VIH suprimidos virológicamente, con DMO baja y que llevan TDF en su TAR.

3.4 Describir la eficacia y la seguridad de la monoterapia con dolutegravir en pacientes con opciones muy limitadas de TAR por efectos adversos, comorbilidades, riesgo de interacciones, o resistencia archivada en la cohorte de pacientes adultos infectados por VIH del Hospital Clínic de Barcelona

3.5 Evaluar la viabilidad de pautas de TAR basadas en dolutegravir con menos de tres fármacos y más específicamente comparar la eficacia y la seguridad de la monoterapia con dolutegravir frente a la biterapia con dolutegravir más lamivudina en adultos infectados por VIH con supresión virológica sostenida.

3.6 Comparar la incidencia de discontinuación en general y más específicamente por toxicidad, evaluar los factores de riesgo de discontinuación y conocer el perfil de toxicidad en la vida real de los tres inhibidores de integrasa disponibles en la cohorte de adultos infectados por VIH en el Hospital Clínic de Barcelona.

3.7 Evaluar la viabilidad, seguridad y eficacia de una pauta con efavirenz/emtricitabina/tenofovir disoproxil fumarato tomada tres días por semana en adultos infectados por VIH con supresión virológica sostenida.

4. METODOLOGÍA

4. Metodología

Se describirá la metodología secuencialmente según el mismo orden de los objetivos.

4.1 Estudio LIPOKAL *(ClinicalTrials.gov NCT00978237)*

Objetivo 3.1 Evaluar el impacto del cambio de efavirenz por lopinavir/ritonavir sobre la grasa corporal en adultos infectados por VIH con lipoatrofia persistente a pesar de estar libres de ITIAN timidínicos

4.1.1 Tipo de estudio

Se trata de un estudio piloto, aleatorizado, abierto, multicéntrico, fase IV a 96 semanas.

4.1.2 Criterios de valoración

- Criterio de ***valoración primario***: La diferencia entre las ramas en el cambio absoluto de la masa de grasa en las extremidades, medido por absorciometría dual (DXA) desde el inicio hasta la semana 96.
- Criterios de **valoración secundarios**:
    - El cambio porcentual en la masa grasa de las extremidades
    - Los cambios en la masa grasa del tronco y la masa grasa corporal total
    - Los cambios en la evaluación subjetiva de la lipoatrofia
    - Los cambios en el tejido adiposo visceral y subcutáneo (medido por tomografía computarizada (TC) abdominal de un solo corte en la escala L4)
    - Los cambios en el índice de masa corporal (IMC)

- Los cambios en el colesterol en ayunas (lipoproteínas de alta densidad (HDL) y baja densidad (LDL)) y triglicéridos.

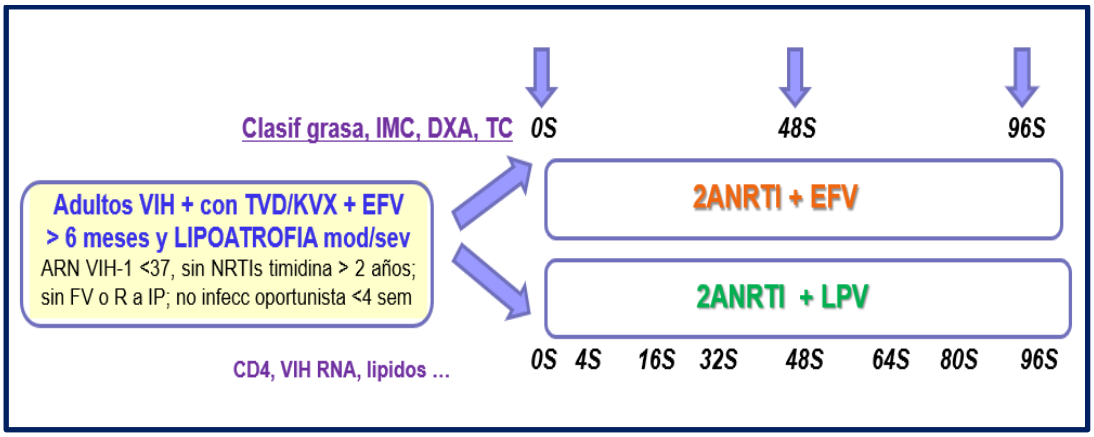
- Las variables de evaluación adicionales incluyeron la discontinuación del tratamiento debido a eventos adversos y el fracaso virológico definido por dos mediciones consecutivas del ARN VIH-1 en plasma > 50 copias/mL.
- Se obtuvieron biopsias de tejido adiposo abdominal subcutáneo en un subgrupo de pacientes al inicio y a la semana 96.

4.1.3 Participantes y diseño del estudio (figura 13)

Los sujetos con lipoatrofia moderada a severa de acuerdo con ***los criterios de HOPS*** [117] o ***Fontdevila*** [118, 119] en uno o más sitios del cuerpo fueron asignados aleatoriamente a continuar su régimen antirretroviral basado en EFV o a cambiar a LPV/r mientras mantenían la combinación de ITIAN a dosis fija sin cambios.

Al inicio del estudio, a las 48 y 96 semanas, se evaluó clínicamente la pérdida de grasa corporal de cada participante según criterios estandarizados. Se utilizaron criterios derivados de HOPS [117] para las extremidades y los glúteos.

Figura 13. Participantes y diseño del estudio



Brevemente, tanto el paciente como el médico calificaron de forma independiente el grado de lipoatrofia en cada lugar: ausente (puntuación de 0), leve (perceptible en una inspección minuciosa, puntuación de (1)), moderada (perceptible fácilmente por el paciente o el médico, puntuación de (2)) o grave (perceptible fácilmente por un observador ocasional, puntuación de (3)).

La clasificación de Fontdevila se utilizó para la evaluación facial [118, 119]. El médico calificó el grado de lipoatrofia en la cara como ausente (puntuación de 0), leve (malar y mejilla aplanadas, puntuación de (1), moderada (hueco de mejilla sin evidencia de estructuras óseas y musculares subyacentes, puntuación de (2), o severa (hueco de mejilla con evidencia de estructuras óseas y musculares subyacentes), puntuación de (3). La peor puntuación en cualquiera de los tres sitios del cuerpo evaluados (extremidades, glúteos o cara) se utilizó para el cálculo.

También al inicio, a las 48 y a las 96 semanas, se midió el peso y la estatura y se realizaron DXA de todo el cuerpo y TC abdominal para evaluar la grasa corporal y los tejidos adiposos viscerales (VAT) y subcutáneos (SAT), respectivamente. El IMC se calculó dividiendo el peso (en kg) por la altura cuadrado (en metros). Las imágenes DXA y TC se realizaron localmente siguiendo protocolos de exploración previamente estandarizados, para cada paciente en la misma de rayos x y con parámetros idénticos cada vez. Al final del estudio, todas las exploraciones fueron leídas de forma centralizada por un radiólogo que desconocía la terapia asignada a cada paciente. No se dieron recomendaciones físicas o dietéticas.

Para las exploraciones DXA, los pacientes fueron colocados directamente sobre la mesa, con todas las partes del cuerpo en el campo de exploración, los brazos separados del tronco y las piernas giradas 25° hacia adentro. Se obtuvieron directamente las mediciones absolutas y porcentuales de la grasa de brazos, piernas y tronco. La grasa de las extremidades se calculó sumando la grasa de brazos y piernas, y el índice de masa grasa (FMR) se calculó como la relación entre el porcentaje de grasa del tronco y el porcentaje de grasa de las extremidades [120]. Para las TC, los pacientes estaban en decúbito supino con los brazos levantados por encima de la cabeza. Todo el tejido blando fue incluido en el campo de visión de la TC. Con un explorador vertebral de mediana longitud como guía, se obtuvo un solo corte axial del abdomen de 5 mm de grosor. Las áreas de VAT y SAT se trazaron manualmente.

En un subgrupo de pacientes de un centro participante *(Hospital Clınic, Barcelona),* se recogieron muestras de tejido adiposo abdominal subcutáneo al inicio y a la semana 96 y se conservaron utilizando 1 mL de RNAlater (Ambion, Huntingdon, Reino Unido) a 80°C hasta que se realizó la extracción de ARN. Para la extracción total del ARN, cada muestra se pulverizó en un mortero solo y un mortero usando nitrógeno líquido, y posteriormente se homogeneizó en 1 ml de reactivo TRIZOL (Invitrogen/ Life Techonologies, Carlsbad, CA, USA) y se precipitó utilizando cloroformo. La concentración de ARN se calculó utilizando la tecnología NanoDrop ND-1000 (Thermo Scientific, Waltham, MA, USA).

La integridad del ARN se evaluó utilizando ARN 6000 Nano LabChips en un bioanalizador Agilent 2100 (Agilent Technologies, Santa Clara, CA, USA). Todos los chips

fueron preparados según las instrucciones del fabricante en la plataforma transcriptómica del Parque Científico de Barcelona (Barcelona, España). La degradación se evaluó revisando los electroferogramas y el número de integridad del ARN de cada muestra. Sólo se seleccionaron muestras con picos conservados de 18 y 28S y valores de RIN > 7 para los análisis de expresión génica. En el estudio se evaluaron los ARN mensajeros (ARNm) de los genes implicados en la adipogénesis, el metabolismo de la glucosa y los lípidos, el metabolismo mitocondrial y la inflamación. Nosotros y otros trabajadores hemos evaluado previamente estos ARNm, in vitro e in vivo, en estudios de grasa corporal asociados con TAR [121-123].

El ARN total (200 ng) se transcribió en forma inversa en 200 uL de acuerdo con las recomendaciones del fabricante utilizando reactivos de transcripción inversa TaqMan (Applied Biosystems, Foster City, CA, EUA). Se realizaron ensayos de expresión génica utilizando cebadores y sondas TaqMan (Applied Biosystems) para genes de control endógeno (18S, Hs99999901_s1) y genes diana (CEBP/A, Hs00269972_s1; PPARc, Hs00234592_m1; ADI POQ, Hs4331182; LEP, Hs00174877_m1; GLUT4, Hs0016 8966_m1; LPL, Hs00173425_m1; COXII, Mm032948 38_g1; COXVI, Hs00266371_m1; TNFa, Hs00174128_m1 y MCP-1, Mm00656886_g1). Cuantificaciones relativas (RQ) se realizaron mediante PCR cuantitativa en el sistema de PCR rápida en tiempo real Applied Biosystems 7900HT. Volúmenes de reacción contenidos: 5 uL de agua, 1 uL de mezcla de cebador/sonda TaqMan (209) para el gen de control diana o endógeno, 10 uL de mezcla maestra de expresión génica (29) y 4 uL de ADNc en una concentración de 4 ng. Las condiciones del termociclador fueron las siguientes: 95°C arranque en caliente

durante 10 min, seguido de 40 ciclos de 95°C durante 15 s y 60°C durante 1 min. Cada muestra se realizó por triplicado y los controles que carecían de ARN o ADNc se incluyeron en cada conjunto de experimentos. Los análisis de las biopsias de grasa fueron realizados por un biólogo que desconocía la terapia asignada a cada paciente.

4.1.4 Análisis estadístico

Los análisis se realizaron por intención de tratar (intention-to-treat analysis). El análisis estadístico se realizó con el uso de Stata 9.2 (StataCorp, College Station, TX, EUA).

$\chi 2$ o las pruebas exactas de Fisher se utilizaron para comparar las proporciones entre las ramas de tratamiento. Las pruebas de U de Mann-Whitney se utilizaron para comparar las variables continuas entre las ramas de tratamiento.

El intervalo de confianza del 95% para las diferencias en el tratamiento en el criterio de valoración primario; se utilizó la regresión lineal para ajustar las variables basales. Los cambios de lípidos entre las ramas de tratamiento se compararon mediante medidas repetidas ANOVA.

Para el análisis de la expresión génica, se obtuvieron los valores de Ct en bruto (umbral de ciclo: el número de ciclos necesarios para que la señal fluorescente cruce el umbral) de la expresión de cada ARNm individual utilizando la versión 2.3 del software SDS. Los valores de Ct fueron luego exportados al software RQ Manager versión 1.2 (Applied Biosystems) para ΔCt (ΔCt = Cttarget gene - Ctendogenous control gene) para la determinación de valores con el fin de cuantificar el nivel de ARNm del gen objetivo

en relación con el del control endógeno (18S). Suponiendo un aumento medio de grasa en las extremidades de 100 y 500 mg en los brazos de control y de tratamiento experimental (respectivamente) a las 96 semanas, se necesitaron dieciséis sujetos por brazo para asegurar un 80% de poder para detectar una diferencia de 400 mg en la masa grasa media de las extremidades entre las dos ramas con una desviación estándar de 400 mg en el nivel del 5% de significación estadística. Suponiendo un 10% de pérdidas al año, la inscripción se planificó en veinte pacientes por rama.

4.2 Estudio KiRilNa

Objetivo 3.2 Evaluar la eficacia y seguridad de abacavir/lamivudina con los ITINAN rilpivirina o nevirapina en pacientes infectados por VIH sin tratamiento previo.

4.2.1 Tipo de estudio

Se trata de un estudio observacional, retrospectivo y multicéntrico realizado en ocho hospitales universitarios españoles.

4.2.2 Criterios de valoración

Criterio de **valoración primario**: Analizar la eficacia en vida real del esquema con abacavir/lamivudina+rilpivirina en pacientes sin tratamiento previo usando un análisis por ITT (fracaso = pérdida, discontinuación, FV) y uno por on-treatment (censurando cualquier causa de fracaso del tratamiento diferente a FV) a los 6 y 12 meses (+/- 1 mes).

4.2.3 Pacientes y diseño del estudio

Se incluyeron todos los pacientes adultos consecutivos infectados con VIH-1 que iniciaron una combinación de abacavir/lamivudina (600/300 mg combinación de dosis una vez al día) más rilpivirina (25 mg una vez al día), así como que el TAR hubiese iniciado antes del 30 de junio de 2015, independientemente de si estaban o no en este régimen actualmente.

Todos los pacientes debían ser negativos para HLA_B*5701 y el antígeno de superficie de la hepatitis B y tuvieron un test de resistencia a nivel basal sin mutaciones antes de iniciar el tratamiento antirretroviral [124].

Los pacientes candidatos fueron seleccionados de la base de datos de VIH específica de cada hospital. Los datos que se definieron se obtuvieron de las historias clínicas de los pacientes y de las historias clínicas electrónicas. El seguimiento fue sometido para análisis el 31 de diciembre de 2015.

Se registraron datos demográficos, datos relacionados con el VIH, comorbilidades y otras condiciones médicas relevantes. También se registró la principal razón para inicio de esquema con abacavir/lamivudina + rilpivirina.

Si se recogió durante el seguimiento por el médico a cargo del paciente información acerca de CD4+, ARN VIH, parámetros de laboratorio (hemograma, renal, hígado y lípidos en ayunas), eventos adversos y razones para discontinuar el abacavir/lamivudina + rilpivirina también se registraron. Si se interrumpió el tratamiento antirretroviral debido a un fracaso virológico (FV), también se analizaron el test de resistencia, el tratamiento prescrito posteriormente y los resultados.

El FV se definió como no alcanzar la CV ARN-VIH < 50 copias/ml, ARN-VIH > 50 copias/ml confirmado tras alcanzar la CV indetectable o una última determinación de ARN–VIH > 50 copias/ml si se cambió el tratamiento o se perdió el seguimiento del paciente. El fracaso del tratamiento incluyo cambio en TAR debido a cualquier razón, muerte o pérdida de seguimiento sin importar la causa.

4.2.4 Análisis estadístico

Para las variables cualitativas, se dio el número de pacientes y los porcentajes. Para las variables cuantitativas se utilizaron la mediana y la IQR.

Las comparaciones entre las variables a nivel basal y de seguimiento se realizaron con el test de Wilcoxon signed-rank. Todas las pruebas estadísticas se realizaron con un nivel de significación estadística de 0,05 (SPSS 20.0; IBM Corp., Armonk, NY, USA).

4.2.5 Aspectos éticos

El protocolo fue aprobado por los Comités Éticos de Investigación Clínica de los centros participantes de acuerdo con la Declaración de Helsinki de 2008.

4.3 Estudio KIVI (ABC/3TC/NVP)

Objetivo 3.2 Evaluar la eficacia y seguridad de abacavir/lamivudina con los ITINN rilpivirina o nevirapina en pacientes infectados por VIH sin tratamiento previo.

4.3.1 Tipo de estudio

Se trata de un estudio de cohorte observacional, retrospectivo y multicéntrico.

4.3.2 Criterios de valoración

El criterio **de valoración primario** fue la CV del ARN- VIH-1 < 40 c/mL a las 48 semanas.

4.3.3 Participantes y diseño del estudio

Se incluyeron pacientes adultos consecutivos infectados por el VIH, sin tratamiento previo, HLA-B*5701-negativos, que iniciaron ABC/3TC/NVP entre 2005-2013, con al menos una visita de seguimiento. Las variables demográficas, clínicas y de laboratorio se evaluaron al inicio, al mes 1 y cada tres - cuatro meses a partir de entonces.

4.3.4 Análisis estadístico

Los datos se analizaron por intención de tratar (ITT) (cambio y pérdida = fracaso) y por análisis de tratamiento (OT).

4.4 Estudio ZEST

Objetivo 3.3 Evaluar el impacto del uso de bifosfonatos (ácido zolendrónico) vs el cambio del tratamiento con tenofovir a otros regímenes en la densidad mineral ósea de adultos infectados por el VIH suprimidos virológicamente, con DMO baja y que llevan TDF en su TAR.

4.4.1 Tipo de estudio

Se trata de un estudio aleatorizado, abierto, multicéntrico, fase IV a 24 meses.

4.4.2 Criterios de valoración

- Como **criterio de valoración primario** se comparó los efectos de la administración de 5mg de ácido zoledrónico intravenoso anual con el cambio de TDF a otro fármaco antirretroviral en la DMO de la columna lumbar durante 24 meses.
- Como **criterio de valoración secundario** se comparó los efectos de la administración de 5mg de ácido zoledrónico intravenoso anual con el cambio de TDF a otro fármaco antirretroviral en la DMO de la cadera durante 24 meses. Se eligió el cambio porcentual medio en la DMO de la columna lumbar desde el valor inicial como la medida de resultado primaria en lugar de la DMO total de la cadera, debido a que la DMO de la columna lumbar responde más rápidamente a las intervenciones, ya que contiene una mayor proporción de hueso trabecular metabólicamente activo [125].
- **Otros criterios** de valoración fueron: comparar los grupos aleatorizados en cuanto a incidencia de osteoporosis (definido por un T-score <2.5), evaluación del riesgo de fractura utilizando la versión australiana o española apropiada de la Evaluación del Riesgo de Fractura (FRAX), la aparición de fracturas y la seguridad (eventos adversos clínicos y de laboratorio de todos los grados, todos los eventos adversos graves,

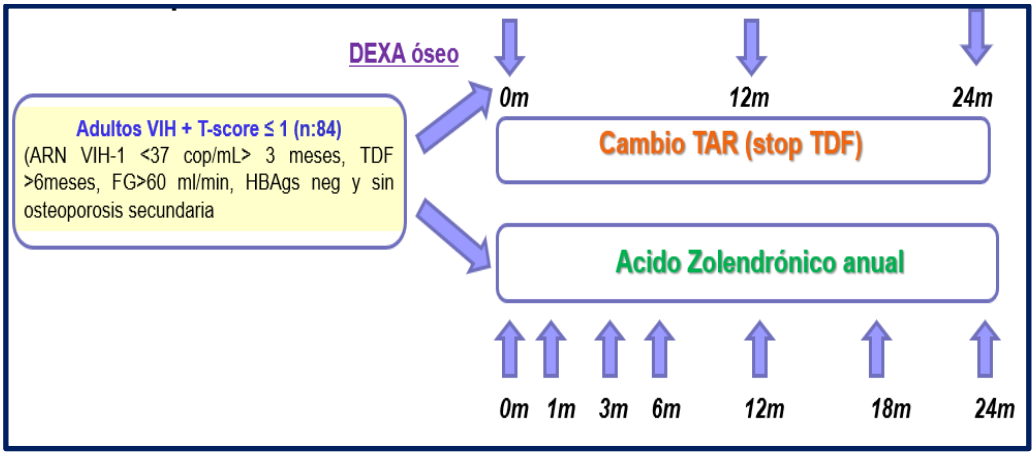
muerte, progresión al SIDA, fracaso virológico definido como un ARN VIH en plasma con más de 200 copias/ml en dos determinaciones con un intervalo de al menos 4 semanas entre cada una y cualquier modificación en el esquema antirretroviral desde la basal).

4.4.3 Participantes y diseño del estudio (figura 14)

- Criterios de inclusión: adultos con infección por VIH, con CV indetectable (ARN VIH <50 copias/ml) durante un mínimo de 3 meses con terapia antirretroviral con TDF durante al menos 6 meses y con una puntuación T-score de menos de 1,0 en la columna vertebral (L1-L4) o en el cuello del fémur izquierdo en la densitometría ósea mediante una absorciometría de rayos X de doble energía (DXA).
- Criterios de exclusión: Haber recibido tratamiento previo con bifosfonatos u otro tratamiento antiosteoporótico para la DMO baja, tener evidencia de osteoporosis secundaria, necesidad de tratamiento para la DMO baja (p.ej. fractura de fragilidad previa) o contraindicaciones para la administración de ácido zoledrónico (p.ej. hipocalcemia, cirugía dental mayor reciente o planificada, vitamina D no corregida (deficiente), necesidad de tratamiento con tenofovir para la hepatitis B crónica, que haya tenido fracaso virológico previo, resistencia, intolerancia o contraindicaciones al esquema TAR propuesto para el cambio (incluyendo positividad HLA-B5701 o enfermedad cardiovascular previa para regímenes que contienen abacavir) o que haya tenido una tasa de filtrado glomerular estimado (eGFR) inferior a 60 ml/min

por cada 1,73 m2. El(los) tratamiento(s) antirretrovirales propuestos para el cambio se seleccionaron antes de la aleatorización.

Figura 14. Participantes y diseño del estudio



El estudio fue un ensayo aleatorizado, abierto de 24 meses de duración, con participantes elegibles asignados aleatoriamente ya sea a comenzar con ácido zoledrónico de 5 mg por vía intravenosa, anual (dos dosis; y continuar con el tratamiento antirretroviral que contiene TDF) o a cambiar el TDF a otro fármaco antirretroviral seleccionado por el investigador (sin añadir un bifosfonato). El estudio se llevó a cabo antes de la disponibilidad de tenofovir alafenamida. La aleatorización fue estratificada por centro de radiología (uno en Sydney, otro en Melbourne y otro en Barcelona) y según la puntuación en la DMO (T-score > 2.0 o < = 2.0).

Todos los participantes recibieron suplementos de calcio de 1500mg diarios, y todos aquellos con vitamina D insuficiente o deficiente recibieron suplementos de

vitamina D al inicio del estudio y en el mes 11 (para el grupo de ácido zoledrónico) o en el mes 12 para el grupo con cambio de TDF.

En caso de insuficiencia en la vitamina D (25-50nmol/l) los participantes de los grupos recibieron una sola dosis de 50000 UI de vitamina D y para aquellos con deficiencia moderada (<25nmol/l) se administró una dosis única de 100000 IU de vitamina D. Los niveles de vitamina D se volvieron a medir en el mes 3 y si persistía la insuficiencia o deficiencia continuaban recibiendo 50000IU de vitamina D mensualmente durante el estudio.

La DMO de la columna lumbar (L1-L4) y de la cadera se midió por DXA anualmente durante 2 años. Todas las imágenes de los DXA fueron obtenidas usando un protocolo estandarizado, con ajuste central de los valores de la DMO para la consistencia transversal y longitudinal basado en los escáneres fantasma adquiridos localmente. Los resultados de la exploración DXA no fue devuelta a los sitios hasta el mes 24, a menos que ocurriera una fractura por trauma leve, una disminución de la DMO de más del 5% o se desarrollara una puntuación T-score de menos de 2.5. Por convención, las puntuaciones T-scores se calcularon en relación con la masa ósea máxima en mujeres blancas jóvenes [126]. Las puntuaciones z-scores se calcularon en relación con las poblaciones de referencia emparejadas por edad, sexo y raza/etnia. La DMO baja para la edad (por debajo del rango esperado) fue definida con una puntuación z (columna vertebral, cadera, cuello femoral) de 2,0 o menos, consistente con las recomendaciones para poblaciones jóvenes de la US National Osteoporosis Foundation y la International Society for Clinical Densitometry [127, 128]. Se consideró que los participantes con

puntuaciones de DMO de T-score < 2,5 en cualquier sitio (columna vertebral L1-L4, cadera total o cuello femoral) tenían osteoporosis [129]. La Herramienta de Evaluación del Riesgo de Fractura (FRAX) se utilizó para generar las puntuaciones de la probabilidad a 10 años de una fractura de cadera o una fractura osteoporótica mayor, utilizando la herramienta para cada participación según su país de origen [130].

4.4.4 Análisis estadístico

El tamaño de la muestra se calculó a partir de datos de estudios publicados sobre el tratamiento en relación con la DMO en VIH [57 - 60, 131, 132], en los que la respuesta media en la columna lumbar en relación con el control a los 2 años fue del 6,1% [desviación estándar (DE) <4%] con un bifosfonato y del 1% (DE 2%) con cambio de TDF [61 - 64]. Asumiendo una diferencia del 4% (DE 6%), el estudio propuesto requeriría 36 participantes en cada grupo para poder rechazar la hipótesis nula de que la población media de los grupos experimental y de control son iguales con un 80% de potencia, y una probabilidad de error de tipo 1 de 0,05. Para permitir una pérdida del 15% durante el seguimiento o la estrategia, se planificó reclutar 42 sujetos para cada grupo.

Todos los análisis se realizaron después de que todos los participantes completaron dos años de seguimiento o se retiraron permanentemente o se perdieron durante el seguimiento. Los análisis por intención de tratar modificado (ITTm) incluyeron a todos los pacientes que fueron asignados al azar, excluyendo a dos participantes que retiraron el consentimiento inmediatamente después de la asignación al azar y no cesaron el TDF; los análisis por protocolo censuraron a los participantes una

vez que reiniciaron el TDF (en el brazo de cambio del TDF) o pararon el TDF (en el brazo del ácido zoledrónico). Aquellos que no tuvieron seguimiento después de la visita basal y aquellos que reiniciaron o suspendieron el TDF como violaciones del protocolo antes del mes 12 (o en la visita siguiente a la basal por toxicidad) fueron excluidos de los análisis por protocolo.

El criterio de valoración primario fue el cambio porcentual en la DMO de la columna vertebral lumbar desde el valor inicial hasta los 24 meses mediante un análisis por ITT. Para los datos continuos, el cambio medio desde la basal hasta los meses 12 y 24 se calculó para los participantes con una visita basal y al menos una visita de seguimiento (ITTm). Tanto los análisis ITT (última observación llevada a cabo) como los análisis por protocolo se realizaron para las variables de DMO y fractura; las variables de evaluación de toxicidad se usaron únicamente para los datos por protocolo. El T test se usó para comparar grupos, a menos que los datos no se distribuyeran normalmente, en cuyo caso se utilizó la prueba de Wilcoxon. La prueba exacta de Fisher se utilizó para evaluar las diferencias en las proporciones. Se realizaron comparaciones formales del número de fracturas entre los brazos con un modelo de Poisson longitudinal de efectos aleatorios. Todos los análisis utilizaron un valor α de 0,05 en ambos lados. No se hizo ningún ajuste por comparaciones múltiples. Los análisis se realizaron con la versión 15.0 de Stata (Statacorp, College Station, Texas, USA).

4.4.5 Aspectos éticos

El estudio fue aprobado por el grupo de revisión institucional de cada centro clínico participante y se llevó a cabo de conformidad con los principios de la Declaración de Helsinki y los requisitos reglamentarios locales. Todos los participantes dieron su consentimiento informado por escrito antes de participar. El estudio fue registrado en el Registro de Ensayos Clínicos de Australia y Nueva Zelanda *(ACTRN 12612000776808).*

4.5 Estudio Doultegravir en monoterapia

Objetivo 3.4 Describir la eficacia y la seguridad de la monoterapia con dolutegravir en pacientes con opciones muy limitadas de TAR por efectos adversos, comorbilidades, riesgo de interacciones, o resistencia archivada en la cohorte de pacientes adultos infectados por VIH del Hospital Clínic de Barcelona

4.5.1 Tipo de estudio

Estudio retrospectivo, no intervencional, unicéntrico, por medio de la búsqueda en la base de datos del Hospital Clínic Barcelona de pacientes infectados por el VIH en los que el médico tratante cambiaba el esquema de tratamiento a Dolutegravir 50 mgs 1 vez al día debido a 1 o más de las siguientes razones: efectos adversos relacionados con el tratamiento antirretroviral; comorbilidades; riesgo de interacciones; o resistencias archivadas que comprometan la eficacia antirretroviral.

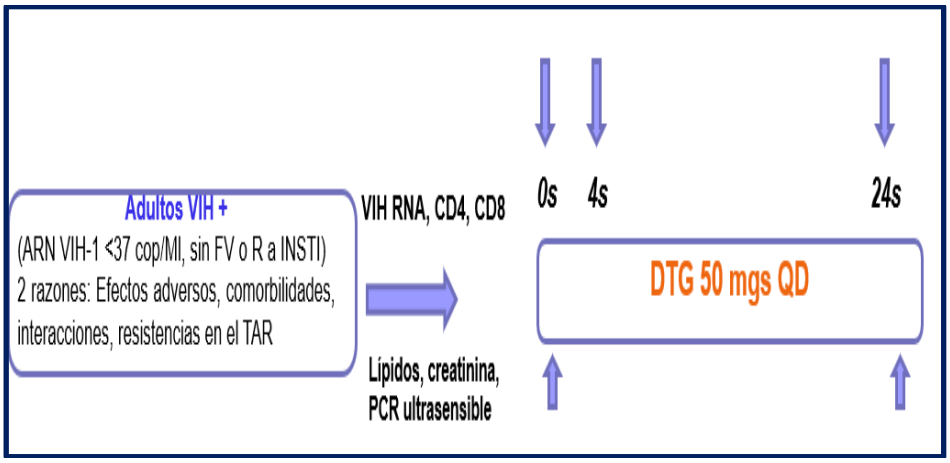
4.5.2 Criterios de valoración

- **Criterio de valoración primario:** proporción de pacientes con VIH-1 <37 copias/mL a las 24 semanas (ITT discontinuación=fracaso).

- **Criterios de valoración secundarios:** Cambios desde la basal a 24 semanas de poblaciones CD4 y CD8, ratio CD4/CD8, lípidos en ayunas, creatinina, FG (estimado según CKD-EPI) y PCR ultras; incidencia de eventos adversos, impacto en las razones que llevaron al cambio, y en caso de FV (mutaciones de R en plasma y PBMC).
    - En caso de fracaso virológico, las mutaciones de resistencia en la transcriptasa inversa, proteasa y la integrasa del VIH se testaron en plasma y PBMCs por medio de secuenciación poblacional (Trugene, Siemens) y secuenciación ultraprofunda (plataforma 454 GS-Junior, Roche), respectivamente siguiendo los protocolos de rutina.

4.5.3 Participantes y diseño del estudio (figura 15)

Figura 15. Participantes y diseño estudio DTG en monoterapia



4.5.4 Análisis estadístico

La carga viral plasmática ≥ 37copias/mL, la interrupción de la monoterapia con dolutegravir o la pérdida durante el seguimiento se consideraron fracasos terapéuticos.

Se utilizaron la prueba exacta de Fisher o la prueba de Wilcoxon para comparar proporciones y las variables continuas, respectivamente, entre la basal y la semana 24.

4.5.5 Aspectos éticos

Según la normativa del Ministerio de Sanidad, este estudio no requería la aprobación de un comité de ética de la investigación.

4.6 Estudio DOLAM

Objetivo 3.5 Evaluar la viabilidad de pautas de TAR basadas en dolutegravir con menos de tres fármacos y más específicamente comparar la eficacia y la seguridad de la monoterapia con dolutegravir frente a la biterapia con dolutegravir más lamivudina en adultos infectados por VIH con supresión virológica sostenida.

4.6.1 Tipo de estudio

Ensayo clínico multicéntrico, paralelo, abierto, aleatorizado y controlado con tratamiento activo, que comprende 2 fases (A y B):

- La fase A tiene como objetivo incluir a 30 pacientes por rama y seguirlos durante al menos 24 semanas; esta se realizó con el fin de determinar si las ramas experimentales estaban sujetas a una tasa inaceptable (definido como 5%) de fracaso virológico.
- La fase B tiene como objetivo incluir el número completo de pacientes y seguirlos durante 48 semanas.

Se consideró la discontinuación prematura si había fracaso virológico (definido como dos CV ARN-VIH > 50 copias/ml consecutivos o una única con CV ARN-VIH > 1000 copias/mL) o la interrupción de la terapia debido a eventos adversos, enfermedad concurrente, desviación del protocolo o deseo del paciente. Los blips fueron registrados. La Junta de Monitoreo de Seguridad de Datos (DSMB) revisa los datos si la proporción de fracasos virológicos en las ramas experimentales es >= 5%.

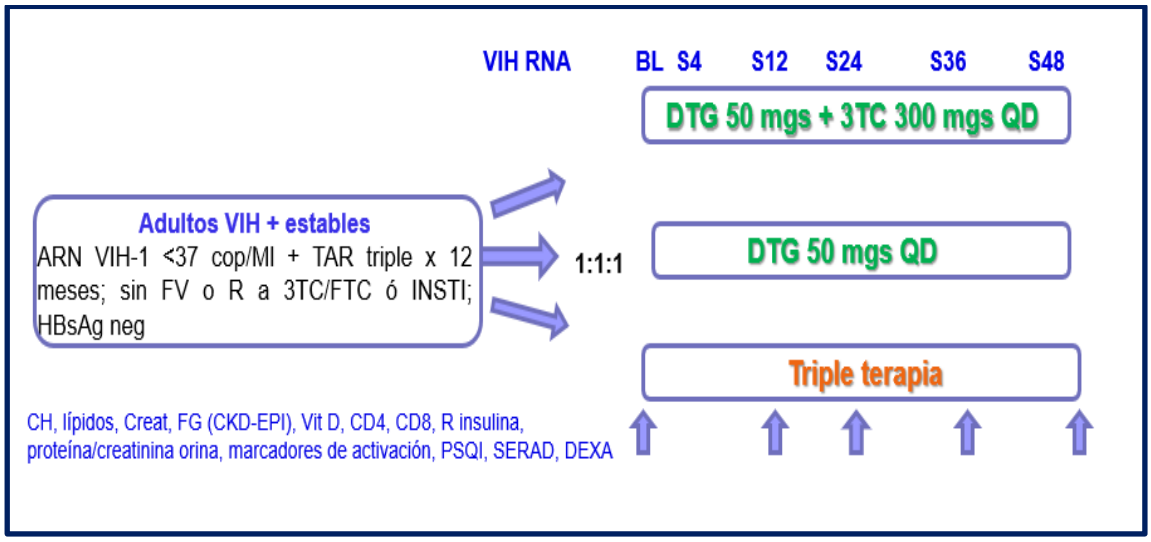
4.6.2 Criterios de valoración

- **Criterio de valoración primario:** evaluar la eficacia terapéutica y virológica (FDA snapshot algoritmo) con la detección de RNA HIV-1 en plasma a las 48 semanas. Dado el propósito de la fase A se reportaron las tasas de fracaso virológico, blips y eventos adversos en la semana 24.
- **Criterios de valoración secundarios:**
    - Cambios en parámetros metabólicos
    - Cambio en los niveles de vitamina D
    - Cambios en densidad mineral ósea (DEXA)
    - Cambios en la distribución de la grasa corporal (DEXA)
    - Detección de RNA VIH-1 ultrasensitive (límite de detección 1 copia/mL)
    - Cambios en el reservorio VIH-1 en PBMCs

4.6.3 Participantes y diseño del estudio (figura 16)

- Criterios de inclusión: adultos (>18 años), con carga virológica <50 copias/ml y tratamiento triple durante al menos 12 meses.
- Criterios de exclusión: mutaciones de resistencia o fracaso virológico a 3TC/FTC o inhibidores de la integrasa. Embarazo, lactancia o previsión de embarazo, CD4 nadir < 200 células/ml y hepatitis B crónica.

Figura 16. Algoritmo diagnóstico



4.6.4 Aspectos éticos

Las juntas de revisión institucional de los centros participantes aprobaron el estudio y se obtuvo el consentimiento informado por escrito de todos los pacientes elegibles antes de la aleatorización. El estudio está registrado en EudraCT, número: *201500027435.*

4.7 Estudio de tolerabilidad de los inhibidores de la integrasa en la vida real

Objetivo 3.6 Comparar la incidencia de discontinuación en general y más específicamente por toxicidad, evaluar los factores de riesgo de discontinuación y conocer el perfil de toxicidad en la vida real de los tres inhibidores de integrasa disponibles en la cohorte de adultos infectados por VIH en el Hospital Clínic de Barcelona.

4.7.1 Tipo de estudio

Estudio retrospectivo seleccionando a los pacientes desde la base de datos de pacientes con infección VIH del Hospital Clínic de Barcelona.

4.7.2 Criterios de valoración

- **Criterio de valoración primario:** detectar discontinuación temprana de los inhibidores de la integrasa en general y debido a toxicidad (se definió discontinuación temprana como la interrupción del INSTI durante el primer año de inicio)
- **Criterios de valoración secundarios:** eventos adversos específicos que han llevado a la discontinuación.

4.7.3 Participantes y diseño del estudio

Se recogieron los datos de todos aquellos con prescripción de raltegravir, elvitegravir o dolutegravir durante el periodo de 2007 a 2015 (tanto naive como cambios desde otras pautas con CV ARN-VIH indetectable).

Se excluyeron los pacientes desde finales de febrero de 2016 (cuando se publicó el informe holandés en la CROI 2016) [54] para evitar cualquier posible interrupción del dolutegravir (por influencia), o cuando cambiaron su inhibidor de la integrasa (el primero), se perdieron en el seguimiento o murieron, lo que ocurriera primero.

Decidimos delimitar los resultados principales dentro de un año de seguimiento por las siguientes razones:

- Las toxicidades más relevantes asociadas con los inhibidores de la integrasa en los ensayos clínicos y los estudios de cohorte han sido generalmente agudas.
- Debido a que cuanto más larga sea la duración de la terapia antirretroviral, menos clara será la relación entre cualquier efecto adverso agudo potencial y un fármaco dado.
- Para evitar sesgos que favorezcan a los fármacos que se pautaron hace tiempo, ya que los pacientes que hayan comenzado bien su tratamiento con el inhibidor de la integrasa antes contribuirían con más años de vida que los que lo iniciaron más recientemente. Las toxicidades especificas se agruparon por órganos/sistemas según la descripción en la base de datos de la historia clínica.

También se realizaron análisis de sensibilidad limitados al período 2014-15, cuando los tres inhibidores de la integrasa estaban disponibles, y los resultados no cambiaron (ver Tablas de datos suplementarios S1-S5, disponibles en JAC Online).

Se recogieron las características basales tanto al momento del diagnóstico como al momento del inicio del INSTI.

En nuestro centro, los datos de los pacientes se registran rutinariamente en una base de datos de historia clínica aprobada por la Junta de Revisión Institucional Local, que incluye información detallada sobre la prescripción de antirretrovirales y las razones para su interrupción. Las posibles razones preespecificadas en la base de datos para la interrupción de medicamentos antirretrovirales incluyen el fracaso virológico, los efectos adversos, la simplificación, el riesgo de interacciones, la decisión médica debido a otras razones, la pérdida de seguimiento y la muerte. Cuando el motivo de la interrupción incluye la posible toxicidad de un medicamento antirretroviral se suele recoger en el curso clínico correspondiente de la visita de seguimiento una descripción de los síntomas clínicos relevantes y/o de los parámetros del laboratorio asociados con el posible efecto adverso.

Si había más de una razón para la discontinuación del tratamiento, se consideró que la discontinuación del fármaco sería debida a la toxicidad siempre que se informaran efectos adversos, independientemente de otras razones concomitantes.

4.7.4 Análisis estadístico

Los datos cuantitativos se compararon con las pruebas de ANOVA o Kruskal-Wallis; los datos cualitativos con las pruebas de chi-cuadrado o la prueba exacta de Fisher. La incidencia se calculó como el número de episodios por 1000 personas-año. Los índices de tasa de incidencia (IRRs) de cada inhibidor de la integrasa se estimaron

considerando de forma arbitraria la referencia de 1 para el raltegravir. Para las comparaciones de IRRs se usaron modelos de regresión binomial negativa utilizando el cociente de probabilidad o pruebas Wald. Se evaluaron los factores de riesgo para la discontinuación mediante modelos Cox multivariados.

4.7.5 Aspectos éticos

De acuerdo con la normativa española vigente, el estudio fue clasificado como estudio de post-autorización con un diseño no prospectivo por parte de la Agencia Española de Medicamentos y Productos Sanitarios; fue aprobado por la Junta de Revisión Institucional Local y no se requirió de un consentimiento informado, por lo que los autores declaran que han sido totalmente independientes en el diseño, análisis y redacción de este estudio.

4.8 Estudio A-TRI-WEEK *(clinicaltrials.gov: NCT01778413)*

Objetivo 3.7 Evaluar la viabilidad, seguridad y eficacia de una pauta con efavirenz/emtricitabina/tenofovir disoproxil fumarato tomada tres días por semana en adultos infectados por VIH con supresión virológica sostenida.

4.8.1 Tipo de estudio

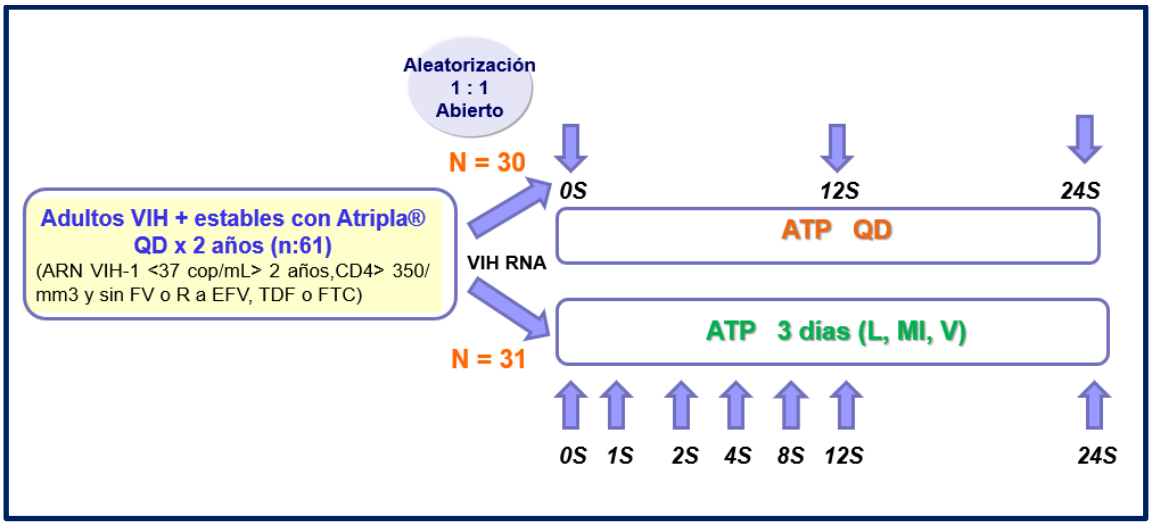
Estudio piloto, aleatorizado, abierto, prospectivo, unicéntrico, fase IV.

4.8.2 Criterios de valoración

- **Criterio de valoración primario:** fracaso terapéutico (VIH RNA >37, progresión a SIDA, muerte, o discontinuación) a las 24s de seguimiento.
- **Criterios de valoración secundarios:** evaluar otros parámetros (PSQI, IMC, DMO, CD4, CD8, CV (1cop/ml), niveles plasmáticos 25OHVitD, y EFV en plasma, FG (CKD-EPI), perfil lipídico; P y proteínas en orina, reservo VIH y parámetros inmunológicos extensivos (marcadores de inmunoactivación e inflamación) a las 0 y 24s.

4.8.3 Participantes y diseño del estudio

Figura 17. Algoritmo estudio



4.8.4 Análisis estadístico

Los pacientes fueron seguidos todo el tiempo del estudio independiente de si discontinuaron la medicación asignada de forma temprana. Todos los pacientes

aleatorizados se incluyeron en el análisis. El análisis estadístico se desarrolló con el uso del Software Stata (reléase 14) (StataCorp., College Station, Texas, USA). La comparación de proporciones entre los grupos de tratamiento se realizó mediante el test de Fisher o la Chi-cuadrado. La comparación de variables continuas entre grupos se realizó con las pruebas de Mann-Whitney o ANOVA. Para comparar la eficacia de la rama experimental con la estándar se calculó el intervalo de confianza del 95% por el método de Newcombe.

5. Resultados

5. Resultados

Se adjuntan los pdf de los diferentes artículos siguiendo el orden de los objetivos mencionados.

5.1 Estudio LIPOKAL *(ClinicalTrials.gov NCT00978237)*

Objetivo 3.1 Evaluar el impacto del cambio de efavirenz por lopinavir/ritonavir sobre la grasa corporal en adultos infectados por VIH con lipoatrofia persistente a pesar de estar libres de ITIAN timidínicos

PDF del artículo 1:

"Improvement of lipoatrophy by switching from efavirenz to lopinavir/ritonavir". J. Rojas, M. Lonca, A. Imaz, V. Estrada, V. Asensi, C. Miralles, et al. HIV Medicine 2016; 17: 340-9. FI: 2,932.

DOI: 10.1111/hiv.12314

HIV Medicine (2016), 17, 340–349

ORIGINAL RESEARCH

Improvement of lipoatrophy by switching from efavirenz to lopinavir/ritonavir

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Objective

To assess whether changes in antiretroviral drugs other than thymidine nucleoside reverse transcriptase inhibitors (NRTI) may have a body fat impact in HIV-infected patients with lipoatrophy.

Methods

Ninety-six-week phase IV, open-label, multicentre, pilot randomized trial. HIV-infected patients with moderate/severe lipoatrophy at one or more body sites despite long-term thymidine NRTI-free therapy were randomized to continue their efavirenz (EFV)-based antiretroviral regimen or to switch from EFV to lopinavir/ritonavir (LPV/r). The primary endpoint was the absolute change in limb fat mass measured by dual X-ray absorptiometry from baseline to 96 weeks. Changes in other body fat measurements, subjective perception of lipoatrophy, subcutaneous fat gene expression and plasma lipids were also assessed.

Results

Thirty-three patients (73% men, median age 52 years) were recruited. At 96 weeks, absolute limb fat mass increased in the LPV/r arm *vs.* the EFV arm (estimated difference +1082.1 g; 95% CI +63.7 to +2103.5; $P = 0.04$); this difference remained significant after adjustment by gender, age, fat mass, body mass index and CD4 cell count at baseline. Subjective lipoatrophy perception scores also improved in the LPV/r arm relative to the EFV arm. Adipogenesis, glucose and lipid metabolism, and mitochondrial gene expression increased in the LPV/r arm compared with the EFV arm at 96 weeks. HDL cholesterol decreased in the LPV/r arm relative to the EFV arm.

Conclusions

Switching from EFV to LPV/r in HIV-infected patients with lipoatrophy may offer further limb fat gain beyond thymidine NRTI discontinuation, although this strategy decreased plasma HDL cholesterol and caused changes in subcutaneous fat gene expression that may be associated with increased insulin resistance.

Keywords: efavirenz, lipoatrophy, lopinavir/ritonavir, pilot study, switch

Accepted 30 July 2015

Introduction

HIV-associated lipodystrophy is clinically characterized by body fat changes including subcutaneous fat loss (lipoatrophy) with or without truncal fat accumulation (lipohypertrophy). Mitochondrial dysfunction and inflammation in subcutaneous adipose tissue are key factors in the pathogenesis of HIV-associated lipoatrophy [1].

The thymidine nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and, to a lesser extent, zidovudine are well-known major contributors for lipoatrophy [1]. The potential differential involvement of other antiretroviral drugs on body fat changes was not apparent until recently. In 2007, two independent randomized clinical

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trials first suggested that efavirenz (EFV)-containing therapy may lead to greater limb fat loss relative to lopinavir/ritonavir (LPV/r)-containing therapy in antiretroviral-naïve HIV-infected adults [2,3]. These studies challenged the long-held view that protease inhibitors may contribute to the development of lipodystrophy. However, the presence of thymidine NRTIs in those studies made it difficult to ascertain by how much LPV/r and EFV really differed in their body fat effects.

Switching away from thymidine NRTIs is the only recommended strategy to restore subcutaneous fat in patients with HIV-associated lipoatrophy, but improvement is slow and limited [4]. Whether or not changes in antiretroviral drugs other than thymidine NRTIs will have an additional body fat impact in HIV-infected patients with lipoatrophy who already had thymidine NRTIs discontinued is unknown.

Methods

Design

This 96-week phase IV, open-label, multicentre, pilot randomized trial aimed to assess the effects of switching from LPV/r to EFV in HIV-infected patients with persistent lipoatrophy despite long-term antiretroviral therapy (ART) free of thymidine NRTIs (LIPOKAL, ClinicalTrials.gov number NCT00978237). The protocol was approved by a central Ethics Committee, later by the corresponding local Ethics Committees and finally by the Spanish Medicines Evaluation Agency. Written informed consent was obtained from patients prior to screening for eligibility.

The primary endpoint was the between-arms difference in absolute limb fat mass change measured by dual X-ray absorptiometry (DXA) scan from baseline to 96 weeks. Secondary endpoints were percentage change in limb fat mass; changes in trunk and total body fat mass; changes in the subjective evaluation of lipoatrophy; changes in visceral and subcutaneous adipose tissue [measured by single-slice abdominal computed tomographic (CT) scan at L4]; changes in body mass index (BMI); and changes in fasting cholesterol [total, high (HDL) and low (LDL) density lipoprotein cholesterol] and triglycerides. Additional endpoints included discontinuation of study drugs due to adverse events, and virological failure defined by two consecutive plasma HIV-1 RNA measurements > 50 copies/mL. Abdominal subcutaneous adipose tissue biopsies were obtained in a subgroup of patients at baseline and at 96 weeks.

Patients

Eligible HIV-1-infected subjects were aged 18 years or over, had been virologically suppressed on current therapy with EFV plus either tenofovir/lamivudine (TDF/3TC) or abacavir/lamivudine (ABC/3TC) for > 6 months, had previously developed lipoatrophy while exposed to therapy containing thymidine NRTIs, and lipoatrophy still remained clinically apparent in their limbs, buttocks or face despite having had thymidine NRTIs discontinued for more than 2 years. Exclusion criteria were: previous failure to protease inhibitor (PI)-containing therapy or with evidence of genotypic mutations of resistance to PIs; any contraindication to receiving LPV/r; mild lipoatrophy; illicit drugs or alcohol abuse; pregnancy or lactation; opportunistic disease in the previous 4 weeks; current therapy with investigational or immunosuppressive or antineoplastic or nephrotoxic agents; acute hepatitis; or estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Eligible subjects with moderate to severe lipoatrophy according to HOPS [5] or Fontdevila [6,7] criteria at one or more body sites were randomized to continue their EFV-based antiretroviral regimen or to switch from EFV to LPV/r while maintaining the fixed-dose NRTI combination unchanged. Women of childbearing potential were requested to use an effective method of contraception. Lipid-lowering therapy was permitted if at a stable dosage and if commenced > 4 weeks before randomization. After recruitment, each patient's anonymized details were faxed to the Clinical Trials Unit at Hospital Clínic (Barcelona), who notified the recruiting clinician of the corresponding random treatment allocation generated by a computer.

Procedures

Participants were assessed at baseline, 4, 16, 32, 48, 64, 80 and 96 weeks. At each visit, clinical data were obtained and blood samples were collected after at least 8-h overnight fast. Complete blood and CD4 cell counts, plasma HIV-1 RNA, triglycerides, and total and HDL cholesterol were measured at each site throughout follow-up. LDL cholesterol was measured indirectly, whenever triglycerides were lower than 400 mg/dL [8]; otherwise, it was measured directly.

At baseline, 48 and 96 weeks, each participant had his or her body fat loss clinically evaluated following standardized criteria. HOPS-derived criteria [5] were used for limbs and buttocks. Briefly, both patient and physician independently rated the degree of lipoatrophy in each site

as absent (score of 0), mild (noticeable on close inspection, score of (1), moderate (readily noticeable by patient or physician, score of (2), or severe (readily noticeable to a casual observer, score of (3). The Fontdevila classification was used for facial evaluation [6,7] (Fig. S1). Briefly, the physician rated the degree of lipoatrophy in the face as absent (score of 0), mild (malar and cheek flattening, score of (1), moderate (cheek hollowness without evidence of underlying bone and muscular structures, score of (2), or severe (cheek hollowness with evidence of underlying bone and muscular structures, score of (3). The worst score in any of the three body sites evaluated (limbs, buttocks, or face) was used for computing.

Also at baseline, 48 and 96 weeks, weight and height were measured and whole body dual X-ray absorptiometry (DXA) and abdominal computed tomography (CT) scans were performed to assess body fat and visceral (VAT) and subcutaneous (SAT) adipose tissues, respectively. BMI was calculated by dividing weight (in kg) by the square of height (in metres). DXA and CT imaging were performed locally following previously standardized scanning protocols, for each patient on the same radiographic machine and with identical parameters each time. At the end of the study, all the scans were read centrally by a radiologist unaware of any patient's assigned therapy (Dr Luis del Rio, CETIR Grup Mèdic, Barcelona). No specific physical or dietary recommendations were given.

For DXA scans, patients were placed straight on the table, with all their body parts in the scan field, arms separated from the trunk and legs rotated inward 25°. Absolute and percentage arm, leg and trunk fat measurements were directly obtained. Limb fat was calculated by summing arm and leg fat, and the Fat Mass Ratio (FMR) was calculated as the ratio between percentage trunk fat and percentage limb fat [9]. For CT scans, patients were supine with arms raised above the head. All soft tissue was included in the CT field of view. With a mid-L4 vertebral scout film as a guide, a single 5-mm-thick axial slice of the abdomen was obtained. VAT and SAT areas were traced manually.

In a subgroup of patients from one participating centre (Hospital Clínic, Barcelona), abdominal subcutaneous adipose tissue samples were harvested at baseline and at 96 weeks and preserved using 1 mL RNAlater (Ambion, Huntingdon, UK) at −80°C until RNA extraction was performed. For total RNA extraction, each sample was powdered in a pestle and a mortar using liquid nitrogen, and later homogenized in 1 ml TRIZOL reagent (Invitrogen/Life Techonologies, Carlsbad, CA, USA) and precipitated using chlorophorm. RNA concentration was calculated using NanoDrop technology ND-1000 (Thermo Scientific, Waltham, MA, USA). RNA integrity was then evaluated using RNA 6000 Nano LabChips on an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). All chips were prepared according to the manufacturer's instructions at the transcriptomic platform of Barcelona Science Park (Barcelona, Spain). Degradation was evaluated by reviewing the electropherograms and the RNA integrity number of each sample. Only samples with preserved 18 and 28S peaks and RIN values > 7 were selected for gene expression analyses. Messenger RNAs (mRNAs) of genes involved in adipogenesis, glucose and lipid metabolism, mitochondrial metabolism and inflammation were assessed in the study. We and other workers have previously assessed these mRNAs, *in vitro* and *in vivo*, in ART-associated body fat studies [10–12]. Selected genes and a brief functional description of each one are shown in Table S1. Total RNA (200 ng) was reverse-transcribed in 200 µLaccording to manufacturer's recommendations using TaqMan Reverse Transcription Reagents (Applied Biosystems, Foster City, CA, USA). Gene expression assays were performed using TaqMan primers and probes (Applied Biosystems) for endogenous control gene (*18S*, Hs99999901_s1) and target genes (*CEBP/A*, Hs00269972_s1; *PPARγ*, Hs00234592_m1; *ADIPOQ*, Hs4331182; *LEP*, Hs00174877_m1; *GLUT4*, Hs00168966_m1; *LPL*, Hs00173425_m1; *COXII*, Mm03294838_g1; *COXVI*, Hs00266371_m1; *TNFα*, Hs00174128_m1 and *MCP-1*, Mm00656886_g1). Relative quantifications (RQ) were performed through quantitative PCR in the Applied Biosystems 7900HT Fast Real-time PCR system. Reaction volumes contained: 5 µL of water, 1 µL of TaqMan primer/probe mix (20×) for target or endogenous control gene, 10 µL of gene expression master mix (2×) and 4 µL of cDNA at a final concentration of 4 ng. Thermocycler conditions were as follows: 95°C hot-start for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. Each sample was run in triplicate and controls lacking RNA or cDNA were included in each set of experiments. Analyses of fat biopsies were performed by a biologist unaware of each patient's assigned therapy (Mireia Arnedo, Hospital Clínic, Barcelona).

Statistical analyses

Analyses were performed on an intention-to-treat basis. Statistical analysis was performed with the use of Stata 9.2 (StataCorp, College Station, TX, USA). χ^2 or Fisher's exact tests were used to compare proportions between treatment arms. Mann–Witney *U*-tests were used for comparisons of continuous variables between treatment arms. Ninety-five percent confidence intervals were calculated for treatment differences in the primary end-point, and linear regression was used to adjust for baseline variables.

Lipid changes between treatment arms were compared by repeated measures ANOVA. For the gene expression analysis, raw C_t (cycle threshold: the number of cycles required for the fluorescent signal to cross the threshold) values of the expression of each individual mRNA were obtained using SDS software version 2.3. C_t values were then exported into RQ Manager version 1.2 software (Applied Biosystems) for ΔC_t ($\Delta C_t = Ct_{\text{target gene}} - C_{\text{tendogenous control gene}}$) value determination in order to quantitate the mRNA level of the target gene relative to that of the endogenous control (*18S*). Assuming mean limb fat gains of 100 and 500 mg in control and experimental treatment arms (respectively) at 96 weeks, sixteen subjects per arm were required to ensure 80% power to detect a 400 mg difference in mean limb fat mass between the two arms with a standard deviation of 400 mg at the 5% level of significance. Assuming 10% losses per year, enrollment was planned at twenty patients per arm.

Results

Patient characteristics

Between 17 March 2010 and 29 April 2011, 33 patients underwent randomization and received at least one dose of study drugs (Fig. 1). A number of candidates declined to participate because they did not accept having their regimen switched into a more complex one. Patients entering the study more frequently had ABC/3TC (73%) than those who did not (22%), but there were no other significant epidemiological or HIV history differences. Sixteen patients were assigned to continue on EFV and 17 patients were assigned to switch to LPV/r. Baseline characteristics are shown in Table 1. One patient in the LPV/r arm discontinued study medication due to gastrointestinal effects at week 4, and one patient assigned to EFV was lost at week 48. One patient in each arm started lipid-lowering therapy during the study; there were no dose or formulation changes in lipid-lowering therapies already taken at baseline. While no patient in the LPV/r arm had virological failure, one patient in the EFV arm experienced virological failure at week 96. Five patients in the LPV/r arm and four patients in the EFV arm had paired fat biopsies at baseline and at 96 weeks available.

Changes in Body Mass Index and body fat

Table 2 shows changes in BMI and body fat at 48 and 96 weeks. At 96 weeks, absolute limb fat mass increased in the LPV/r arm relative to the EFV arm (estimated difference +1082.1 g; 95% CI +63.7 to +2103.5; $P = 0.04$). This difference remained significant after adjustment by gender, age, fat mass, BMI and CD4 cell count at baseline. Although trunk fat progressively tended to decrease in the LPV/r arm, it showed an opposite direction in the EFV arm (estimated difference at 96 weeks -1558.1 g; 95% CI −3341.3 to +225.1; $P = 0.09$). Owing to the differential behaviour of limb and trunk fat in both arms, FMR increased in the EFV arm while it decreased in the LPV/r arm (estimated difference at 96 weeks −1.32; 95% CI −1.91 to −0.73; $P = 0.004$). SAT significantly increased in the LPV/r arm relative to the EFV arm, but

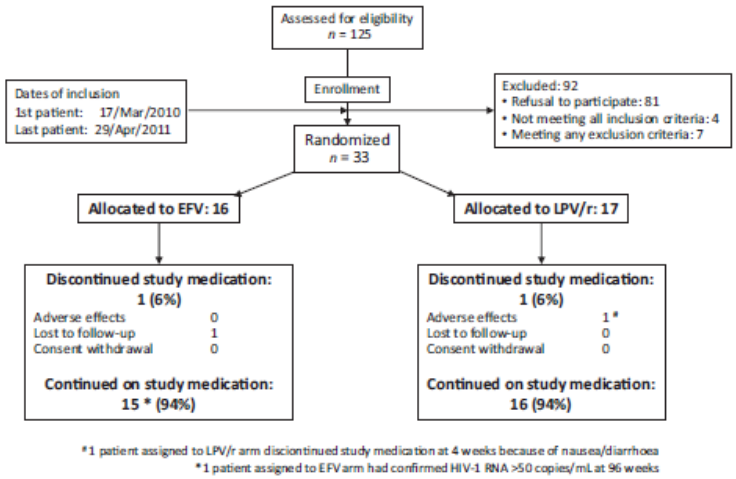

Fig. 1 Trial profile. EFV, efavirenz; LPV/r, lopinavir/ritonavir.

Table 1 Baseline characteristics

	EFV (n = 16)	LPV/r (n = 17)
Age (years)	53 (46–60)	51 (45–60)
Male (%)	12 (75%)	12 (70.6%)
Risk for HIV infection		
MSM	6 (37.5%)	6 (35.3%)
Heterosexual	6 (37.5%)	6 (35.3%)
IVDU	4 (25%)	5 (29.4%)
Years on ART	13 (8–18)	12 (7–17)
NRTIs at entry		
ABC/3TC	12 (75%)	12 (70.6%)
TDF/FTC	4 (25%)	5 (29.4%)
Off thymidine NRTIs (years)	4 (3–5)	4 (3–6)
Lipid-lowering therapy	2 (12.5%)	2 (11.8%)
Body mass index (kg/m^2)	22.3 (19.7–25.0)	23.1 (19.5–26.6)
CD4 cell count (cells/microL)	467 (312–636)	455 (278–689)
Plasma lipids		
Total cholesterol (mg/dL)	229 (202–339)	231 (189–485)
LDL cholesterol (mg/dL)	130 (122–142)	128 (102–156)
HDL cholesterol (mg/dL)	49 (42–59)	51 (43–62)
Triglycerides (mg/dL)	159 (112–194)	168 (87–217)
DXA scan		
Arm fat (g)	963 (770–1342)	990 (746–1467)
Arm fat (%)	13 (8–19)	14 (10–20)
Leg fat (g)	1473 (1231–2398)	1672 (1243–2720)
Leg fat (%)	10 (8–14)	11 (9–14)
Limb fat (g)	2436 (2001–3740)	2662 (1989–4187)
Limb fat (%)	11 (8–15)	12 (9–16)
Trunk fat (g)	5992 (4086–8359)	6074 (5233–9012)
Trunk fat (%)	25 (21–29)	24 (21–28)
Total fat (g)	8420 (6188–12 297)	8565 (7339–13 233)
Total fat (%)	21 (18–24)	21 (18–25)
Fat mass ratio	2.5 (2.1–2.9)	2.2 (1.9–2.7)
CT scan		
SAT (cm^2)	117 (80–169)	119 (78–175)
VAT (cm^2)	146 (88–207)	139 (80–200)

EFV, efavirenz; LPV/r, lopinavir/ritonavir; MSM, Male homosexual; IVDU, Intravenous drug user; ABC/3TC, abacavir/lamivudine; TDF/FTC, tenofovir/emtricitabine; NRTI, nucleoside reverse transcriptase inhibitors; DXA, dual X-ray absorptiometry; CT, computed tomography; SAT, subcutaneous abdominal fat; VAT, visceral abdominal fat.
Data are median values (interquartile range) unless otherwise expressed.

there were no significant changes between arms in BMI, total body fat or VAT.

Table 3 shows the scores in the clinical evaluation of lipoatrophy at baseline, 48 and 96 weeks. Out of 96 evaluations performed, patients scored worse than physicians in 67, physicians scored worse than patients in 12, and patients and physicians scored similarly in 17. Scores remained mostly unchanged in the EFV arm but tended to decrease in the LPV/r arm after 96 weeks.

Changes in subcutaneous fat gene expression

Figure 2 shows changes between arms in subcutaneous fat gene transcript expression at 96 weeks. Messenger

Table 3 Clinical evaluation of lipoatrophy. Both patient and physician independently rated the degree of lipoatrophy according to HOPS-derived criteria [5] for limbs and buttocks, and Fontdevila classification [6,7] for facial evaluation. The worst score from either patient or physician in any of the three body sites evaluated (limbs, buttocks or face) was used for the analysis of scoring changes. Patients scored worse than physicians in 67 evaluations, physicians scored worse than patients in 12 evaluations, and patients and physicians scored similarly in 17 evaluations

	No (score of 0)	Mild (score of 1)	Moderate (score of 2)	Severe (score of 3)	P-value
Baseline					
EFV (n = 16)	0	0	8	8	0.71
LPV/r (n = 17)	0	0	12	5	
Week 48					
EFV (n = 16)	0	1	7	8	0.25
LPV/r (n = 16)	1	7	7	1	
Week 96					
EFV (n = 15)	0	0	6	9	0.06
LPV/r (n = 16)	2	8	6	0	

Table 2 Change from baseline in body composition parameters at 48 and 96 weeks

	48 weeks			96 weeks		
	EFV (n = 16)	LPV/r (n = 16)	P-value	EFV (n = 15)	LPV/r (n = 16)	P-value
BMI (kg/m^2)	+0.1 (−1.6, +2.0)	−0.7 (−2.1, +1.7)	0.88	+0.9 (−0.3, +2.3)	−0.5 (−2.0, +1.8)	0.73
Arms (g)	−8.4 (−74.0, +135.3)	+131.7 (−31.5, +359.4)	0.79	+13.6 (−80.2, +165.5)	+314.4 (+12.2, +605.3)	0.44
Arm (%)	−6.4 (−1.9, +6.0)	+11.0 (+3.0, +20.2)	0.73	+2.5 (−4.9, +12.8)	+17.3 (+9.8, +25.8)	0.37
Legs (g)	+16.5 (−154.0, +790.9)	+294.6 (−222.8, +465.9)	0.15	−177.2 (−350.4, +487.6)	+717.3 (+348.9, +1180.2)	0.06
Legs (%)	+1.5 (−6.3, +12.0)	+12.9 (+1.5, +23.7)	0.23	−4.4 (−10.1, +13.6)	+21.8 (+16.3, +29.8)	0.05
Limbs (g)	+9.3 (−175.3, +888.3)	+412.6 (−137.6, +702.3)	0.10	−68.5 (−410.2, +507.4)	+1043.2 (+402.6, +1687.5)	0.04
Limbs (%)	+1.1 (−5.7, +10.9)	+12.3 (+1.5, +27.4)	0.25	+0.4 (−4.6, +13.1)	+23.5 (+15.7, +32.9)	0.05
Trunk (g)	+706.6 (−496.7, +1950.8)	−47.5 (−1049.7, +954.8)	0.17	+1028.8 (−68.5, +2394.6)	−637.2 (−1544.6, +414.5)	0.09
Trunk (%)	+15.2 (−11.7, +28.8)	−3.6 (−9.1, +13.8)	0.14	+21.8 (−1.0, +37.9)	−10.6 (−15.6, −6.9)	0.08
Total fat (g)	+889.3 (−820.1, +3122.3)	+358.9 (−1228.7, +1425.1)	0.87	+1275.1 (−567.3, +3308.1)	+463.9 (−1112.3, +2388.2)	0.67
Total fat (%)	+17.8 (−14.9, +36.5)	+8.7 (+2.1, +12.5)	0.79	+26.9 (−6.9, +43.5)	+13.9 (+6.8, +19.7)	0.57
Fat mass ratio	+0.34 (+0.21, +0.49)	−0.15 (−0.02, −0.25)	0.02	+0.68 (+0.51, +0.86)	−0.66 (−0.45, −0.88)	0.004
SAT (cm^2)	+2.1 (−8.6, +13.2)	+14.3 (−13.1, +21.4)	0.08	+3.3 (−6.1, +10.1)	+19.7 (+11.4, +27.1)	0.03
VAT (cm^2)	+7.2 (+0.2, +14.5)	−2.6 (−9.1, +5.5)	0.24	+9.4 (+1.2, +15.6)	−2.3 (−10.2, +5.9)	0.14

BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
Data are median values (interquartile range).

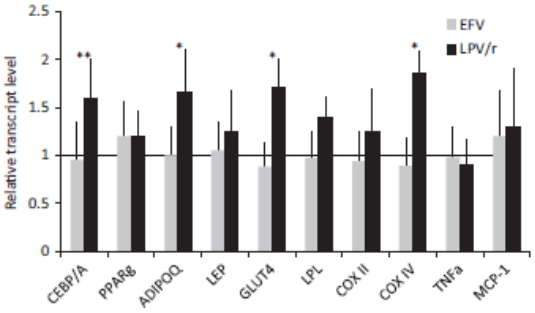

Fig. 2 Transcript expression changes from baseline until 96 weeks in the subcutaneous fat genes assessed in efavirenz (EFV) and lopinavir/ritonavir (LPV/r) study arms. Data are expressed relative to the housekeeping gene (*18S*), baseline transcript levels were set to 1 (dotted line). Bars represent mean ± SEM (standard error mean) of the patients included in each group. Statistically significant differences between baseline and week 96 are indicated by $^{*}P < 0.05$; $^{**}P < 0.01$.

RNAs for markers of adipogenesis including *CEBP/A* ($P = 0.007$) and *ADIPOQ* ($P = 0.02$), and glucose and lipid metabolism including *GLUT4* ($P = 0.03$) and *LPL* ($P = 0.06$), and the mitochondrial marker *COXIV* ($P = 0.03$) were significantly upregulated in the LPV/r arm compared with the EFV arm at 96 weeks.

Changes in plasma lipids

Table 4 shows changes in plasma lipids at different timepoints. HDL cholesterol decreased in the LPV/r arm relative to the EFV arm (repeated measures ANOVA, $P = 0.03$). Differences in the rest of the plasma lipid changes between arms were not significant.

Discussion

Switching away from thymidine NRTIs has been the only evidence-based intervention to improve lipoatrophy [4]. This pilot randomized clinical trial demonstrated the proof of concept that switching antiretroviral drugs other than thymidine NRTIs may improve body fat distribution further in HIV-infected patients with persistent lipoatrophy despite being off thymidine NRTIs. Increases in limb fat in patients switching from EFV to LPV/r were progressive over 96 weeks of follow-up. The direction of changes in subjective perception scores was in agreement with that of objective limb fat changes.

With body composition sub-studies being more common in clinical trials comparing between-antiretroviral regimens and thymidine NRTIs no longer used in these studies, it has been possible to know that regimens con-

Table 4 Median (interquartile range) changes in plasma lipids from baseline until 96 weeks. HDL cholesterol decreased in LPV/r arm relative to EFV arm (repeated measures ANOVA, $P = 0.03$). Differences in the rest of plasma lipid changes between arms throughout the study were not significant

	Week 4	16	32	48	64	80	96
Total cholesterol (mg/dL)							
EFV	−0.1 (−7.5, +16.5)	−0.9 (−21.0, +9.0)	+6.4 (−21, +21.5)	+3.5 (−15.1, +23.0)	+4.0 (−23.0, +12.9)	−9.5 (−18.0, +2.0)	+3.5 (−13.0, +17.5)
LPV/r	+6.4 (−11.0, +22.0)	+17.0 (0, +38.0)	+0.5 (−15.1, +16.8)	+0.5 (−26.0, +16.0)	−3.0 (−18.0, +3.0)	+6.0 (−4.0, +12.4)	+14.0 (−6.0, +25.0)
LDL cholesterol (mg/dL)							
EFV	+7.0 (−17.0, +20.0)	+6.9 (−12.0, +11.0)	+6.5 (−13.0, +17.0)	+10.0 (−1.9, +17.0)	+4.0 (−16.0, +5.4)	−9.0 (−23.0, −7.0)	0 (−16.0, +16.0)
LPV/r	+15.0 (−1.0, +30)	+24.2 (+7.0, +34.0)	+7.0 (−4.0, +34.0)	+12.0 (−3.2, +17.0)	+4.0 (−2.0, +15.0)	+5.0 (+3.9, +6.2)	+13.4 (−3.1, +21.2)
HDL cholesterol (mg/dL)							
EFV	−2.5 (−4.0, +1.0)	−5.0 (−10.0, +6.6)	+3.0 (−13.0, +10.0)	+2.0 (−8.0, +6.6)	0 (−7.8, +5.8)	+0.8 (−3.0, +7.0)	+1.0 (−9.0, +7.0)
LPV/r	−11.9 (−15.0, −5.0)	−11.0 (−19.0, −0.5)	−8.5 (−19.0, +4.0)	−6.0 (−12.0, −4.0)	−9.6 (−14.0, +1.0)	−13.0 (−22.0, −4.0)	−3.3 (−12.0, +8.0)
Triglycerides (mg/dL)							
EFV	−12.4 (−49.1, +37.5)	0 (−40.0, +27.0)	−28.0 (−103.0, +75.0)	+18.5 (−41.3, +63.5)	−2.0 (−38.3, +62.5)	+8.5 (−34.4, +77.6)	+23.5 (−31.0, +60.4)
LPV/r	+60.0 (+22.0, +79.7)	+33.1 (−40.5, +115.2)	+35.5 (−19.0, +46.0)	+36.3 (+9.0, +116.9)	−8.0 (−39.0, +36.3)	+17.7 (−2.5, +61.6)	+10.6 (−1.0, +32.8)
Total-to-HDL cholesterol ratio							
EFV	+0.1 (0, +0.5)	+0.3 (−0.4, +0.8)	0 (−0.8, +0.6)	+0.1 (−0.2, +0.5)	−0.2 (−0.5, +0.6)	−0.2 (−0.9, +0.4)	+0.1 (−0.6, +0.7)
LPV/r	+1.0 (+0.7, +2.9)	+0.7 (+0.4, +2.1)	+0.7 (−0.3, +1.0)	+0.4 (−0.1, +0.5)	+0.3 (−0.1, +1.2)	+0.7 (+0.3, +1.7)	+0.3 (−0.5, +1.2)

HDL, high-density lipoprotein; EFV, efavirenz; LPV/r, lopinavir/ritonavir.

taining antiretroviral drugs other than thymidine NRTIs may show differential effects on body fat. The ALTAIR study [13] and ACTG A5224S substudy [14] in which HIV-infected patients started TDF/3TC-based ART, have shown that atazanavir/ritonavir may lead to significantly higher limb fat increase than EFV after 96 weeks. In ACTG 5142 [2], patients treated with the NRTI backbone TDF plus emtricitabine (FTC) showed twice as many subjects with limb fat loss ≥ 20% in the EFV arm (12%) compared with the LPV/r arm (6%) after 96 weeks, although this difference was not statistically significant. Body composition data from older studies in antiretroviral-naïve patients such as BMS089 and COL100758 showed higher limb fat increase when atazanavir was ritonavir-boosted than when it was not [15], and when fosamprenavir was boosted with ritonavir 200 mg instead of 100 mg [16], respectively. Taken together, all of these data suggest that at least some protease inhibitors (relative to EFV), when administered ritonavir-boosted (relative to ritonavir-unboosted) and with a higher dose of ritonavir boosting (relative to a lower dose), will lead to higher limb fat gains in antiretroviral-naïve HIV-infected patients starting ART. Switching from non-NRTIs to LPV/r while preserving NRTIs (mostly thymidine NRTIs, stavudine 48% and zidovudine 34%) in patients failing first-line non-NRTI-based therapy also led to significant limb fat increase at 48 weeks [17], in accordance with our results. Whether the effect of LPV/r switch on promoting limb fat gain may be shared by switching to protease inhibitors other than LPV/r is plausible but currently unknown.

Our study also suggested a differential trend between EFV and LPV/r regarding trunk fat by DXA and VAT by CT scan. Subcutaneous and intra-abdominal fat depots show biological and genetic differences both in the general population [18] and in HIV-infected patients with lipodystrophy [19]. In HIV-infected patients, lipoatrophy and lipohypertrophy do not necessarily present concurrently [20,21]. The old protease inhibitor indinavir was reported to promote visceral fat gain (the so-called 'crix-belly') [22]. An increase in VAT following the initiation of ART has been commonly described; increase in VAT usually correlates with increase in limb fat and both changes may reflect the 'return-to-health' phenomenon instead of direct drug effects [23]. However, in the MITOX study in which HIV-infected patients with lipoatrophy had their antiretroviral regimens switched with the aim of increasing limb fat, it is remarkable that VAT also tended to decrease in the experimental arm over a 96-week period [24] in agreement with our results.

Recent *in vitro* data have shed more light into the potential toxic effects of EFV on human adipose and hepatic cells. When compared with LPV/r [11], nevirapine [25] or rilpivirine [26], EFV showed greater effects on impairing human adipogenesis, and increasing the expression and release of inflammatory cytokines. EFV (but nor nevirapine) has also been shown to induce mitochondrial toxicity by acutely inhibiting complex I of the respiratory chain, which in turn leads to a rapid accumulation of lipids in the hepatocyte cytoplasm mediated by activation of 5′ adenosine monophosphate-activated protein kinase [27,28]; hepatic steatosis has been associated with insulin resistance, dyslipidaemia and visceral abdominal obesity [29]. Although these *in vitro* toxic effects of EFV might be compensated *in vivo* by upregulatory mechanisms, they might have a role in maintaining body fat abnormalities in patients with lipoatrophy by both preventing limb fat gain and promoting visceral fat accumulation. In a recent nonrandomized study assessing 48-week changes in molecular markers of adipocyte biology and function in subcutaneous adipose tissue biopsies from antiretroviral-naïve HIV-infected patients starting either EFV or LPV/r with TDF/FTC [30], EFV was associated with increased expression of genes encoding for inflammatory cytokines relative to LPV/r. In our study, *CEBP/A*, *ADIPOQ*, *GLUT4*, *LPL* and *COXIV* expression in subcutaneous adipose tissue was significantly higher with LPV/r than with EFV after 96 weeks, although there were no differences between arms in inflammatory gene expression. These trends were similar to those observed in a 48-week randomized clinical trial performed by our group in antiretroviral-naïve HIV-infected patients starting either EFV or LPV/r [12], although in the latter study body fat changes between arms were not significant. Because the mRNAs for *CEBP/A*, *ADIPOQ*, *GLUT4*, *LPL* and *COXIV* genes and their corresponding protein levels are decreased in HIV-infected patients with lipodystrophy [31], our results might suggest a potential beneficial impact of the switch strategy on lipoatrophic adipose tissue. Nevertheless, the increased transcription of *GLUT4* in patients switching to LPV/r may alternatively reflect a compensatory mechanism for the known PI-mediated inhibition of GLUT4, a mechanism leading to insulin resistance [32]. Unfortunately, plasma markers of insulin sensitivity were not measured in this study.

Switching from EFV to LPV/r decreased HDL cholesterol. No effects were seen in other lipids than HDL cholesterol, although this may be due at least in part to the low sample size. Our group reported years ago that clinically evident lipodystrophy was an independent risk factor for developing early dyslipidaemia on starting LPV/r-based therapy in antiretroviral-experienced HIV-infected patients [33]. Although the limb fat increase and trunk fat decrease seen after LPV/r switching in this study

might reflect a more healthy body fat distribution and therefore contribute to a more favourable lipid profile, the use of LPV/r has been consistently associated with dyslipidaemia [34] and myocardial infarction [35,36].

Our study had important limitations. Participants were unintentionally selected with only 33 out of 125 screened patients agreeing to be randomized, although we could not find major epidemiological or HIV history differences between patients declining or accepting entry to the study. Due to a lower than expected attrition rate, we were able to maintain the sample size estimated to detect differences in the primary end-point. The open label administration of antiretroviral drugs might have induced some bias in making patients who had their therapy switched to adopt diet or lifestyle measures different from those who had their therapy continued. Nevertheless, these factors usually exert impact through weight change and we found significant differences in body fat changes between arms despite no difference in body mass index. We did not assess plasma insulin resistance markers and therefore we do not know whether body fat changes on switching to LPV/r ultimately led to a better or a worse insulin sensitivity status. We have previously observed that body fat changes, even in the subcutaneous fat compartment, in antiretroviral-naive patients treated with some ritonavir/boosted protease inhibitors may be associated with insulin resistance [22]. Due to the small sample size, we were unable to assess more detailed information about factors influencing body fat changes. Findings were restricted to lipoatrophic patients with clearly defined inclusion and exclusion criteria who had EFV replaced by LPV/r and may not be extrapolated to other types of patients or antiretroviral therapies. Most participants were men and our findings cannot be generalized to women. We found it extremely difficult to enroll patients because they simply did not accept switching to a more complex regimen despite fulfilling all inclusion and exclusion criteria; the advent of new once-daily PI/r-based single tablet combinations could improve this limitation. Although the results of our study suggest an improvement in lipoatrophy and body fat distribution by switching from EFV to LPV/r, this strategy should be balanced against the well-established inconveniences of a more complex regimen and also the potential risks for LPV/r-associated adverse effects [34–36].

Lipoatrophy still remains as a prevalent problem in developing countries and other HIV settings despite the decreasing use of thymidine NRTIs. Our study suggests that switching from EFV to LPV/r in HIV-infected patients with clinically apparent lipoatrophy may offer further improvement in limb fat gain beyond thymidine NRTI discontinuation, although it may be also accompanied by well-known LPV/r-related adverse effects such as insulin resistance, dyslipidaemia and cardiovascular disease. Further studies that consider switching to other more convenient and better tolerated PI/r-based regimens will be needed to confirm this strategy and to determine their clinical relevance.

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Authors' contributions: EM and JMG designed the study. IP undertook the statistical analyses. JR, ML, AI, VE, VA, CM, PD, MM, LdR, JF, IP, AC, MA, JMG and EM were involved in the interpretation of data. JR and EM wrote the manuscript. All authors critically reviewed and subsequently approved the final version.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Fontdevila classification used for evaluation of facial lipoatrophy [6,7].

Table S1. Selected genes for subcutaneous adipose tissue assessment in the LIPOKAL study.

5.2 Estudio KiRilNa

Objetivo 3.2 Evaluar la eficacia y seguridad de abacavir/lamivudina con los ITINN rilpivirina o nevirapina en pacientes infectados por VIH sin tratamiento previo.

PDF del artículo 2:

"Effectiveness and safety of an abacavir/lamivudine1rilpivirine regimen for the treatment of HIV-1 infection in naive patients". A. Curran, J. Rojas, A. Cabello, J. Troya, A. Imaz, P. Domingo, et al. J Antimicrob Chemother 2016; 71: 3510–4. FI: 5,217.

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Effectiveness and safety of an abacavir/lamivudine + rilpivirine regimen for the treatment of HIV-1 infection in naive patients

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Objectives: To describe the effectiveness and safety of an abacavir/lamivudine + rilpivirine regimen in naive HIV-1-infected patients, as there is a lack of data with this combination.

Methods: This was an observational, retrospective, multicentre study in eight Spanish hospitals. All antiretroviral-naive patients ≥18 years old and starting abacavir/lamivudine + rilpivirine were included. Effectiveness (ITT and on-treatment) and safety (adverse events and laboratory parameters) were assessed during follow-up. Values are expressed as *n* (%) or median (IQR). The Wilcoxon signed-rank test was used to compare baseline and 6 and 12 month values.

Results: Eighty-four patients were included [93% males, age = 36 (30–45) years]. Time since HIV diagnosis was 12 (4–35) months. Fifty-one per cent of patients had comorbidities. Baseline CD4+ was 425 (340–519) cells/mm^3 and baseline HIV-RNA was 19000 (9500–42000) copies/mL. Median follow-up was 18 (9–22) months; 100% and 68% patients with at least 6 and 12 months, respectively. At 6 and 12 months effectiveness was 94% and 86% by ITT analysis and 96% and 97% by on-treatment analysis. At 12 months, there were significant increases in CD4+ (+262 cell/mm^3) and HDL cholesterol (+4 mg/dL) and a significant decrease in the total cholesterol/HDL cholesterol ratio (−0.2). There were two (2.4%) virological failures (HIV-RNA 50–100 copies/mL); one patient later achieving virological suppression without changing the treatment. Six patients (7.1%) changed treatment due to reasons other than virological failure or side effects. One patient discontinued treatment due to gastrointestinal complaints attributed to abacavir/lamivudine.

Conclusions: Abacavir/lamivudine + rilpivirine was an effective and safe option in a selected group of HIV-1-infected treatment-naive patients.

Introduction

Current ART against HIV is highly effective and physicians have to take into consideration other characteristics when selecting the ART regimen, such as convenience, toxicity or cost.

Abacavir/lamivudine offers some advantages compared with tenofovir/emtricitabine, mainly avoiding potential renal and bone toxicity.[1,2] It is also a fixed-dose combination, allowing once-daily regimens with low pill burden, and a reduced cost compared with tenofovir/emtricitabine.

Rilpivirine is a second-generation NNRTI approved for the treatment of HIV-infected patients with HIV-RNA <100000 copies/mL in combination with other ART.[3]

Efficacy and safety of rilpivirine in naive patients has been demonstrated in randomized clinical trials, combined with two NRTIs.[4–6] Most of these patients were receiving tenofovir/emtricitabine as the backbone.[4] Only 35 patients (10%) in the THRIVE study received abacavir/lamivudine.[5]

However, abacavir/lamivudine + rilpivirine is not considered a preferred option in naive patients in guidelines,[6–9] probably due to scarce data from clinical trials.

The aim of this study is to describe in the clinical practice the effectiveness and safety of abacavir/lamivudine + rilpivirine in naive HIV-infected patients.

Methods

This was an observational, retrospective, multicentre study carried out in eight Spanish university hospitals (KiRilNa study).

Subjects and design

All consecutive HIV-1-infected adult patients having started a combination of abacavir/lamivudine (600/300 mg fixed-dose combination once daily) plus rilpivirine (25 mg once daily) as their first ART before the 30 June 2015 were included, irrespective of being currently on this regimen or not. All patients tested negative for HLA_B*5701 and hepatitis B surface antigen and had baseline resistance testing without mutations before initiating ART.[9]

Eligible patients were selected from each hospital-specific HIV database. Study-defined data were obtained from patient clinical charts and electronic medical records. The follow-up was censored for analyses on the 31 December 2015.

Demographic data, HIV-related data, comorbidities and other relevant medical conditions were recorded. The main reason for initiating the abacavir/lamivudine + rilpivirine regimen was also recorded. During follow-up, decided by the physician in charge of the patient as routine clinical care, information regarding CD4+, HIV-RNA, laboratory parameters (blood count, renal, liver and fasting lipids), adverse events and reasons for discontinuing abacavir/lamivudine + rilpivirine if any were recorded. If ART was stopped due to virological failure (VF), the results of resistance testing when performed, the subsequent prescribed therapy and outcomes were analysed.

VF was defined as not achieving HIV-RNA <50 copies/mL, confirmed HIV-RNA >50 copies/mL after achieving undetectable viral load or last determination >50 copies/mL if treatment was changed or patient was lost to follow-up. Treatment failure included VF, ART change due to any reason, death or loss irrespective of follow-up.

The primary objective was to analyse in real life the effectiveness of abacavir/lamivudine + rilpivirine in naive patients, using ITT (missing/discontinuation/VF equals failure) and on-treatment (censoring any cause of treatment failure other than VF) analyses at 6 and 12 months (±1 month).

Ethics

The protocol was approved by the Clinical Research Ethics Committees of the participating centres in accordance with the 2008 Declaration of Helsinki.

Statistical analysis

For qualitative variables, number of patients and percentages were given. For quantitative variables, median and IQR were used.

Comparisons between baseline and follow-up variables were performed with the Wilcoxon signed-rank test.

All statistical tests were two-tailed and performed at a level of statistical significance of 0.05 (SPSS 20.0; IBM Corp., Armonk, NY, USA).

Results

Eighty-four patients were included. Baseline characteristics are described in Table 1. Median follow-up with the study regimen was 18 (9–22) months, with 100% and 68% patients reaching 6 and 12 months, respectively.

Forty-three patients (51%) had comorbidities [five (6%) patients had more than one comorbidity]. Fourteen patients had bone disease (osteopenia/osteoporosis), seven chronic liver disease, seven depression, five diabetes, five hypertension, four dyslipidaemia, two cardiovascular disease and four other diseases.

The main reasons for starting the abacavir/lamivudine + rilpivirine regimen were due to pre-existing comorbidities or to prevent toxicities in 50 (60%) patients and other reasons (cost, trust in the regimen) in 34 (40%) patients.

Table 1. Baseline characteristics; $N = 84$

Male	78 (93)
Age (years)	36 (30–45)
HIV infection diagnosis (months)	12 (4–35)
HIV transmission route	
IVDU	3 (4)
MSM	64 (76)
heterosexual	15 (18)
others	2 (2)
Baseline CD4+ (cells/mm^3)	425 (340–519)
<200	3 (4)
200–350	21 (25)
>350–500	36 (43)
>500	24 (28)
Baseline HIV-RNA (copies/mL)	19000 (9500–42000)
<10000	21 (25)
10000–50000	47 (56)
>50000	16 (19)
AIDS-defining illness	0
Positive for hepatitis C virus	5 (6)
Comorbidities	43 (51)
Creatinine (mg/dL)	0.90 (0.79–0.98)
Total cholesterol (mg/dL)	158 (138–190)
HDL cholesterol (mg/dL)	40 (35–47)
LDL cholesterol (mg/dL)	95 (77–122)
Triglycerides (mg/dL)	89 (66–126)
Total cholesterol/HDL cholesterol ratio	4.02 (3.36–4.82)

Results are expressed as *n* (%) or median (IQR).

Effectiveness by ITT analysis was 94% (95% CI = 87%–98%) at 6 months and 86% (95% CI = 76%–92%) at 12 months (Figure 1a). By on-treatment analysis the effectiveness was 96% (95% CI = 90%–99%) and 97% (95% CI = 91%–99%) at 6 and 12 months, respectively (Figure 1b). There was a significant increase in CD4+ cell count at 12 months (262 cells/mm^3, $P < 0.005$).

At 12 months there were two VF. One patient had HIV-RNA of 96 and 94 copies/mL and ART was switched to abacavir/lamivudine + raltegravir, achieving undetectable HIV-RNA. The other patient had HIV-RNA 90 and 66 copies/mL and virological suppression was achieved later without changing the treatment. Resistance testing could not be performed in these patients due to low HIV-RNA.

At 12 months seven patients had stopped abacavir/lamivudine + rilpivirine due to reasons other than VF: two patients were lost to follow-up, three switched to abacavir/lamivudine/dolutegravir (two due to omeprazole use and one for simplification), one switched to zidovudine/lamivudine + nevirapine due to pregnancy and one switched to tenofovir/emtricitabine/rilpivirine due to adverse events attributed to abacavir (gastrointestinal complaints). Five patients reported mild gastrointestinal disturbances without discontinuing ART. One patient started atorvastatin.

After 12 months there were significant increases in serum creatinine [0.07 (−0.03 to 0.14) mg/dL, $P = 0.015$] and HDL cholesterol [+4 (−1 to 10) mg/dL, $P < 0.001$] and significant decreases

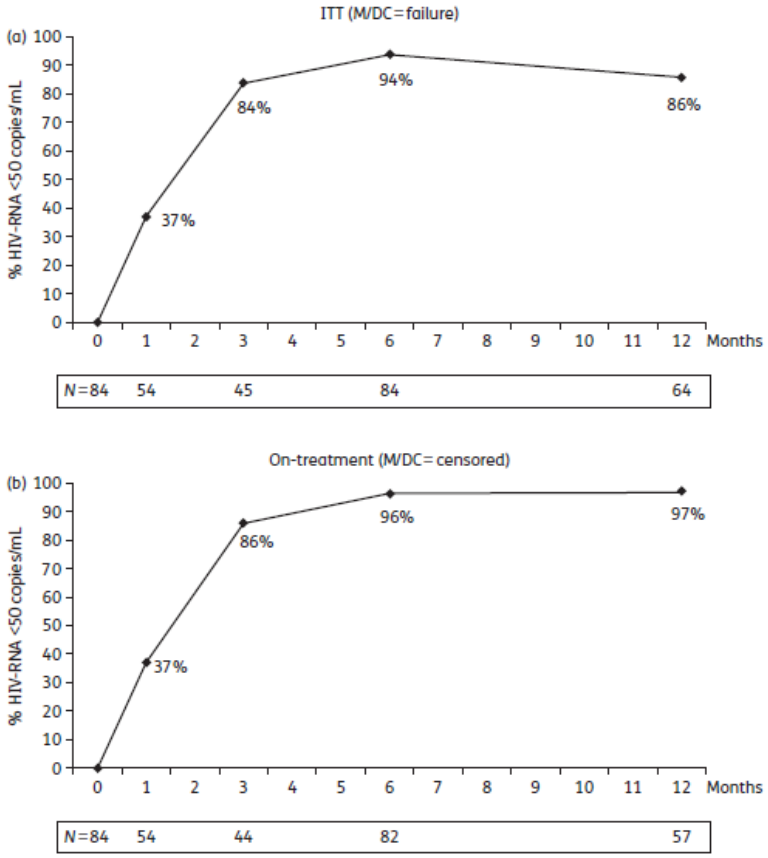

Figure 1. (a) Effectiveness by ITT (missing/discontinuation equals failure) analysis. (b) Effectiveness by on-treatment (missing or discontinuation censored) analysis. M, missing; DC, discontinuation.

in the total cholesterol/HDL cholesterol ratio [−0.20 (−0.74 to 0.10), $P=0.006$]. One patient presented a grade 3 increase in liver enzymes at month 6 with spontaneous recovery without modifying ART.

Discussion

We have observed that, in clinical practice, an abacavir/lamivudine+rilpivirine regimen is effective and safe in this selected group of naive HIV-1-infected patients.

There are scarce data in the literature using this combination. In naive patients, in the THRIVE study only 10% ($n=35$) of the included patients received abacavir/lamivudine+rilpivirine. The overall efficacy was 86%, without apparent differences depending on the NRTI backbone.[5] Recently, a study evaluating this combination has been presented following 33 patients for 12 months. Only one VF was seen in a patient with intermittent adherence (with NRTI and NNRTI resistance) and seven patients discontinued treatment (for toxicity/intolerance in four).[10]

In patients with undetectable HIV-RNA, this regimen has been used as a switch strategy. Imaz *et al.*[11] presented a series of 80 patients with effectiveness at 6 months of 85% (ITT) and 92% (on-treatment), improvement in lipid profile and two discontinuations due to adverse events. In the SIMKE study, 85 patients were switched to abacavir/lamivudine+rilpivirine. After 12 months the effectiveness was 96%; there was one VF and four discontinuations due to adverse events.[12] In the SIMRIKI study, the effectiveness after 12 months in 205 patients was 91% (ITT) and 97% (on-treatment), with five VF and four discontinuations due to toxicity.[13]

There are several arguments in favour of using this combination in selected patients. One is avoiding the potential renal and bone side effects of tenofovir. Even when tenofovir

alafenamide (a pro-drug with less renal and bone toxicity than tenofovir disoproxil fumarate)[14] becomes available, it will be more expensive than abacavir. Another reason for using abacavir/lamivudine + rilpivirine is the good tolerability of the regimen, as previously described.[15] Furthermore, we observed a good metabolic profile, significantly increasing HDL cholesterol without changes in total cholesterol or LDL cholesterol, resulting in a small but significant decrease of the total cholesterol/HDL cholesterol ratio. These HDL cholesterol increases have also been seen with abacavir/lamivudine in larger randomized trials, but without significant decreases in total cholesterol/HDL cholesterol ratios.[16,17] Rilpivirine is a weak inhibitor of OCT2 transporters in the proximal tubular cell and can slightly increase serum creatinine due to inhibition of the renal active tubular secretion, as seen in our patients, without affecting the actual glomerular filtration rate.[18]

It is also a convenient regimen, containing only two pills (rilpivirine being the smallest ART tablet available) taken once daily. The potential for drug–drug interactions with rilpivirine is low.[15] Last but not least, it is a relatively cheap regimen.

Of course, some precautions have to be taken, all inherent to the drugs that form the combination. Rilpivirine is only approved for patients with HIV-RNA <100000 copies/mL[3] and probably not recommended in patients with CD4+ cell counts <200 cells/mm^3. It has to be taken with food and the patient cannot take proton pump inhibitors,[3] but these precautions are applicable irrespective of the drugs that accompany rilpivirine. Regarding abacavir use in patients with high cardiovascular risk, evidence in the literature is inconsistent, with an association found in some cohorts[19] but not in others nor in a meta-analysis performed by the FDA.[20] However, some guidelines recommend caution when using abacavir in these patients.[5,8] Furthermore, patients must have a negative HLA_B*5701 before starting abacavir.

The retrospective, observational nature of this study is a clear limitation that can entail a selection bias and does not allow controlling for factors such as adherence or adverse events that might have not been reported. Furthermore, not all patients have the same follow-up. Longer evaluation of these patients will be very useful to determine the real effectiveness and safety of this regimen in the clinical setting.

In conclusion, abacavir/lamivudine + rilpivirine was an effective and safe option in a selected group of HIV-1-infected treatment-naive patients.

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Transparency declarations

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Author contributions

A. Cu. and E. R. conceived the study, participated in its design, coordination and data analysis, and drafted the manuscript. J. R., A. Ca., J. T., A. I., P. D., E. M., P. R, M. G., D. P., H. K. and F. G. recruited patients, carried out the study protocol and supervised data integrity and analysis. All the authors contributed to the final version of the manuscript.

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5.3 Estudio KIVI (ABC/3TC/NVP)

Objetivo 3.2 Evaluar la eficacia y seguridad de abacavir/lamivudina con los ITINN rilpivirina o nevirapina en pacientes infectados por VIH sin tratamiento previo.

PDF póster:

"Effectiveness and tolerability of abacavir-lamivudine-nevirapine (ABC/3TC/NVP) in a multicentre cohort of HIV-infected, ARV-naive patients". D. Podzamczer, J. Rojas, I. Neves, E. Ferrer, J. Llibre, J.M. Leal, et al. Abstracts of the HIV Drug Therapy Glasgow Congress 2014 Podzamczer D et al. Journal of the International AIDS Society 2014, 17(Suppl 3): 19773. FI: 5,131.

Abstracts of the HIV Drug Therapy Glasgow Congress 2014
Podzamczer D et al. *Journal of the International AIDS Society* 2014, **17(Suppl 3)**:19773
http://www.jiasociety.org/index.php/jias/article/view/19773 | http://dx.doi.org/10.7448/IAS.17.4.19773

Poster Sessions – Abstract P241

Effectiveness and tolerability of abacavir-lamivudine-nevirapine (ABC/3TC/NVP) in a multicentre cohort of HIV-infected, ARV-naïve patients

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Purpose: Very scarce information has been published to date with the combination of ABC/3TC/NVP but it is currently being used in clinical practice in Spain and Portugal. Our aim was to present the clinical experience with this regimen in a cohort of adult HIV-infected antiretroviral (ARV)-naïve patients.
Methods: Retrospective, multicentre, cohort study. Consecutive adult HIV-infected ARV-naïve HLA-B*5701-negative patients, who started ABC/3TC/NVP between 2005-2013, with at least one follow-up visit, were included. Demographic, clinical and laboratory variables were assessed at baseline, month 1, and every three–four months thereafter. The primary end point was HIV-1 viral load (VL) <40 c/mL at 48 weeks. Data were analyzed by intent-to-treat (ITT) (switch = failure, and missing = failure) and on treatment (OT) analyses.
Results: 78 patients were included. Median follow up was 26 (0.1-84) months. 86% were male, median age 41 (23-69) years, 9% had AIDS, 8% were HCV+, baseline CD4 was 275 (10-724) cells/μL and median VL 4.58 (3.02-6.92) log. After 48 weeks, VL was <40 c/mL in 89.8% (OT), 79.7% (M = F) and 65.4% (S = F) and at 96 weeks in 88.5%, 78.9% and 61.6%, respectively. CD4 increased +246 ($p < 0.001$) and +292 ($p < 0.001$) cells/uL after 48 and 96 weeks, respectively. One or more drugs of the regimen were discontinued in 33 (42.3%) patients. In 15 (19.2%) patients (13 NVP, 2 ABC/3TC) therapy was stopped due to toxicity after a median of one month (in only two cases after six months of follow up): 80% of them had rash/liver toxicity. Six (7.7%) patients discontinued ART due to virologic failure, five (6.4%) because of other reasons and seven (9%) were lost to follow-up. ALT but not AST significantly increased (+0.07 ukat/L at 96 weeks, $p = 0.033$). A significant increase of 25%, 26% and 42% in total cholesterol, LDLc and HDLc, respectively, and a significant decrease in TC/HDL ratio (6%, $p = 0.008$) was observed after 96 weeks.
Conclusions: Despite a considerable proportion of patients had to stop therapy due to toxicity (most associated with NVP), those initially tolerating this regimen presented a high virologic and immunologic response after 96 weeks, as well as a favourable lipid profile. ABC/3TC/NVP may be a suitable alternative first regimen, mainly in countries with economic constraints.

Published 2 November 2014

5.4 Estudio ZEST

Objetivo 3.3 Evaluar el impacto del uso de bifosfonatos (ácido zolendrónico) vs el cambio del tratamiento con tenofovir a otros regímenes en la densidad mineral ósea de adultos infectados por el VIH suprimidos virológicamente, con DMO baja y que llevan TDF en su TAR.

PDF del artículo 3:

"Zoledronic acid is superior to tenofovir disoproxil fumarate-switching for low bone mineral density in adults with HIV". J.F. Hoy, R. Richardson, P.R. Ebeling, J. Rojas, N. Pocock, S.J. Kerr, et al. AIDS 2018; 32: 1967-75. FI: 4,914.

Zoledronic acid is superior to tenofovir disoproxil fumarate-switching for low bone mineral density in adults with HIV

Jennifer F. Hoy[a], Robyn Richardson[b], Peter R. Ebeling[c], Jhon Rojas[d], Nicholas Pocock[b], Stephen J. Kerr[b,e], Esteban Martinez[d], Andrew Carr[b], for the ZEST Study Investigators

Objective: To compare the effects of switching tenofovir disoproxil fumarate (TDF) or treatment with an intravenous bisphosphonate on bone mineral density (BMD) in HIV-positive adults with low bone mass.

Design: Two-year, randomized, open-label study at 10 sites in Australia and Spain.

Participants: Of 112 adults on TDF-based antiretroviral therapy (ART) screened, 87 with low BMD (*T*-score < -1.0 at hip or spine by dual-energy X-ray absorptiometry) and undetectable plasma HIV viral load were randomized to either switch TDF to another active antiretroviral drug or to continue TDF-based ART and receive intravenous zoledronic acid (ZOL) 5 mg annually for 2 years.

Primary outcome measure: Change in lumbar spine BMD at 24 months by intention-to-treat analysis. Secondary outcomes included changes in femoral neck and total hip BMD, fractures, safety, and virological failure.

Results: Forty-four participants were randomized to TDF switch and 43 to ZOL, mean age 50 years (SD 11), 96% men, mean TDF duration 5.9 years (SD 3.1), and mean spine and hip *T*-scores −1.6 and −1.3, respectively. At 24 months, mean spine BMD increased by 7.4% (SD 4.3%) with ZOL vs. 2.9% (SD 4.5%) with TDF-switch (mean difference 4.4%, 95% CI 2.6–6.3; $P < 0.001$). Mean total hip BMD increased by 4.6 (SD 2.6%) and 2.6% (SD 4%), respectively (mean difference 1.9%, 95% CI 0.5–3.4; $P = 0.009$). There was one fracture in the ZOL group vs. seven fractures in four TDF-switch participants. Virological failure occurred in one TDF-switch participant. Other safety endpoints were similar.

Conclusion: ZOL is more effective than switching TDF at increasing BMD in HIV-positive adults with low bone mass.

AIDS 2018, **32**:1967–1975

Keywords: bone mineral density, HIV, osteoporosis, tenofovir, zoledronic acid

Background

Adults with HIV infection have a higher prevalence of low bone mineral density (BMD) (40–83%) than HIV-uninfected adults [1], and HIV-positive adults on antiretroviral therapy (ART) have lower BMD than ART-naïve, HIV-infected adults [2]. Initiation of ART is associated with loss of BMD [3]. BMD declines by 3–5% at the hip and spine in the first year of tenofovir disoproxil fumarate (TDF)-based ART, and these declines are

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significantly greater (approximately two-fold) than for ART regimens not including TDF [4–6]. In some studies, BMD continues to decline by approximately 1% per year, a rate higher than in healthy controls [7,8]. TDF is the most popular component of the nucleoside reverse transcriptase backbone in ART regimens in low-income and middle-income countries, so measures to minimize its adverse effects on bone are desirable.

Fragility fractures are the clinical consequence of low BMD. Prospective cohort studies report a significant increase in fractures in HIV-infected relative to HIV-uninfected men [9,10]. Use of ART is also associated with a significant increase in fractures [11], whereas cumulative and current use of TDF was associated with a significant increase in fractures in a large European cohort study [12,13]. Fracture prevalence increases with age to a greater extent in HIV-positive patients [12,14], which has implications for the HIV population that is successfully aging because of effective ART.

There are several proven interventions for low BMD in HIV-positive adults: either antiresorptive therapy with a bisphosphonate or switching TDF to another active antiretroviral drug. Trials of bisphosphonate therapy in HIV-positive adults have reported increases in BMD with oral alendronate 70 mg per week or zoledronic acid 5 mg intravenously once a year [15–18]. BMD also increases after switching TDF to abacavir, raltegravir or tenofovir alafenamide (TAF) in virologically suppressed adults [19–22]. Cross-study comparisons suggest that the effects of bisphosphonate therapy may be greater than for TDF switching at 2 years, but there has been no head-to-head study to determine which strategy is superior. The aim of the ZolEdronic acid versus Switching Tenofovir for low BMD (ZEST) study was to compare the effects of zoledronic acid 5 mg intravenously yearly for 24 months to switching from tenofovir to another antiretroviral drug on lumbar spine and hip BMD in HIV-infected adults with low BMD. We hypothesised that zoledronic acid would increase BMD more effectively over 24 months than switching from TDF.

Methods

Study outcomes

The primary objective of the study was to compare the effects of an annual intravenous infusion of 5 mg zoledronic acid to switching from TDF to another antiretroviral drug on lumbar spine BMD (primary endpoint) and hip BMD (secondary endpoint) over 24 months. Mean percentage change in lumbar spine BMD from baseline was chosen as the primary outcome measure in preference to total hip BMD, because of lumbar spine BMD responding more rapidly to interventions as it contains a higher proportion of metabolically active trabecular bone [23]. The secondary objectives of the study were to compare the randomized groups for mean percentage change in hip BMD, incidence of osteoporosis (defined by a T-score < -2.5), fracture risk assessment using the appropriate Australian or Spanish version of the Fracture Risk Assessment equation (FRAX), occurrence of fractures, and safety (clinical and laboratory adverse events of all grades, all serious adverse events, death, progression to AIDS, and virological failure defined by a plasma HIV RNA greater than 200 copies/ml on two occasions at least 4 weeks apart, and any antiretroviral regimen modification after baseline).

Study design and participants

The study was a randomized, open-label, 24-month trial, with eligible participants randomly assigned to either commence zoledronic acid 5 mg intravenously, yearly (two doses; and continue TDF-containing ART) or to switch from TDF to another potent antiretroviral drug selected by the investigator (without commencing a bisphosphonate). The study was conducted prior to the availability of tenofovir alafenamide. Randomization was stratified by radiology facility (one each in Sydney, Melbourne, and Barcelona), and by screening BMD (T-score greater than -2.0 or less than or equal to -2.0). The study was approved by the institutional review board at each participating clinical site, and was performed in compliance with the principles of the Declaration of Helsinki and local regulatory requirements. All participants provided written, informed consent prior to enrolment. The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN 12612000776808).

Eligible patients were adults with confirmed HIV infection, virologically suppressed (HIV RNA <50 cop-copies/ml) for a minimum of 3 months on TDF-containing ART for at least 6 months, and had a T-score of less than -1.0 at the spine (L1–L4) or the left neck of femur on bone densitometry using dual-energy X-ray absorptiometry (DXA). Participants were not eligible if they had received prior bisphosphonate therapy, had received other anti-osteoporotic therapy for low BMD, had evidence of secondary osteoporosis, required treatment for low BMD (e.g. prior fragility fracture) or contraindications to administration of zoledronic acid (e.g. hypocalcaemia, recent or planned major dental surgery, uncorrected vitamin D deficiency), required tenofovir for treatment of chronic hepatitis B, had prior virological failure, resistance, intolerance or contra-indications to the proposed ART-switch regimen (including HLA-B*5701 positivity or prior cardiovascular disease for abacavir-containing regimens) or had an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2. The switch antiretroviral drug(s) was/were selected prior to randomization.

All participants received calcium supplementation of 1500 mg daily, and all participants with vitamin D

insufficiency or deficiency received vitamin D supplementation at baseline and either month 11 (for the zoledronic acid group) or month 12 for the TDF-switch group. For vitamin D insufficiency (25–50 nmol/l) participants in either group received a single tablet of 50 000 IU vitamin D, and for those with moderate deficiency (<25 nmol/l) a single dose of 100 000 IU Vitamin D (two tablets) was administered. Vitamin D levels were rechecked at month 3 and, if persistent insufficiency or deficiency was identified, participants continued to receive vitamin D 50 000 IU monthly for the duration of the study.

BMD at the lumbar spine (L1–L4) and hip were measured annually by DXA for 2 years. All DXA images were obtained using a standardized protocol, with central adjustment of BMD values for cross-sectional and longitudinal consistency based on locally acquired phantom scans. DXA scan results were not returned to sites until month 24, unless a minimal trauma fracture occurred, a BMD decline of greater than 5% occurred or a *T*-score less than −2.5 developed. By convention, *T*-scores were calculated relative to peak bone mass in young white women [24]. *z*-scores were calculated relative to reference populations matched by age, sex and race/ethnicity. Low BMD for age (below the expected range) was defined by a *z*-score (spine, hip, femoral neck) −2.0 or less, consistent with recommendations for young populations by the US National Osteoporosis Foundation and the International Society for Clinical Densitometry [25,26]. Participants with BMD *T*-scores of −2.5 or less at any site (L1–L4 spine, total hip or femoral neck) were considered to have osteoporosis [27]. The Fracture Risk Assessment Tool was used to generate FRAX scores for the 10-year probability of a hip fracture or a major osteoporotic fracture, using the relevant country of participation tool for each participant [28].

Statistical analysis

The sample size was calculated using data from published HIV BMD treatment studies [15–18,29,30], in which the mean response at the lumbar spine relative to control at 2 years was 6.1% [standard deviation (SD) <4%] with a bisphosphonate and 1% (SD 2%) with TDF switching [19,22]. Assuming a 4% (SD 6%) difference, the proposed study would require 36 participants in each group to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with 80% power, and a type-1 error probability of 0.05. To allow for 15% loss to follow-up or strategy, we planned to recruit 42 subjects to each group.

All analyses were performed after all participants completed 2 years of follow-up or had permanently withdrawn or been lost to follow-up. The modified intention-to-treat (mITT) analyses include all patients who were randomized excluding two participants who withdrew consent immediately after randomization and did not cease TDF, and the per-protocol analyses censored participants once they restarted TDF (in the TDF-switch arm) or ceased TDF (zoledronic acid arm). Those with no follow-up after baseline and those who restarted or stopped TDF as protocol violations before month 12 (or the first postbaseline study visit for toxicity endpoints) were excluded from the per-protocol analyses.

The primary outcome was percentage change from baseline in BMD at the lumbar spine at 24 months by ITT analysis. For continuous data, mean change from baseline to months 12 and 24 was calculated for participants with baseline and at least one follow-up visit (mITT). Both ITT (last observation carried forward) and per-protocol analyses were performed for the BMD and fracture endpoints; toxicity endpoints used per-protocol datasets only. *T*-tests were used to compare groups, unless data was not normally distributed, in which case Wilcoxon's test was used. Fisher's exact test was used to assess differences in proportions. Formal comparisons of fracture numbers between arms were made with a random effects longitudinal Poisson model. All analyses used a two-sided α of 0.05. No adjustment was made for multiple comparisons. Analyses were performed with Stata version 15.0 (Statacorp, College Station, Texas, USA).

Results

Participants and interventions

The study was performed at 10 clinical sites (9 in Australia and one in Spain). Of the 112 volunteers screened, 87 participants were randomized between July 2012 and January 2015. Two of the 44 participants randomized to the TDF switch arm revoked consent prior to ceasing TDF, and were excluded from analysis (Fig. 1, CONSORT diagram). Table 1 shows the baseline characteristics of the 85 participants analysed (43 in the zoledronic acid group and 42 in the TDF-switch group). The study population was predominantly Caucasian, with median age of 50 years; only 4% were women; the median $CD4^+$ T-cell count was 618 cells/μl. The median duration of prior TDF exposure was 6.2 (IQR 3.4–8.1) years. Twenty-three participants (27%) had osteoporosis (*T*-score ≤−2.5) whereas 32 (38%) had low BMD for age (*z*-score ≤−2.0) at the spine, total hip or femoral neck. There was no difference in major osteoporotic or hip fracture probability between study arms at baseline.

In the TDF switch arm, the predominant switch occurred from TDF to abacavir (62%) or to raltegravir (19%). Of those randomized to the zoledronic acid arm, one participant died by month 3 and one moved overseas before month 6, one was lost to follow-up at the month 24 visit. One participant in the TDF-switch arm was incarcerated prior to month 12, but returned for

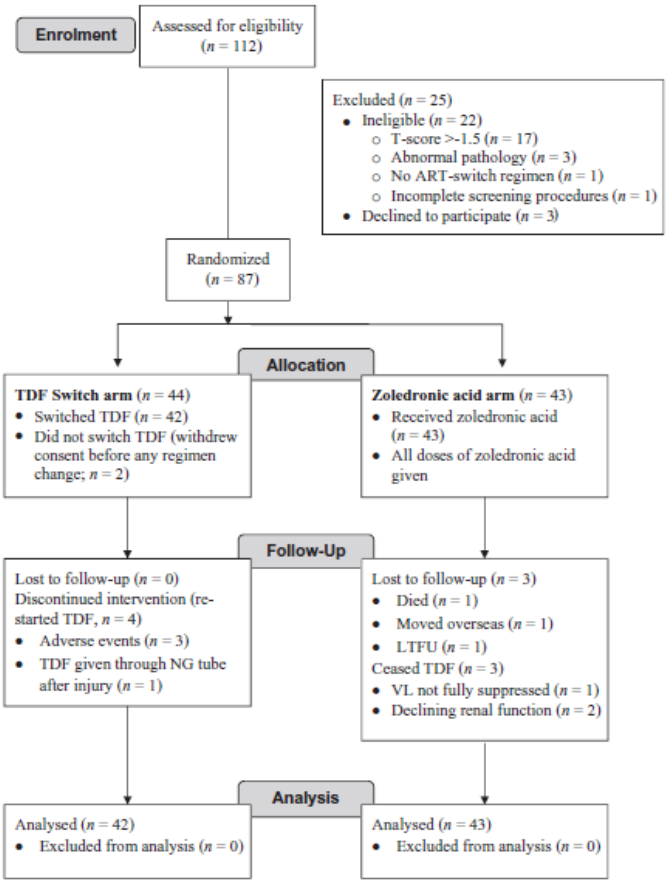

Fig. 1. CONSORT diagram.

continued follow-up by month 24. All planned zoledronic acid infusions were given (one was delayed because of dental work). Strategy was maintained in 40 (93%) of those allocated to zoledronic acid (three participants ceased TDF) and in 38 (90%) of those allocated to cease TDF (four participants restarted TDF, none received zoledronic acid).

Primary study endpoint: change in lumbar spine bone mineral density at 24 months

The mean percentage changes in BMD in the zoledronic acid and TDF-switch groups and the estimated overall mean treatment differences at month 24 were 7.4 vs. 2.9% [difference 4.4% (95% CI 2.6–6.3), $P < 0.001$] at the lumbar spine; 4.6 vs. 2.9% [difference 1.9% (95% CI 0.5–3.4), $P = 0.009$] by ITT analysis (Table 2). The increase in BMD was the greatest in the first 12 months for both strategies. The rate of increase slowed in the second year for the zoledronic acid group whereas the BMD change plateaued from 12 to 24 months in the TDF-switch group (Fig. 2). The per protocol analyses yielded similar treatment differences (Table S1, http://links.lww.com/QAD/B312).

Secondary outcomes

The mean percentage changes in BMD in the zoledronic acid and TDF-switch groups and the estimated overall mean treatment differences at month 24 were 4.6 vs. 2.9% [difference 1.9% (95% CI 0.5–3.4), $P = 0.009$] at the total hip; and 4.0 vs. 2.1% [difference 1.9% (0.04–3.7), $P = 0.045$] at the femoral neck by ITT analysis (Table 2). Per protocol analyses are shown in Table S1, http://links.lww.com/QAD/B312.

The prevalence of osteoporosis at the hip or spine decreased from 30 and 24% at baseline to 12% in both

Table 1. Baseline characteristics.

	Zoledronic acid (N=43)	TDF switch group (N=42)	Total (N=85)
Demographics			
Age (years)	49 [11]	51[12]	50 [11]
Male	40 (93)	42 (100)	82 (96)
Race			
Asian	4 (9)	4 (10)	8 (9)
Caucasian	32 (74)	34 (81)	66 (78)
Hispanic	6 (14)	3 (7)	9 (9)
Other	1 (2)	1 (2)	2 (4)
Clinical factors			
$CD4^+$ T-cell count (cells/μl)	626 (293)	609 (285)	618 (287)
TDF duration (median, IQR, years)	5.8 (2.7-8.9)	6.7 (3.9–7.9)	6.2 (3.4–8.1)
Protease inhibitor-based regimen	10 (23)	15 (36)	25 (29)
BMI (kg/m^2)	24.6 (3.9)	24.8 (3.1)	24.7 [3.5]
Current smoker	16 (37)	22 (52)	38 (45)
Alcohol at least three standard units/day	1 (2)	5 (12)	6 (7)
Vitamin D status			
Normal (>50 nmol/l)	28 (65)	28 (67)	56 (66)
Insufficient (25–50 nmol/l)	14 (33)	11 (26)	25 (29)
Deficient (<25 nmol/l)	1 (2)	3 (7)	4 (5)
Bone mineral density (median, IQR)			
Spine			
BMD (g/cm^2)	0.97 [0.85–1.10]	1.01 [0.88–1.11]	0.98 [0.87–1.09]
T-score[a]	−1.7 [−2.7 to −1.1]	−1.6 [−2.3 to −0.9]	−1.6 [−2.5 to −1.1]
z-score[b]	−1.3 [−2.4 to −0.6]	−1.2 [−2.1 to −0.7]	−1.3 [−2.1 to −0.7]
Total hip			
BMD (g/cm^2)	0.88 [0.80–0.95]	0.91 [0.81–0.98]	0.90 [0.81–0.97]
T-score[a]	−1.4 [−1.9 to −1.0]	−1.1 [−1.7 to −0.7]	−1.3 [−1.9 to −0.9]
z-score[b]	−1.1 [−1.5 to −0.4]	−0.7 [−1.3 to −0.3]	−0.9 [−1.4 to −0.3]
Femoral neck			
BMD (g/cm^2)	0.83 [0.73–0.89]	0.86 [0.77–0.92]	0.84 [0.75–0.9]
T-score [a]	−1.6 [−2.0 to −1.4]	−1.4 [−1.9, −1.1]	−1.6 [−2.0 to −1.4]
z-score [b]	−0.9 [−1.3 to −0.2]	−0.7 [−1.1 to −0.4]	−0.9 [−1.3 to −0.2]
T-score −2.5 or less at spine, hip or femoral neck	13 (30)	10 (24)	23 (27)
FRAX probability (%) of major osteoporotic fracture	2.2 (1.1)	2.1 (1.1)	
FRAX 10-year probability (%) of hip fracture	0.6 (0.5)	0.6 (0.5)	

Data are presented as mean [SD] or *N* (%) unless otherwise indicated. BMD, bone mineral density; FRAX, fracture risk assessment tool; TDF, tenofovir disoproxil fumarate.
[a]BMD *T*-scores were standardized relative to young adult Caucasian women.
[b]BMD *z*-scores were standardized relative to age, sex and race/ethnicity (black/white/hispanic)-matched reference populations. White reference populations are used for all other races/ethnicities.

groups at month 12, and was similar at 24 months (Table 3). The odds ratio for having osteoporosis at any visit after baseline in the zoledronic acid vs. TDF-switch groups was 0.96 (95% CI 0.0003–10.8), $P=0.29$.

Five participants experienced eight fractures over the 24 months of follow-up. In the zoledronic acid group, one participant had a vertebral compression fracture (deemed a fragility fracture). In the TDF-switch group,

Table 2. Percentage change in bone mineral density at the spine (L1–L4), hip and femoral neck, compared between the tenofovir disoproxil fumarate switch and zoledronic acid groups by modified intention-to-treat analysis.

	Zoledronic acid group		TDF Switch group		Zoledronic acid TDF switch group	
	N	Mean (SD)	*N*	Mean (SD)	Estimated difference (95% CI)	*P*
Spine (L1–L4)						
Baseline to month 12	43	6.1 (3.2)	42	2.9 (3.9)	3.2 (1.7–4.7)	<0.001
Baseline to month 24	43	7.4 (4.3)	42	2.9 (4.5)	4.4 (2.6–6.3)	<0.001
Total hip						
Baseline to month 12	42[a]	3.4 (2.9)	42	1.8 (4.1)	1.6 (0.1, 3.1)	0.04
Baseline to month 24	42	4.6 (2.6)	42	2.6 (4.0)	1.9 (0.5, 3.4)	0.009
Femoral neck						
Baseline to month 12	42[a]	3.2 (4.8)	42	1.4 (4.7)	1.8 (-0.3, 3.9)	0.09
Baseline to month 24	42	4.0 (3.8)	42	2.1 (4.6)	1.9 (0.04, 3.7)	0.045

Mean changes in BMD from baseline to month 12 and month 24 were calculated without adjustments, differences at each year were compared using a *t*-test. Month 12 data carried forward for one participant in each group because of intervening left hip replacement. One participant was incarcerated at month 12 visit but had a month 24 visit. BMD, bone mineral density; TDF, tenofovir disoproxil fumarate.
[a]One patient in the zoledronic acid arm had silicone implants in his buttocks precluding measurement of femoral neck and hip BMD.

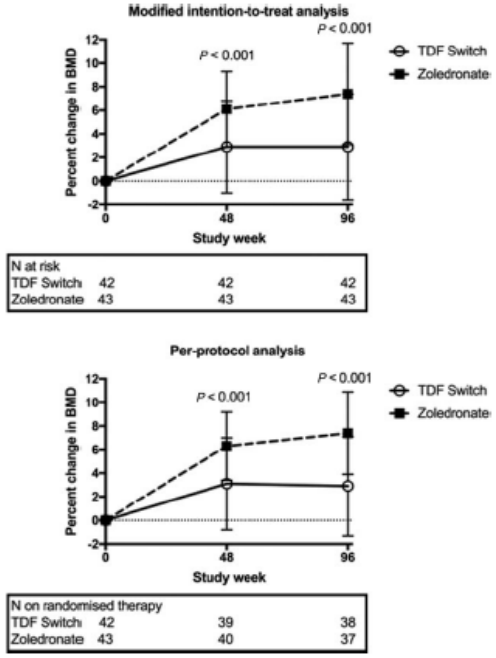

Fig. 2. Mean percentage change (95% confidence intervals) in lumbar spine (L1–L4) bone mineral density by treatment group over 48 weeks, by intention-to treat analysis and per-protocol analysis.

four participants experienced seven fractures [hands/foot (three participants), multiple rib (two participants), wrist, and spine] of which only one was categorized as a fragility fracture. Although there were fewer fractures in the zoledronic acid group, the difference in the number of participants with fractures between strategies was not significant. Fracture numbers did not differ between the ITT and per protocol analyses.

There was no significant difference in the number of serious adverse events between arms during study follow-up, and none were considered related to the study arm. The rate of clinical or laboratory adverse events (grades 1–3) was not different between arms, and neither was the rate of events related to study strategy or study procedure (Table 3). There was some recovery in eGFR [mean (SD) increase of 3.3 (12.6) ml/min per 1.73 m^2] in those allocated to the TDF-switch arm, and a continued mean decline of 5.4 (13.4) ml/min per 1.73 m^2 in those allocated to zoledronic acid (and to continue TDF). In a random effects model adjusting for baseline eGFR, the mean (95% CI) change in eGFR over 24 months follow-up between the zoledronic acid arm vs. TDF switch was −3.1 (−6.4 to 0.13) ml/min per 1.73 m^2; $P = 0.06$.

One participant in the zoledronic acid arm with low-level viraemia (which did not meet the definition of virological failure) had their ART regimen changed by their physician (ceasing TDF). Another participant in the TDF-switch arm experienced confirmed virological failure. This participant switched coformulated tenofovir–emtricitabine to abacavir–lamivudine at baseline. However, the participant continued his prestudy raltegravir but, for reasons that could not be clarified, did not take the abacavir–lamivudine. The patient's viral load was less than 50 copies/ml at month 3, but 17 400 copies/ml at month 6. The patient resuppressed on abacavir–lamivudine with ritonavir-boosted darunavir for the duration of the study.

Table 3. Secondary outcomes.

	Zoledronic acid group ($N = 43$), mean or %	TDF switch group ($N = 42$), mean or %	Total ($N = 85$), mean [SD] or N (%)	P value
Prevalence of osteoporosis[a] (T-score ≤−2.5)				
Baseline	13 (30%)	10 (24%)	23 (27%)	
Month 12	5 (12%)	5 (12%)	10 (12%)	
Month 24	4 (9%)	6 (14%)	10 (12%)	
Fractures (n, %)				
Participants	1 (2%)	4 (10%)	5 (7%)	0.20
Fracture events	1 (2%)	7 (17%)	8 (9%)	0.17
Adverse events				
Serious adverse events	9	10	19	
Participants with an SAE	8 (19%)	6 (14%)	14 (16%)	0.57
Adverse events	114	163	277	
Participants with any AE	37 (86%)	33 (79%)	70 (82%)	0.41
AEs related to study arm	14 (12%)	22 (13%)	36 (13%)	1.0
Grade 3 laboratory events	4 (9%)	3 (7%)	7 (8%)	1.0
HIV RNA >200 copies/ml	0	1 (2%)	1 (1%)	0.49

AE, adverse event; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate.
[a]After adjustment for baseline osteoporosis, the odds ratio for having osteoporosis at any visit after baseline in the zoledronic acid arm vs. TDF-switch arm was 0.06 [95% confidence interval (CI) 0.0003–10.8], $P = 0.29$.

Discussion

In this randomized, controlled, strategy trial, annual infusions of zoledronic acid resulted in significantly greater increases in BMD over 24 months vs. TDF switching in virologically suppressed, HIV-infected adults on TDF-containing ART with osteopenia. Treatment with intravenous zoledronic acid was also associated with a significant reduction in the proportion of people with osteoporosis. The majority of the BMD increases occurred in the first 12 months in the zoledronic acid arm, with a slowing of the increase thereafter. In the TDF-switch arm, all the BMD increase occurred in the first 12 months, with BMD plateauing in the second 12 months. Both strategies were well tolerated.

The results of our study are in keeping with the increase in BMD over 1–2 years seen in the six randomized trials of bisphosphonate treatment in HIV-positive patients. Four of these studies used alendronate 70 mg weekly, and two trials used intravenous zoledronic acid 5 mg yearly, with all participants receiving calcium and vitamin D supplementation (usually 1000 mg/day and 400 IU/day, respectively). In these trials, BMD was higher at 2 years than at 1 year, and BMD increases were similar or greater at the lumbar spine than at the femoral neck and appeared similar or greater with zoledronic acid (3.7–8.9% at the spine, and 3.2–3.8% at the hip) than with alendronate (3.4–5.2% at the spine, and 1.8–4% at the hip) [15–18,29,30]. The 7.4% increase in spine BMD in our study was similar to the approximate 6% BMD increase with zoledronic acid relative to controls at 2 years in HIV-positive patients, and to that observed in large phase 3 trials in postmenopausal women with osteoporosis [31–33]. There was a suggestion that the BMD increase was greater in those receiving TDF vs. non-TDF ART in one alendronate trial, but this was not significant [16]. The mean increase of 2.9% in BMD at the spine and the hip in our study is slightly greater than that seen in other TDF-switch studies in which change in BMD was evaluated where improvement in BMD was generally 1–2.5% [21,22,34]. The greater magnitude of change in BMD in our study may be because of the vitamin D supplementation for vitamin D insufficient and deficient individuals and calcium supplementation. Vitamin D with or without calcium has been shown in several studies to improve BMD in those on TDF-containing ART [35–37].

Although both alendronate and zoledronic acid were well tolerated in the above trials, zoledronic acid may be preferable to weekly alendronate for several reasons: the main side effect of alendronate is nausea, which is a common reason for poor adherence to this regimen. Nausea is also a common ART side effect, and the ART side effect most likely to cause ART nonadherence and cessation [38]. Also, the addition of zoledronic acid would not increase pill burden or hinder ART adherence.

Only one individual experienced virological failure in the switch arm, and required a new treatment regimen. Switching ART in virologically suppressed individuals is always associated with a risk of new adverse events or loss of virological control and future treatment options [39]. In this study, one participant in the TDF-switch arm experienced virological failure because of poor adherence to their new ART regimen, and four participants experienced new adverse effects and restarted TDF while maintaining virological suppression. One participant in the zoledronic acid arm experienced low-level viraemia only, with an ART-regimen switch (ceasing TDF) initiated by his physician. Another two participants in the zoledronic acid arm ceased TDF because of declining renal function. Continued decline in eGFR was seen in the zoledronic acid arm, compared with an increase in eGFR in the TDF-switch arm, most likely because of continued use of TDF in those allocated to zoledronic acid.

Our study has limitations. There were very few women recruited with the study population being predominantly Caucasian, adult men. The current follow-up is short at 24 months; follow-up is ongoing to 36 months. Although significantly more fractures occurred in the TDF-switch group, there was no difference in the number of participants experiencing a fracture between the two study arms. The study was not powered for fracture events and much larger and longer studies will be required to determine the impact on fracture outcomes. Finally, the study was initiated prior to the availability of TAF, which has been shown to be associated with less bone loss than with TDF, and reduced renal toxicity. However, the BMD increase seen after switching from TDF to TAF is similar to that seen after TDF switching to abacavir or an integrase inhibitor [19–22] so, although both strategies are likely to be effective in increasing BMD, it is also likely that treatment with intravenous zoledronic acid will be superior to switching from TDF to TAF in adults with HIV and low bone mass.

Although TDF switching is a reasonable approach in improving low BMD in HIV-infected adults on TDF, we have demonstrated that treatment with zoledronic acid is a superior strategy over 24 months. Continued follow-up to month 36 will be important to establish whether the effect of zoledronic acid is durable (participants received a 5 mg infusion at baseline and month 12 only), and whether there is a continued increase in BMD beyond month 24 in either group. Although the use of zoledronic acid is likely to be preferred for those with osteoporosis, the clinical significance of this strategy will also depend on the underlying absolute risk for fracture, which for the HIV population and the general population alike, increases with age.

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Conflicts of interest

A.C. received research funding from Gilead Sciences and ViiV Healthcare; lecture and travel sponsorships from Bristol-Myers Squibb, Gilead Sciences, and ViiV Healthcare; and has served on advisory boards for Gilead Sciences and ViiV Healthcare. P.R.E.'s institution has received research funding from Novartis and honoraria from Gilead Sciences. J.F.H.'s institution receives reimbursement for her participation in Advisory Boards for Gilead Sciences, Merck, Sharp & Dohme, and ViiV Healthcare. E.M. received research funding from Merck, Sharp & Dohme; lecture and travel sponsorships from Gilead Sciences, Janssen, Merck, Sharp & Dohme, and ViiV Healthcare; and has served on advisory boards for Janssen, Merck, Sharp & Dohme, and ViiV Healthcare. R.R., N.P., J.R., and S.J.K. report no conflicts of interest.

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5.5 Estudio Doultegravir en monoterapia

Objetivo 3.4 Describir la eficacia y la seguridad de la monoterapia con dolutegravir en pacientes con opciones muy limitadas de TAR por efectos adversos, comorbilidades, riesgo de interacciones, o resistencia archivada en la cohorte de pacientes adultos infectados por VIH del Hospital Clínic de Barcelona

PDF del artículo 4:

"Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression".

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Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression

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Objectives: We reviewed the 24 week outcomes of HIV-infected patients from our hospital who had their ART switched to dolutegravir monotherapy on an individual clinical basis.

Methods: Retrospective hospital database assessment of virally suppressed patients in whom the treating physician had switched to 50 mg of dolutegravir once daily due to one or more of the following reasons: antiretroviral-related adverse effects; comorbidities; risk of interactions; or archived resistance. Patients had ≥24 weeks of follow-up. Population, virological and immunological responses and safety and tolerability are described.

Results: Thirty-three (22 on PIs, of whom 18 had ritonavir-boosted PI monotherapy) patients were identified: median (IQR) age of 56 (50–62) years, 55% women, median (IQR) of 19 (17–23) years of known HIV infection, 39% prior AIDS events, median (IQR) of 8 (4–13) years with undetectable plasma HIV-1 RNA and median (IQR) CD4 cell count of 596 (420–843) cells/mm^3. Twenty-five (76%) patients had antiretroviral-related adverse effects, 32 (97%) patients had comorbidities, 28 (85%) patients had risk of interactions and 16 (48%) patients had archived resistance. One patient with suboptimal adherence had low-level virological failure through weeks 4–24. HIV RNA genotypic resistance tests detected no integrase mutations at weeks 4 and 24, but 118R was detected in 7% of the integrated HIV DNA at 24 weeks. Patients had significant median decreases in triglycerides (−117 mg/dL), total cholesterol (−36 mg/dL), the total cholesterol/HDL cholesterol ratio (−0.7) and high-sensitivity C-reactive protein (−0.05 mg/dL) ($P \leq 0.007$), although the Chronic Kidney Disease Epidemiology Collaboration equation also decreased (−7.1 mL/min) ($P < 0.0001$).

Conclusions: These data suggest the efficacy of dolutegravir monotherapy as a maintenance strategy to be further confirmed in randomized clinical trials.

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] Patients living longer with HIV infection may develop comorbidities as they get older and these comorbidities require them to take additional medications that may increase the risk of significant interactions with some antiretrovirals.[2] In addition, some patients that started treatment when ART was suboptimal or when few drugs were available may harbour archived resistance, particularly to non-nucleoside reverse transcriptase analogues and lamivudine/emtricitabine due to their lower genetic barrier, but also to some extent to other NRTIs and to PIs as these drugs had been extensively used.[3] Despite better tolerability, some patients may experience direct toxicities with contemporary antiretrovirals (e.g. digestive and metabolic with boosted PIs, renal and bone with tenofovir etc.).

Standard ART contains three drugs,[4,5] but decreasing the number of antiretrovirals represents a strategy aimed to avoid the negative impact of drug exposure. Our hospital (i.e. Hospital Clinic of Barcelona) is a reference centre caring for >4500 HIV-infected adults by the end of 2014, of whom ~10% were treated with PI monotherapy and 20% with dual therapies including one ritonavir-boosted PI or one integrase inhibitor or both; reasons for these non-standards regimens differed among patients, but were overwhelmingly due to limited therapeutic options due to toxicity, interactions or resistance issues. The major concern with boosted PI monotherapy is a risk of viral rebound higher than with standard triple therapy, despite the apparent lack of resistance emergence.[4,5] In addition, PI monotherapy may still have issues of digestive, metabolic or other PI-related adverse effects and risk of clinically significant interactions due to PI boosters.[6,7]

Dolutegravir has several favourable characteristics resembling those of boosted PIs, including high potency, a high inhibitory

quotient and a high barrier to resistance, that make it appealing for monotherapy; however, dolutegravir also has a lack of interference with comorbidities, a low risk of interactions, a longer half-life and is easier to take and better tolerated than boosted PIs.[8] We review in this report the characteristics and 24 week outcomes of HIV-infected patients from our centre who had their ART switched to dolutegravir monotherapy on an individual clinical basis.

Methods

Study population

We conducted a retrospective non-interventional study searching the hospital database for HIV-infected patients in whom the treating physician had switched their ART to 50 mg of dolutegravir once daily for reasons other than virological failure and had ≥24 weeks of follow-up irrespective of maintaining or not dolutegravir monotherapy. Information on the reasons for therapy switch was categorized for the purpose of this study as one or more of the following: antiretroviral-related adverse effects; comorbidities overlapping antiretroviral toxicity; need for chronic non-ART with risk of clinically significant interactions with antiretroviral drugs; or archived resistance compromising antiretroviral efficacy.

Patients had usually been visited at least at 4 and 24 weeks after switching therapy. We collected HIV-related data including: known duration of HIV infection; duration of antiretroviral exposure and viral suppression; AIDS-defining events; prior virological failure or genotypic resistance mutations; history of any toxicity to antiretroviral drugs; comorbidities and current non-HIV therapies; current ART; and immediate reasons for switch. Results of human leucocyte antigen HLA-B*5701 allele testing were collected whenever available; a positive result for the HLA-B*5701 allele was considered as abacavir toxicity for the purpose of this study.

Plasma HIV-1 RNA, CD4 and CD8 cell counts, fasting plasma lipids and creatinine measured at each visit following routine protocols were also collected. The CD4/CD8 ratio was calculated. Plasma HIV-1 RNA was measured with a commercially available PCR assay, which has a detection threshold of 37 copies/mL (VERSANT HIV-1 RNA kPCR Assay, Siemens Healthcare Diagnostics). Plasma lipids included triglycerides and total, HDL and LDL cholesterol; LDL cholesterol was measured indirectly whenever triglycerides were <400 mg/dL. The total cholesterol/HDL cholesterol ratio was calculated. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate.

Using stored serum samples from routine blood tests, high-sensitivity C-reactive protein (hsCRP) was also measured at the time of switch and 24 weeks later. hsCRP was determined by particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany); the intra-assay coefficient of variation was 3.1% and the lowest limit of detection was 0.01 mg/dL.

Ethics

According to the regulations of the Spanish Ministry of Health,[9] this study did not require approval by a research ethics committee.

Outcomes

We assessed the proportion of patients with plasma viral load <37 copies/mL at 24 weeks by a modified ITT (non-completer=failure) analysis. For the purpose of this report, plasma HIV-1 RNA results below the detection threshold at baseline and 24 weeks were further categorized either as 'negative PCR signal' or 'positive PCR signal, but <37 copies/mL' viraemia according to routine results obtained at the Microbiology Laboratory.[10]

We also evaluated changes from baseline to 24 weeks for: CD4 and CD8 cell counts and the CD4/CD8 ratio; fasting plasma lipids, creatinine and estimated glomerular filtration rate (CKD-EPI), and hsCRP; incidence of adverse events; impact on the reasons underlying ART switch; and HIV resistance mutations in plasma and PBMCs in case of virological failure.

In case of viral failure, plasma and PBMCs were tested for HIV reverse transcriptase, protease and integrase resistance mutations by population sequencing (Trugene, Siemens) and ultradeep sequencing (454 GS-Junior platform, Roche), respectively, following routine protocols.

Statistical analysis

Plasma viral load ≥37 copies/mL, discontinuation of dolutegravir monotherapy or loss to follow-up were considered therapeutic failures. Fisher's exact or Wilcoxon signed-rank tests were used to compare proportions and continuous variables, respectively, between 24 weeks and baseline.

Results

Population characteristics

Until 31 July 2015, we identified 33 patients in the hospital database who had their ART switched to 50 mg of dolutegravir once daily as monotherapy according to their treating physician and had a follow-up of ≥24 weeks. Two additional patients were excluded from this report because of detectable HIV-1 RNA at baseline ($n=1$) or lack of available data ($n=1$). Baseline characteristics

Table 1. Baseline characteristics of the cohort ($N=33$)

Age (years), median (IQR)	56 (50–62)
Female, *n* (%)	18 (55)
Years since HIV diagnosis, median (IQR)	19 (17–23)
AIDS-defining events, *n* (%)	13 (39)
Years with plasma HIV-1 RNA below the detection threshold, median (IQR)	8 (4–13)
CD4 cells (/mm^3), median (IQR)	596 (420–843)
CD8 cells (/mm^3), median (IQR)	990 (624–1288)
CD4/CD8 ratio, median (IQR)	0.64 (0.46–1.01)
PI/r-based ART, *n* (%)	22 (67)
DRV/r ($n=17$)	
LPV/r ($n=1$)	
ATV/r+MVC ($n=2$)	
DRV/r+MVC ($n=1$)	
ABC/3TC+ATV ($n=1$)	
NNRTI-based ART, *n* (%)	9 (27)
NVP+TDF/FTC ($n=3$)	
NVP+ABC/3TC ($n=1$)	
RPV/TDF/FTC ($n=1$)	
EFV/TDF/FTC ($n=1$)	
EFV+ABC/3TC ($n=1$)	
ETV+TDF/FTC ($n=1$)	
ETV+ABC/3TC ($n=1$)	
INSTI-based ART, *n* (%)	2 (6)
RAL+NVP ($n=1$)	
ELVc/TDF/FTC ($n=1$)	

PI/r, ritonavir-boosted PI; INSTI, integrase strand transfer inhibitor; DRV/r, ritonavir-boosted darunavir; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; MVC, maraviroc; ABC, abacavir; 3TC, lamivudine; ATV, atazanavir; NVP, nevirapine; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ETV, etravirine; RAL, raltegravir; ELVc, elvitegravir/cobicistat.

Table 2. Antiretroviral regimens at study entry and underlying reasons for switching to dolutegravir monotherapy in each patient

Patient	ART switched	Toxicity of antiretrovirals	Comorbidities	Non-antiretroviral medications	Previous resistance mutations
1	DRV/r	digestive (PI/r), HLA-B*5701+ (ABC), skin (NVP/EFV)	lipodystrophy, osteoporosis	—	—
2	NVP+RAL	—	cardiovascular disease, diabetes, chronic kidney disease, dyslipidaemia	fluoxetine, gabapentin, omeprazole, enalapril, bisoprolol, nitrites, atorvastatin	—
3	ABC/3TC+ATV	—	hypertension, chronic kidney disease, dyslipidaemia	lisinopril, atorvastatin	65R, 74V, 77I, 101E, 190S
4	DRV/r	dyslipidaemia (PI/r)	hypertension, depression	paliperidone, trazodone, lorazepam, losartan, pitavastatin	62V, 106I, 118I, 15V, 63P
5	DRV/r	dyslipidaemia (PI/r)	cardiovascular disease, diabetes, hypertension, osteoporosis	losartan, aspirin, atorvastatin, alendronate, vitamin D	115F, 181I
6	DRV/r	kidney (TDF), dyslipidaemia (PI/r)	panhypopituitarism, obesity, hypertension, chronic kidney disease, depression	venlafaxine, hydrocortisone, L-thyroxine, desmopressin, enalapril, atorvastatin	—
7	ABC/3TC+EFV	—	hypertension, chronic kidney disease, dyslipidaemia	enalapril, hydrochlorothiazide, atorvastatin	—
8	TDF/FTC/RPV	CNS (EFV)	hypertension, chronic kidney disease, dyslipidaemia, gastro-oesophageal reflux	enalapril, hydrochlorothiazide, omeprazole, simvastatin	—
9	TDF/FTC+ETV	CNS (EFV)	hypertension, depression, osteoporosis	telmisartan, fluoxetine, omeprazole, atorvastatin	—
10	DRV/r	digestive (PI/r)	cardiovascular disease, depression, osteoporosis, sciatica	gabapentine, escitalopram, omeprazole, atorvastatin, alendronate, vitamin D	—
11	DRV/r	dyslipidaemia (PI/r)	hypertension, osteoporosis	enalapril, rosuvastatin, fenofibrate, vitamin D	103N, 118I, 184V
12	LPV/r	digestive (PI/r), dyslipidaemia (PI/r)	hypertension, osteoporosis	enalapril, atorvastatin, omeprazole, vitamin D	—
13	TDF/FTC/EFV	HLA-B*5701+ (ABC)	lipodystrophy, dyslipidaemia, osteoporosis	atorvastatin, omeprazole, alendronate, vitamin D	—
14	TDF/FTC+NVP	—	cardiovascular disease, hypertension, osteoporosis	enalapril, hydrochlorothiazide, atorvastatin, vitamin D, calcium	—
15	DRV/r	dyslipidaemia (PI/r)	lipodystrophy	—	103N, 41L, 67N, 69D, 210W, 63P, 77I, 90M
16	TDF/FTC+NVP	digestive (PI/r)	cardiovascular disease, hypertension, osteoporosis	enalapril, omeprazole, aspirin	—
17	ATV/r+MVC	kidney (TDF), dyslipidaemia (PI/r)	lipodystrophy, cardiovascular disease	amlodipine, ranitidine, atorvastatin, alprazolam	—
18	DRV/r	dyslipidaemia (PI/r)	—	—	181C, 184V, 62V, 65R, 219E
19	DRV/r	CNS (EFV), dyslipidaemia (PI/r)	hypertension, osteoporosis	losartan, atorvastatin, omeprazole, aspirin	—
20	TDF/FTC+NVP	—	lipodystrophy, diabetes, hypertension, dyslipidaemia, depression, osteoporosis	gliclazide, lisinopril, atorvastatin, reboxetine, escitalopram, omeprazole, risperidone	—
21	DRV/r	CNS (EFV), digestive (PI/r)	osteoporosis	vitamin D, calcium	—
22	DRV/r	digestive (PI/r)	COPD, osteopenia	bronchodilators, corticosteroids	103N, 65R, 184V
23	DRV/r	digestive (PI/r)	lipodystrophy, osteopenia	—	103N, 108I, 184V, 215Y, 219Q, 41L, 67N, 69D, 70R, 74V

Continued

Table 2. *Continued*

Patient	ART switched	Toxicity of antiretrovirals	Comorbidities	Non-antiretroviral medications	Previous resistance mutations
24	DRV/r	—	hypogonadism, depression, hypertension	testosterone, venlafaxine, sildenafil, atorvastatin	103N, 210W, 215F, 41L, 98G, 46I/L, 50L, 71V, 73S
25	DRV/r	digestive (PI/r), dyslipidaemia (PI/r)	osteopenia	—	103N, 184V, 210S, 215Y
26	ABC/3TC + ETV	—	hypertension, diabetes, dyslipidaemia, osteoporosis	metformin, losartan, hydrochlorothiazide, atorvastatin, aspirin	—
27	DRV/r + MVC	—	lipodystrophy, osteoporosis	alendronate, vitamin D	103N, 184V
28	ATV/r + MVC	skin (NVP), digestive (PI/r)	hypertension, diabetes, depression	sitagliptin, metformin, valsartan, hydrochlorothiazide, sertraline, atorvastatin	103N, 219Q, 67N, 70R, 98G
29	TDF/FTC/ELVc	digestive (TDF/FTC/ELVc)	depression, osteoporosis	escitalopram, lorazepam	181C, 106A, 67N, 70R
30	TDF/FTC + NVP	kidney (TDF)	cardiovascular disease, hypertension	enalapril, aspirin, atorvastatin, omeprazole	—
31	DRV/r	digestive (PI/r)	COPD	bronchodilators, corticosteroids	103N, 184V
32	DRV/r	digestive (PI/r)	lipodystrophy, hypertension, osteopenia	losartan	103N, 184V, 215F, 41L, 98G, 63P, 77I
33	DRV/r	digestive (PI/r)	osteoporosis	vitamin D	103N, 118I, 181C, 210W, 215Y, 41L, 44D, 74V, 184V

DRV/r, ritonavir-boosted darunavir; LPV/r, ritonavir-boosted lopinavir; ATV/r, ritonavir-boosted atazanavir; MVC, maraviroc; ABC, abacavir; 3TC, lamivudine; ATV, atazanavir; NVP, nevirapine; TDF, tenofovir; FTC, emtricitabine; RPV, rilpivirine; EFV, efavirenz; ETV, etravirine; RAL, raltegravir; ELVc, elvitegravir/cobicistat; PI/r, ritonavir-boosted PI.

are shown in Table 1. In contrast to the whole HIV cohort at our centre, patients on dolutegravir monotherapy were older and there was no sexual predominance. They had been exposed to HIV infection for a long period and approximately one-third of them had prior AIDS-defining events. The median (IQR) CD4 count at diagnosis of HIV infection was 230 (136–313) cells/mm^3. Patients had received a median (IQR) of 9 (7–11) different antiretroviral regimens for a median (IQR) of 19 (17–23) years. Patients had maintained plasma HIV-1 below the detection threshold for a median (IQR) of 8 (4–13) years. At the time of switch, 22 (67%) patients were receiving a ritonavir-boosted PI-containing regimen (including 18 on monotherapy and 3 on dual therapy), 9 (27%) were receiving a triple NNRTI-based regimen and 2 (6%) were receiving regimens containing integrase inhibitors.

Table 2 summarizes antiretroviral regimens at study entry and underlying reasons for switching to dolutegravir monotherapy in each patient. Twenty-five (76%) patients had current or past toxicity to antiretrovirals, 32 (97%) had comorbidities, 28 (85%) were receiving chronic non-ART and 16 (48%) had archived resistance mutations. The immediate reasons for switching ART according to the treating physician were: interactions in 13 (39%) patients (ritonavir, $n=10$; nevirapine, $n=2$; and rilpivirine, $n=1$); gastrointestinal symptoms in 11 (33%) patients; dyslipidaemia in 9 (27%) patients; osteoporosis in 6 (18%) patients; high cardiovascular risk (Framingham score $\geq$20%) in 3 (9%) patients; cardiovascular disease (myocardial infarction) in 1 (3%) patient; and progression of chronic kidney disease in 1 (3%) patient. Some patients had more than one immediate reason for switching ART.

Virological and immunological response

At 24 weeks, the therapeutic efficacy of dolutegravir monotherapy in this cohort was 97% (95% CI 83%–100%). There were no significant differences in the proportion of patients showing 'negative PCR signal' viraemia between baseline ($n=22$, 67%) and at 24 weeks ($n=26$, 79%) ($P=0.4075$).

One patient had viral failure at week 4 (88 copies/mL; confirmed as 155 copies/mL) and 'positive PCR signal, but <37 copies/mL' viraemia at baseline. He was a 52-year-old man with known HIV-1 infection for 12 years who had received as many as 10 different regimens with intermittent periods of detectable HIV-1 RNA because of lack of adherence due to multidrug abuse. He had been abstinent of drug abuse and maintained viral suppression for the last 2 years with darunavir/ritonavir monotherapy, but he had comorbidities and risk of potential interactions that made his doctor consider switching his ART. He was also receiving psychotropic therapy including paliperidone, trazodone and lorazepam, antihypertensive therapy including losartan and lipid-lowering therapy including pitavastatin. Previous plasma HIV-1 reverse transcriptase and protease genotypic resistance tests had shown the following mutations: 62V, 106I, 118I, 15V and 63P. He had had previous viral failure to a raltegravir-containing regimen without integrase genotypic resistance testing at that time. After detecting viral failure on dolutegravir monotherapy, he was recommended to increase the dolutegravir dose to 50 mg twice daily, but he continued 50 mg once daily. Plasma HIV-1 RNA remained detectable at 24 weeks

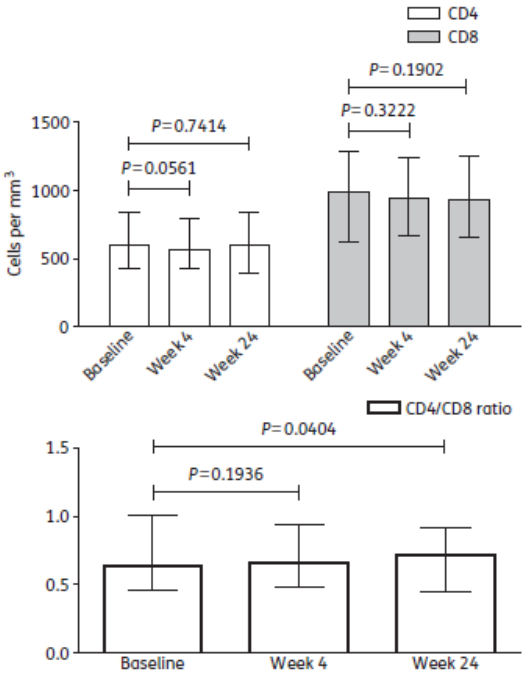

Figure 1. CD4 and CD8 cell counts and the CD4/CD8 ratio at baseline, 4 weeks and 24 weeks. Data are presented as median (IQR). The CD4/CD8 ratio was significantly higher at 24 weeks compared with baseline ($P=0.0404$).

(79 copies/mL; confirmed as 101 copies/mL). HIV RNA genotypic resistance tests in confirmation samples at 4 and 24 weeks detected no integrase mutations. HIV DNA genotypic resistance tests detected the integrase mutation 118R in 7% of the integrated DNA in PBMCs at 24 weeks.

Figure 1 shows CD4 and CD8 cell counts and the CD4/CD8 ratio at baseline, 4 weeks and 24 weeks. The CD4/CD8 ratio was significantly higher at 24 weeks compared with baseline ($P=0.0404$).

Safety and tolerability

Dolutegravir monotherapy was apparently well tolerated. No patient discontinued therapy. Two patients had adverse events reported during follow-up: foot amputation due to chronic ischaemia in a diabetic patient and secondary syphilis. None of these events was attributed to dolutegravir.

Table 3 compares selected chemistry parameters between baseline and 24 weeks. There were significant median decreases in triglycerides (−117 mg/dL), total cholesterol (−36 mg/dL), the total cholesterol/HDL cholesterol ratio (−0.7) and hsCRP (−0.05 mg/dL) ($P \leq 0.007$), although CKD-EPI also decreased (−7.1 mL/min) ($P < 0.0001$).

Regarding the impact on the immediate reasons for ART switch, there were no clinically evident interactions in the 13

Table 3. Comparison of selected chemistry parameters between baseline and 24 weeks

	Baseline	24 weeks	*P*
Glucose (mg/dL)	93 (89–101)	93 (86–104)	0.2501
Triglycerides (mg/dL)	205 (160–303)	112 (95–160)	<0.0001
Total cholesterol (mg/dL)	221 (185–255)	185 (171–211)	<0.0001
LDL cholesterol (mg/dL)	129 (109–161)	119 (100–135)	0.0004
HDL cholesterol (mg/dL)	46 (37–53)	42 (37–55)	0.5157
Total cholesterol/HDL cholesterol ratio	4.62 (4.14–5.79)	3.89 (3.21–5.12)	0.1971
hsCRP (mg/dL)	0.08 (0.04–0.21)	0.07 (0.04–0.10)	0.0054
Creatinine (mg/dL)	0.83 (0.64–0.95)	0.90 (0.73–1.05)	0.0203
CKD-EPI (mL/min/1.73 m^2)	97 (80–107)	89 (72–98)	<0.0001

Data are presented as median (IQR).
There were significant decreases in triglycerides, total and LDL cholesterol and hsCRP. Creatinine significantly increased and the estimated glomerular filtration rate (CKD-EPI) significantly decreased.

patients who were at risk at baseline, gastrointestinal symptoms improved or disappeared in 9 of 11 patients, plasma lipids improved in the 9 patients with dyslipidaemia at baseline and Framingham score decreased in all 3 patients with high cardiovascular risk at baseline. Two patients with osteoporosis had dual-X absorptiometry conducted at baseline and 24 weeks, but lumbar spine and femur T-scores remained unchanged. In the patient with progression of chronic kidney disease at baseline, estimated glomerular filtration (CKD-EPI) further decreased from 59 to 52 mL/min/1.73 m^2, but urinary protein/creatinine improved, decreasing from 330 to 146 mg/mg at 24 weeks.

Discussion

This study emerged from the coincidence of two factors in a large cohort of HIV-infected adults receiving clinical care. On the one hand, the numerous difficulties that a number of patients experienced to satisfactorily maintain their ART despite having achieved sustained viral suppression.[1] Characteristics of the patients included in this cohort outlined in Table 2 make evident the multiple limitations that they had and the need for further improvement in their antiretroviral regimens. On the other hand, the availability of an antiretroviral drug such as dolutegravir with characteristics that allowed for potential consideration of monotherapy.[8]

Dolutegravir has compared favourably with efavirenz[11] and darunavir/ritonavir[12] and similarly with raltegravir[13] in naive patients and it is currently recommended as a first option for antiretroviral-naive patients. Dolutegravir also compared favourably with raltegravir in patients with viral failure, but no prior exposure to integrase inhibitors.[14] Besides its outstanding efficacy, dolutegravir is also characterized by its high genetic barrier and robustness in the prevention of viral resistance. In antiretroviral-naive patients,[11–13] dolutegravir-treated patients with viral failure did not show resistance mutations to both dolutegravir and NRTIs, a characteristic known for boosted PIs, but not for antiretrovirals from other drug classes or even the other integrase inhibitors currently available, raltegravir and

elvitegravir. This characteristic is also supported by clinical data from antiretroviral-experienced, but integrase inhibitor-naive, patients with viral failure[14] and by laboratory data.[15] Dolutegravir also showed fewer discontinuations than comparator drugs and had no effect on lipids or liver enzymes in antiretroviral-naive patients, although an increase in creatinine can be expected by tubular blockade that is not considered a toxic effect. Dolutegravir is conveniently administered as a single, small pill once daily and with no food restrictions. Dolutegravir does not require boosting and plasma levels have been reported to be above the 90% inhibitory concentration 24 h after dosing.[16] Dolutegravir has no expected major interactions with other drugs, a characteristic also shared by raltegravir. All these factors together make dolutegravir different from the other antiretrovirals available and it may be particularly important for patients with limitations to pre-existing ART.

The results in this cohort of patients who received dolutegravir monotherapy are remarkable, because almost all were able to maintain viral suppression after 24 weeks, with improvements in the immediate reasons that made them have their therapies switched and no deleterious effects on immune function or major adverse events. All patients in the cohort, except for the one who had viral failure, have maintained dolutegravir monotherapy for almost 1 year of follow-up at the time of writing this report and plasma HIV RNA has remained suppressed in all of them. These results are surprising because they would have not been possible with any other single drug. For the last 30 years, the vulnerability to develop resistance has been a serious limitation to every antiretroviral drug. This was why early studies using single and dual combinations produced only very short-term benefits.

We observed one patient developing viral failure in our cohort. This patient had a previous viral failure to a raltegravir-containing regimen, although no resistance mutations to integrase inhibitors were found when viral failure to dolutegravir monotherapy was initially detected. Although this patient denied missing dolutegravir doses, there were reasons to suspect that his adherence to therapy was not optimal. This patient had persistent low-level viraemia and developed mutation 118R in the integrase gene, which confers intermediate resistance to raltegravir and elvitegravir and potential low-level resistance to dolutegravir according to the Stanford University HIV Resistance Database (http://sierra2.stanford.edu/sierra/servlet/JSierra). In another 24 week French cohort study including patients with similar epidemiological characteristics as those in our cohort, 3 (11%) out of 28 patients who switched to dolutegravir monotherapy experienced viral failure with development of resistance mutations to integrase inhibitors.[17] As with the patient who failed in our cohort, all three patients with viral failure in the French study had previously been exposed to integrase inhibitors. These patients had dolutegravir plasma levels measured at several timepoints during follow-up; although they were well above the *in vitro* 90% inhibitory concentration and within therapeutic levels at the time of viral failure, plasma levels in the weeks or few months before viral failure were not measured and thus we cannot confirm whether optimal adherence to therapy had been continuously maintained in these three failing patients. What it is evident from the French study and from ours is that viral failure to dolutegravir monotherapy may lead to the appearance of resistance mutations to integrase inhibitors and this is something different from what we knew about boosted PI monotherapy. The existence of resistance mutations to raltegravir might cause cross-resistance to dolutegravir, which may result in less positive results when dolutegravir is employed as a second-line maintenance regimen.[18] Although dolutegravir has a high genetic barrier to resistance, it is definitely lower than that of boosted PIs. Both R263K and G118R as single mutations can confer resistance to dolutegravir[19] and resistance may be even higher when secondary mutations are also present.[20] Dolutegravir-containing monotherapy and dual therapy[17,21–23] are non-standard strategies and further research is needed before they can be generalized into the clinical setting.

Our study was not controlled, included a low number of patients and had a short follow-up. We acknowledge that reasons for switching therapy differed among participants and other non-standard regimens could have been used instead of dolutegravir monotherapy. Limitations with ART in our cohort are exemplified by the common use of non-standard treatments (e.g. monotherapy with boosted PIs) in a substantial number of patients. Patients from our cohort were therefore highly selected and their results may not be applied to other patients. As with any retrospective study, we had no accurate information of potential adverse effects on starting dolutegravir, but we did not identify any patient discontinuing therapy. The major strength for our study is that switching allowed patients to be released from limitations with their previous antiretroviral regimens while they were able to maintain the benefits of sustained viral suppression.[24]

In summary, these data suggest the efficacy of dolutegravir monotherapy as a maintenance strategy to be further confirmed in randomized clinical trials. Several studies with monotherapy or dual therapy with dolutegravir have been registered already or are being planned. They will provide us with more definitive data to determine whether dolutegravir monotherapy or dual therapy can challenge the paradigm of standard triple therapy.

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5.6 Estudio DOLAM

Objetivo 3.5 Evaluar la viabilidad de pautas de TAR basadas en dolutegravir con menos de tres fármacos y más específicamente comparar la eficacia y la seguridad de la monoterapia con dolutegravir frente a la biterapia con dolutegravir más lamivudina en adultos infectados por VIH con supresión virológica sostenida.

PDF del artículo 5:

"Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24-week analysis of the DOLAM randomized clinical trial". J.L. Blanco, J. Rojas, R. Paredes, E. Negredo, J. Mallolas, M. Casadella, et al. J Antimicrob Chemother 2018; 73: 1965–71. FI: FI: 5,217.

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Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial

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Background: No controlled comparisons between dolutegravir/lamivudine or dolutegravir maintenance therapy have been done. We hypothesized that these options would have similar efficacy to triple ART.

Methods: We used an open-label non-inferiority randomized controlled trial comprising two phases: phase A was established to test that experimental arms did not have an unacceptable (≥5%) failure rate; phase B was intended to include the full number of patients followed for 48 weeks. Treated HIV-1-infected adults with viral load <50 copies/mL for ≥12 months, no prior viral failure or resistance mutations to study drugs, nadir CD4 >200 cells/mm^3, and hepatitis B virus surface antigen negative 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. Premature discontinuation was considered if viral failure or therapy interruption due to adverse events, concurrent illness, protocol deviation or patient's wish occurred. Blips were registered. Planned phase A results at 24 weeks are reported here. The study is registered at EudraCT: 201500027435.

Results: Ninety-one (control, $n = 31$; dual therapy, $n = 29$; monotherapy, $n = 31$) patients were randomized. Three patients (none previously exposed to integrase inhibitors) prematurely discontinued treatment due to viral failure: dolutegravir/lamivudine ($n = 1$), no resistance mutations (subject A); dolutegravir ($n = 2$), N155H, S147G and Q148R resistance mutations (subject B), and E138K, G140S and N155H resistance mutations (subject C). There were no discontinuations for other reasons. One patient (dolutegravir/lamivudine) experienced a blip in viral load. The Data Safety Monitoring Board recommended stopping the dolutegravir monotherapy arm.

Conclusions: In contrast to dolutegravir/lamivudine, a higher than expected risk of viral failure with development of cross-resistance integrase mutations occurred with dolutegravir maintenance monotherapy.

Introduction

Standard ART contains three drugs,[1,2] but reducing the number of antiretrovirals to simplify therapy and to avoid the negative impact of drug exposure is an attractive strategy. Boosted PI maintenance monotherapy has a risk of viral rebound higher than that with standard triple therapy but fortunately no major resistance emergence has been reported so far.[3] In contrast to monotherapy, dual therapy with boosted PIs plus lamivudine has shown non-inferiority compared with standard triple therapy in antiretroviral-experienced HIV-infected patients.[4] PI dual therapy or monotherapy may nevertheless cause digestive, metabolic and other PI-related adverse effects, and bring the risk of clinically significant interactions due to PI boosters.[5]

Dolutegravir shares several favourable characteristics with boosted PIs, including high potency, high inhibitory quotient and high barrier to resistance, that make it appealing for antiretroviral regimens with fewer than three drugs. Furthermore, dolutegravir also demonstrates a lack of interference with comorbidities, a low risk for interactions, a longer half-life and is easier to take and better tolerated than boosted PIs.[6] Lamivudine, the most commonly used antiretroviral drug to date, is still considered in major guidelines, has shown no major related toxicities, has a low likelihood of

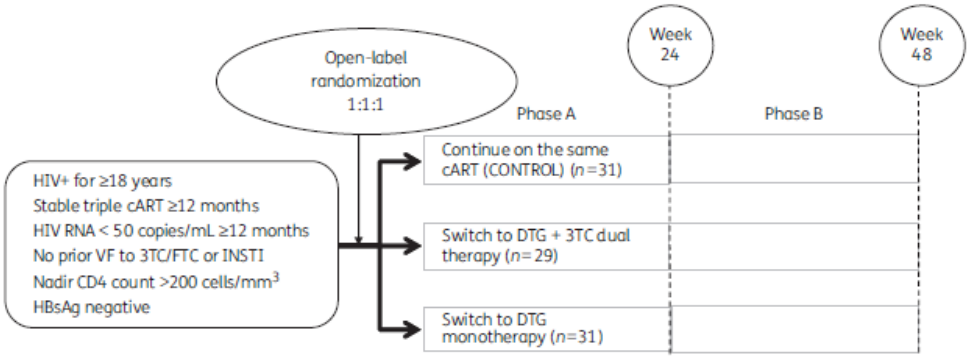

Figure 1. DOLAM study design. cART, combination antiretroviral therapy; VF, viral failure; 3TC, lamivudine; FTC, emtricitabine; INSTI, integrase inhibitor; DTG, dolutegravir; HBsAg, hepatitis B virus surface antigen.

drug–drug interactions, and promising data have emerged from PI-based dual-therapy maintenance studies.[1,2,4]

A preliminary review of 33 HIV-infected patients from Hospital Clinic (Barcelona, Spain) who had their ART switched to dolutegravir monotherapy on an individual clinical basis showed 97% efficacy at 24 weeks;[7] although one patient developed viral failure, this patient had a psychiatric comorbidity with suboptimal adherence to ART. Clinical experience of dual therapy with dolutegravir/lamivudine in antiretroviral-experienced patients has been also promising.[8,9] Based on these data, we hypothesized that dolutegravir/lamivudine dual therapy or dolutegravir monotherapy would have efficacy similar to that of triple ART in patients with sustained viral suppression.

Methods

Study design

The DOLAM Study is a multicentre, randomized, controlled with active treatment, open-label, parallel clinical trial comprising two phases, A and B. Phase A aimed to include 30 patients per arm and follow them for at least 24 weeks. This phase was performed for futility purposes to assess whether experimental arms were subjected to an unacceptable (defined as ≥5%) rate of viral failure. Phase B was intended to include the full number of patients and follow them for 48 weeks. Figure 1 shows the design of the DOLAM Study.

In phase A, eligible participants were randomly assigned in a 1:1:1 ratio to one of the following arms: to continue current treatment (control arm), to switch to dolutegravir (50 mg)/lamivudine (300 mg) once daily (dual-therapy arm), or to switch to 50 mg of dolutegravir once daily (monotherapy arm) (Figure 1). A random sequence was generated by a computer stratifying by anchor drug (PI, NNRTI or integrase inhibitor). The assignment was centralized and communicated by telephone.

Premature discontinuation was considered if there was viral failure (defined as two consecutive plasma HIV RNA measurements ≥50 copies/mL or a single HIV-1 RNA value >1000 copies/mL) or therapy interruption due to adverse events, concurrent illness, protocol deviation or patient's wish. Blips were registered. The study is currently ongoing and the planned phase A results at 24 weeks are reported here. The Data Safety Monitoring Board (DSMB) reviews the data if the proportion of confirmed viral failures in any of the experimental arms reaches ≥5%.

Ethics

Institutional review boards from participating centres approved the study and written informed consent was obtained from all eligible patients before randomization. The study is registered at EudraCT, number: 2015000027435.

Patients

Consecutive clinically stable HIV-infected adults (≥18 years old) on stable (defined as at least the previous 12 months) triple ART based on PIs, NNRTIs or integrase inhibitors with sustained viral suppression (defined by plasma HIV RNA <50 copies/mL in two or more consecutive determinations during at least the 12 months prior to inclusion; blips up to 200 copies/mL were permitted) were invited to participate (Figure 1). For women of childbearing age, a negative pregnancy test within 10 days prior to 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 if genotypic testing had been previously performed; nadir CD4 <200 cells/mm^3; any disease or history of disease that, in the opinion of the investigator, might confound the results of the study or pose additional risk to patient treatment; and chronic hepatitis B (defined by positivity for hepatitis B surface antigen).

Outcomes

The major endpoint of the DOLAM Study is to determine therapeutic efficacy and viral failure rate (FDA snapshot algorithm) assessed with standard plasma HIV-1 RNA detection (defined by a limit of detection of 50 copies/mL) at 48 weeks. For the purpose of the phase A analysis reported here, we described rates of viral failure and blips, and adverse events at 24 weeks among the three arms.

In the event of viral failure, plasma and PBMCs were tested for HIV reverse transcriptase, protease and integrase resistance mutations by population sequencing (Trugene, Siemens) and ultra-deep sequencing (MiSeq platform, Illumina), respectively, following routine protocols.

At each visit, whole blood samples were collected in test tubes containing heparin sodium ~24 h after administration of dolutegravir. The blood samples were centrifuged at 1200 **g** for 10 min to isolate 2 mL of plasma

and 3–4 aliquots with 5 mL of pellet, which were stored at −80°C until assayed. In patients developing viral failure, dolutegravir, raltegravir and elvitegravir plasma concentrations were measured in samples available using mass spectrometry at a mass-to-charge ratio of 420 using the MassLynx analysis software version 4.0 (Waters Corp., Milford, MA). Raltegravir and elvitegravir plasma concentrations were measured to rule out potential exposure to these integrase inhibitors influencing the development of resistance mutations. Dolutegravir plasma concentrations were compared with the *in vitro*, protein-adjusted 90% inhibitory concentration (IC_{90}) of dolutegravir for WT virus (64 ng/mL).[10]

Procedures

All patients were visited at baseline, 12 and 24 weeks. At baseline, patients' characteristics, including age, gender, suspected route of HIV transmission and anchor drug, were collected. At each visit, participants had a complete physical examination done and blood drawn for CD4 and CD8 cell counts and standard plasma HIV-1 RNA (limit of detection 20 copies/mL at Hospital Clínic, and 40 copies/mL at Hospital Universitari Germans Trias i Pujol, but homogenized for the purpose of this study to <50 copies/mL to define plasma viral suppression). Patients allocated to the experimental arms had also blood drawn for standard plasma HIV-1 RNA at 4 weeks to detect potential early viral failure. At each follow-up visit, information on adverse events and use of drugs other than ART was collected, a simplified adherence questionnaire was administered,[11] and a pregnancy test for women of childbearing age was performed. Intensity of adverse events was assessed according to the Division of AIDS table for grading the severity of adult and paediatric adverse events.[12]

Results

Baseline characteristics

There were 91 patients included in the phase A of the DOLAM Study: 31 patients in the control arm, 29 patients in the dual-therapy arm and 31 patients in the monotherapy arm. Table 1 shows the characteristics of the patients. Most patients were middle-aged adult men who had sex with men. The mean absolute CD4 cell concentration was 739 cells/mm^3, and the mean CD4/CD8 ratio was nearly 1. The anchor drug was most commonly an NNRTI (70%) followed by an integrase inhibitor (17%) and a PI (13%), reflecting the use of these drugs in the population to whom the study was addressed.

Table 1. Baseline characteristics

Characteristic	Controls ($n = 31$)	Dolutegravir/lamivudine ($n = 29$)	Dolutegravir ($n = 31$)	Total
Age, years	46 (12)	44 (9)	47 (13)	46 (12)
Men, *n* (%)	27 (87)	23 (79)	28 (90)	78 (86)
MSM, *n* (%)	22 (76)	21 (75)	24 (77)	67 (76)
CD4, cells/mm^3	675 (265)	753 (214)	791 (393)	739 (303)
CD4 cells, *n* (%)	33 (6)	33 (7)	33 (7)	33 (7)
CD8/mm^3	711 (269)	861 (269)	902 (416)	824 (334)
CD8 cells, *n* (%)	35 (7)	37 (7)	38 (9)	37 (8)
CD4/CD8 ratio	1.01 (0.36)	0.95 (0.36)	0.95 (0.35)	0.97 (0.35)
Prior ART, *n* (%)				
NNRTI	22 (71)	21 (72)	21 (68)	64 (70)
PI	3 (10)	4 (14)	5 (16)	12 (13)
INSTI	6 (19)	4 (14)	5 (16)	15 (17)

Data are mean (SD) unless otherwise stated. INSTI, integrase inhibitor.

Patients' disposition at 24 weeks

Three patients prematurely discontinued due to viral failure. None of them had been previously exposed to integrase inhibitor therapy. One of these patients (subject A) had been assigned to dual therapy and viral failure occurred at week 12. The other two patients (subjects B and C) had been assigned to monotherapy and viral failure occurred at week 24 in both cases. No patient assigned to the control arm experienced viral failure. There were no discontinuations for other reasons. Only one patient (assigned to dual therapy) experienced a blip at week 4.

Viral failures

The patient assigned to dual therapy who developed viral failure (subject A) (Figure 2a) had been diagnosed with HIV-1 infection in 2003. The patient began therapy with efavirenz, lamivudine and tenofovir disoproxil fumarate in 2004. Lamivudine was switched to emtricitabine for simplification purposes in 2006. Efavirenz was switched to darunavir plus ritonavir in 2012 due to sleep problems potentially associated with efavirenz. The patient, who had been virally suppressed for 8 years, experienced viral rebound due to lack of adherence to the new regimen because of gastrointestinal adverse effects. The patient was switched again to the previous regimen, regaining viral suppression for 122 weeks until entering the DOLAM Study and was randomized to dual therapy. The plasma dolutegravir concentration at week 4 was 1776 ng/mL, well above the *in vitro*, protein-adjusted IC_{90} of dolutegravir for WT virus. At 12 weeks, viral load showed a low-level rebound and viral failure was confirmed. No resistance mutations were detected in plasma and some low-abundance variants to NRTIs and NNRTIs were detected in PBMCs. The patient switched to dolutegravir/lamivudine/abacavir, regaining viral suppression in plasma.

One of the two patients assigned to monotherapy who developed viral failure (subject B) (Figure 2b) had been virally suppressed with efavirenz/emtricitabine/tenofovir disoproxil fumarate for at least 9 years before participating in the DOLAM Study. The patient remained virally suppressed until week 24 when the patient experienced viral rebound to 96 copies/mL, later confirmed as 1266 copies/mL. Plasma dolutegravir levels before and at the moment of viral failure largely exceeded those of the *in vitro*, protein-adjusted IC_{90} of dolutegravir for WT virus. *De novo* integrase mutations S147G and N155H were detected in plasma at the time of virological failure and virological failure confirmation, and low-abundance Q148R mutation (3%) also appeared at the time of virological failure confirmation. The patient switched to emtricitabine/tenofovir disoproxil fumarate plus rilpivirine, and later from rilpivirine to darunavir/cobicistat, regaining viral suppression in plasma.

The other patient assigned to monotherapy who developed viral failure (subject C) (Figure 2c) had been diagnosed with HIV-1 infection in 2008. The patient began therapy with efavirenz, emtricitabine and tenofovir disoproxil fumarate in 2012. The patient remained virally suppressed for >3 years until the patient was recruited for the DOLAM Study. The patient remained virally suppressed until week 24 when the patient's plasma viral load was

(a)

		28/10/2015	1/12/2015	27/01/2016	02/03/2016	06/04/2016
Sample Information	Study week	0	4	12	17 (VF confirmation)	24
	ART	EFV/FTC/TDF →DTG+3TC	DTG+3TC	DTG+3TC	DTG+3TC	ABC/3TC/DTG
	HIV-1 RNA	40	40	110	110	48
	Drug levels (ng/mL)					
	DTG	<LLQ	1776.000	-	-	-
	RAL	<LLQ	<LLQ	-	-	-
	ELV	<LLQ	<LLQ	-	-	-
	DRM by Sanger	-	Plasma • RT: No mutations • Integrase: No mutations	Plasma • RT: No mutations • Integrase: No mutations	-	-
	DRM by MiSeq	-	-	-	Plasma • RT: No mutations • Integrase: No mutations	PBMC • *NRTI*: K70E (1.5%), K219E (1.2%) • *NNRTI*: G190R, M230I

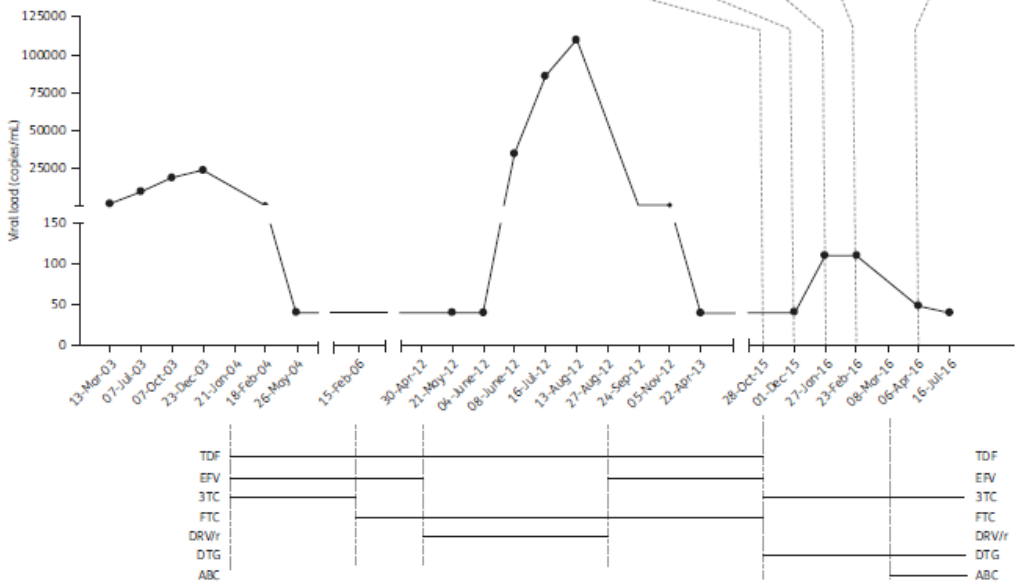

Figure 2. (a) Subject A (dolutegravir/lamivudine dual-therapy arm). (b) Subject B (dolutegravir monotherapy arm). (c) Subject C (dolutegravir monotherapy arm). EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; DTG, dolutegravir; 3TC, lamivudine; ABC, abacavir; ELV, elvitegravir; NVP, nevirapine; COBI, cobicistat; RPV, rilpivirine; DRM, drug resistance mutation; LLQ, lower limit of quantification.

50 copies/mL. The patient did not attend for confirmation of viral failure until 10 weeks later. At that time, the plasma viral load was 106 copies/mL and 2 weeks later it was 426 copies/mL. *De novo* integrase mutations E138K and N155H were detected in plasma at both timepoints, and low-abundance G140S mutation (4%) also appeared in the first genotypic resistance analysis. Dolutegravir plasma levels were not measured in this patient, but self-reported and pharmacy-measured adherence was excellent. The patient switched to darunavir/cobicistat monotherapy, regaining viral suppression in plasma.

Adverse events

Table 2 shows the profile and intensity of adverse events in the three study arms. Patients assigned to both dual-therapy and monotherapy arms experienced more adverse effects than patients assigned to the control arm, but most adverse effects were Grade 1. Infections and neuropsychiatric effects were more common in both experimental arms compared with the control arm. No patient discontinued therapy due to adverse effects.

(b)

		21/12/2015	18/01/2016	10/03/2016	06/06/2016	30/06/2016
Sample Information	Study week	0	4	12	24	24 (VF confirmation)
	ART	TDF/FTC+NVP	DTG	DTG	DTG	DTG
	HIV-1 RNA	<40	<40	<40	98	1266
	Drug levels (ng/mL)					
	DTG	<LLQ	3503.916	1052.520	2899.466	-
	RAL	<LLQ	<LLQ	<LLQ	<LLQ	-
	ELV	<LLQ	<LLQ	<LLQ	<LLQ	-
	DRM by Sanger	-	-	Plasma RT: E138A	Plasma RT: E138A	Plasma RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G N155H
	DRM by MiSeq		-	Plasma RT: E138A	Plasma RT: E138A	Plasma RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G Q148R (3%) N155H

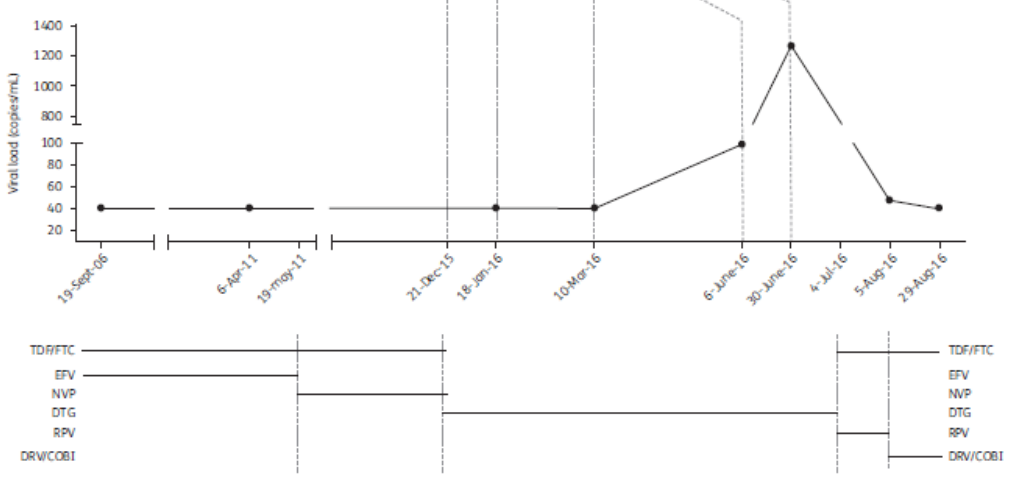

Figure 2. Continued

DSMB report

As pre-planned in the protocol, the DSMB was convened to review the data because the proportion of confirmed viral failures in the monotherapy arm reached ≥5%. The Board considered that the rate of viral failure in the dolutegravir monotherapy arm exceeded the safety threshold stated in the protocol and was clinically relevant because it was associated with resistance mutations. The Board recommended the immediate interruption of the dolutegravir monotherapy arm of the DOLAM Study. In contrast, the occurrence of one viral failure not associated with resistance mutations in the dolutegravir/lamivudine dual-therapy arm was not deemed by the DSMB as sufficiently relevant to recommend the interruption of this study arm. These decisions were unanimously taken in a written report by the three members of the DOLAM Study DSMB.

Following the DSMB report, the investigators of the DOLAM Study decided to stop the dolutegravir monotherapy arm, and to amend the protocol to continue with the control and dual-therapy arms only until completion of the study. Patients assigned to the dolutegravir monotherapy arm were advised on the higher risk of viral failure and the potential development of resistance mutations. They were strongly recommended to switch their therapy to a safer regimen but the final decision depended on each patient's wishes.

Discussion

To our knowledge, DOLAM is the only study that has directly compared dolutegravir/lamivudine dual therapy versus dolutegravir monotherapy as potential dolutegravir-based simplification strategies in a face-to-face randomized clinical trial. In the phase A of the DOLAM Study reported here, we found that the incidence of viral failures in the dolutegravir monotherapy arm exceeded the protocol pre-established threshold of 5% at 24 weeks. Viral failures in patients under dolutegravir monotherapy did not occur early but at the end of the 24 week period. In addition, the two patients experiencing viral failure under dolutegravir monotherapy developed *de novo* mutations, suggesting cross-resistance to all currently licensed integrase inhibitors.[13]

(c)

Sample	Data	22/05/2008	10/05/2012	18/11/15	01/06/2016	06/09/2016	20/09/16	10/11/2016	09/05/2017
	Study week	-	-	0	24	24 (VF confirmation)	-	-	-
	ART	No	TDF/FTC/EFC	DTG	DTG	DTG	DTG	DRV/COBI	DRV/COBI
	HIV-1 RNA	14700	<LLQ	<LLQ	50	106	426	<20	<20
	DRM by Sanger	V245E-RT					ND		
	DRM by MiSeq					Plasma	Plasma:		
						IN-138K (82%)	IN-138K (87%)		
						IN-155H (16%)	IN-155H (4%)		
						IN-140S (4%)			

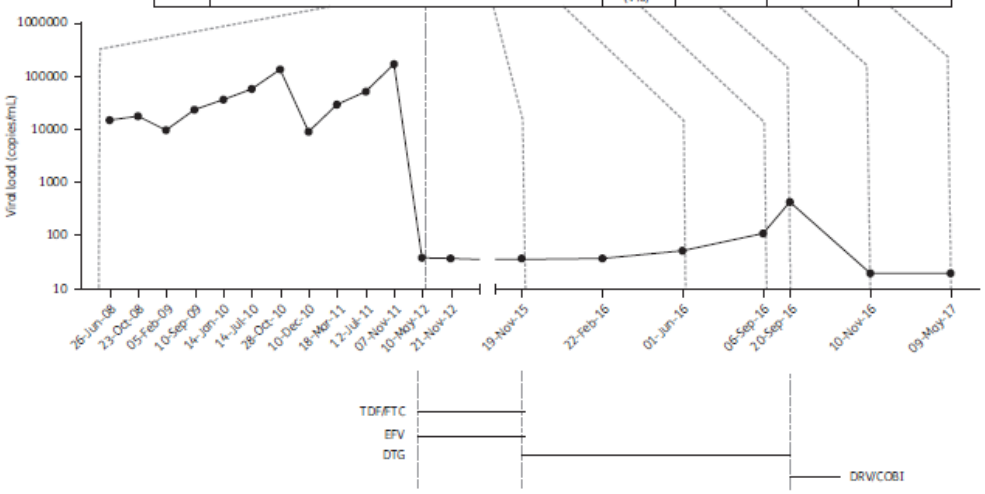

Figure 2. Continued

In both patients, multiple mutations were developed in the presence of low-level viraemia and despite adequate dolutegravir plasma levels and adherence to therapy. These results are in accordance with those of a recently published randomized clinical trial comparing maintenance dolutegravir monotherapy with combination ART.[14] In that trial, eight (8%) patients treated with dolutegravir monotherapy experienced viral failure and three of them showed one resistance mutation each (S230R, R263K and N155H) despite adequate plasma dolutegravir levels and self-reported adherence. In addition, a recent systematic review and meta-analysis of dolutegravir-based simplified therapy in HIV-infected patients[15] that provided precise estimates of viral failure rate on dolutegravir-based mono- and dual-therapy maintenance (including not only dolutegravir/lamivudine, but also dolutegravir/rilpivirine) showed that the rate of viral failure was 10-fold higher for dolutegravir monotherapy (3.18%) than for dolutegravir-based dual therapy (0.32%) at 24 weeks, but the difference increased further to 20-fold higher at 48 weeks (8.91% versus 0.41%), suggesting that the risk of viral failure and development of resistance mutations with dolutegravir monotherapy may be higher after the first 24 weeks. All together, these data suggest that dolutegravir used as monotherapy is not potent enough and/or its genetic barrier to resistance is insufficient to prevent development of resistance despite optimal adherence, and therefore this strategy should not be used.

In summary, in the planned 24 week analysis of two dolutegravir-based simplification strategies (DOLAM Study), the dolutegravir monotherapy arm showed an unacceptable risk of viral failure with development of integrase inhibitor cross-resistance mutations and this arm was stopped and not further recommended, whereas the dolutegravir + lamivudine dual-therapy arm showed no warning signs. Based on the phase A results, the DOLAM Study protocol has been amended to two arms only (dolutegravir/lamivudine dual therapy versus control), the sample size has been recalculated and additional centres have been invited to complete phase B of the study.

Table 2. Profile and intensity of adverse events in the three study arms

	Controls ($n = 31$)	Dolutegravir/ lamivudine ($n = 29$)	Dolutegravir ($n = 31$)	Total
Group				
infection	2	4	12	18
neuropsychiatric	0	5	8	13
genitourinary	2	4	1	7
muscular	1	0	5	6
gastrointestinal	2	0	3	5
laboratory	2	1	2	5
ocular/visual	0	1	1	2
respiratory	0	1	1	2
endocrine	1	0	0	1
systemic	0	1	0	1
Grade				
1	8	17	28	53
2	2	0	6	8

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Members of the DOLAM Study Team

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Author contributions

Study design: E. M.; secured funding: B. C., J. M. G., E. M.; recruitment of patients: J. L. B., J. R., R. P., E. N., J. M., E. M.; analysis of data: M. C. (resistance analysis), E. de L. (statistical analysis); redaction of the draft: E. M.; critical evaluation of the final version of the manuscript: all authors.

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5.7 Estudio de tolerabilidad de los inhibidores de la integrasa en la vida real

Objetivo 3.6 Comparar la incidencia de discontinuación en general y más específicamente por toxicidad, evaluar los factores de riesgo de discontinuación y conocer el perfil de toxicidad en la vida real de los tres inhibidores de integrasa disponibles en la cohorte de adultos infectados por VIH en el Hospital Clínic de Barcelona.

PDF del artículo 6:

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Tolerability of integrase inhibitors in a real-life setting

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Background: Integrase inhibitors have shown better tolerability than other drugs in clinical trials, but some post-marketing data have suggested potential differences among them.

Aims: We compared rates and reasons for discontinuation of raltegravir-, elvitegravir- and dolutegravir-based regimens in a large cohort of HIV-infected patients.

Methods: Retrospective analysis of a prospectively followed cohort including all antiretroviral-naive and all virologically suppressed antiretroviral-experienced patients prescribed a first regimen containing raltegravir, elvitegravir or dolutegravir with at least one follow-up visit. Major outcomes were early discontinuation (≤1 year) due to any reason and more specifically due to toxicity. Incidence was calculated as number of episodes per 1000 person-years. Risk factors for discontinuation were assessed by multivariate Cox models.

Results: Early discontinuations due to any reason were 271 (raltegravir), 168 (elvitegravir) and 264 (dolutegravir) per 1000 patient-years ($P = 0.0821$). Early discontinuations due to toxicity were 76 (raltegravir), 103 (elvitegravir) and 81 (dolutegravir) per 1000 patient-years ($P = 0.6792$). Overall, the most common toxicities leading to discontinuation were neuropsychiatric, osteomuscular or digestive. Most frequent neuropsychiatric manifestations reported at discontinuation were insomnia, dizziness, headache and anxiety irrespective of the integrase inhibitor. Among discontinuations due to toxicity, neuropsychiatric effects were more common with dolutegravir than with raltegravir or elvitegravir ($P = 0.0046$). Age (HR 1.04, 95% CI 1.02–1.07, $P = 0.0007$) was the only independent risk factor for early discontinuation due to toxicity.

Conclusions: Discontinuations due to any reason tended to be less common with elvitegravir, but discontinuations due to toxicity did not differ among integrase inhibitors. Neuropsychiatric toxicity leading to drug discontinuation was more frequent with dolutegravir.

Introduction

Currently available integrase inhibitors have become preferred anchor drugs for antiretroviral-naive patients in different guidelines worldwide[1–3] because they have compared favourably with efavirenz[4–6] and boosted protease inhibitors[7–9] in randomized clinical trials. Discontinuation of raltegravir, elvitegravir or dolutegravir due to adverse effects in clinical trials has been usually lower than that of the comparator drug, ranging between 1% and 4% of patients at 48 or 96 weeks.[4–9] No specific organ toxicity associated with integrase inhibitors was identified in clinical trials. Raltegravir was the first integrase inhibitor approved (US FDA, October 2007; EMA, January 2008) but its initial use was preferentially addressed to salvage antiretroviral therapy. Elvitegravir [as a single-tablet regimen (STR) combination with tenofovir disoproxil fumarate, emtricitabine and cobicistat] was subsequently approved (FDA, August 2012; EMA, May 2013) and dolutegravir has been the one most recently approved first as a single drug (FDA, August 2013; EMA, November 2013) and later as an STR in combination with abacavir plus lamivudine (FDA, August 2014; EMA, September 2014). In contrast with raltegravir, elvitegravir and dolutegravir use was preferentially aimed at antiretroviral-naive patients or to treated patients requiring antiretroviral switch for reasons other than virological failure.

Initial publications on the tolerability of integrase inhibitors focused on raltegravir-associated muscular toxicity that usually consisted of mild or asymptomatic transient increases in muscular enzymes and was reported as a severe event in just a handful of patients.[10,11] However, last year an observational Dutch cohort study

reported an unexpectedly high rate of dolutegravir discontinuation due to toxicity, mainly neuropsychiatric effects.[12] It was followed by other cohort reports at major HIV conferences informing on variable rates of dolutegravir discontinuation due to adverse effects.[13–21] Preliminary 24 week data from the STRIIVING open-label randomized clinical trial assessing the efficacy and safety of switching from boosted protease inhibitors to dolutegravir in virologically suppressed HIV-infected patients also showed several patients discontinuing dolutegravir due to neuropsychiatric effects in the first days of therapy.[22] In contrast, switching from efavirenz to dolutegravir in virologically suppressed patients with ongoing efavirenz-associated CNS side effects was associated with significant improvement in CNS toxicity, with a reduction in overall CNS score and improvement in depression, dizziness and quality of sleep, without affecting antiretroviral efficacy.[23,24] Interestingly, the potential for neuropsychiatric effects is acknowledged in the current EMA Summary of Product Characteristics of all three available integrase inhibitors.[25–27] Whether there may be differences in the rate of discontinuation due to toxicity among currently available integrase inhibitors and whether neuropsychiatric adverse effects leading to discontinuation may be more common with dolutegravir than with other integrase inhibitors is currently unclear.

We aimed to compare the rates and reasons for discontinuation due to any reason and more specifically due to adverse effects of raltegravir-, elvitegravir- and dolutegravir-based regimens in a large cohort of HIV-infected patients.

Patients and methods

This retrospective analysis used prospectively registered data from all antiretroviral-naive patients and all antiretroviral-experienced patients with plasma HIV-RNA below the detection level prospectively followed at the Hospital Clinic of Barcelona (Spain) who were prescribed a first regimen containing raltegravir, elvitegravir or dolutegravir and had at least one follow-up visit. Our plan was to restrict the study population to these two groups of patients to avoid selection bias, as raltegravir was the only integrase inhibitor available for several years and almost exclusively used in salvage therapy. In our centre, patients' data are routinely registered into a clinical history database approved by the Local Institutional Review Board that includes detailed information on antiretroviral prescription and reasons for discontinuation. Potential reasons pre-specified in the database for antiretroviral drug discontinuation include virological failure, adverse effects, therapy simplification, risk of interactions, medical decision due to other reasons, lost to follow-up and death. Whenever the reason for discontinuation includes potential toxicity to any antiretroviral drug, a description of relevant clinical symptoms and/or laboratory parameters associated with the potential adverse effect is usually collected in the clinical course of the corresponding follow-up visit.

For the purpose of this study, changes in integrase inhibitor therapy involving dose (either total daily dose or number of doses per day) or pharmacological presentation (either as an individual drug or as a fixed-dose combination) were not considered as discontinuations as long as the originally prescribed integrase inhibitor remained in the regimen. If more than one reason for discontinuation was present in a given patient, we considered the drug discontinuation as due to toxicity whenever adverse effects were reported irrespective of other concomitant reasons. Patients were censored at the end of February 2016 (when the Dutch report at CROI 2016[12] became available, to avoid any potential influence on dolutegravir discontinuation), or when they switched their first integrase inhibitor, were lost to follow-up or died, whichever came first.

We pre-defined the following two major outcomes: early discontinuation (≤1 year), and early discontinuation due to toxicity. We decided to frame major outcomes within 1 year of follow-up for the following reasons: (i) most relevant toxicities associated with integrase inhibitors in clinical trials and cohort studies have been usually acute; (ii) because the longer the duration of antiretroviral therapy, the less clear the relationship between any potential acute adverse effect and a given drug; and (iii) to avoid bias favouring drugs from earlier time points, since patients doing well who started their first integrase inhibitor earlier would contribute more patient-years than those who started more recently. Specific toxicities were grouped by organs/systems according to the description in the clinical history database. We also performed sensitivity analyses restricted to the period 2014–15, when all three integrase inhibitors were available, and results did not change (see Supplementary data Tables S1–S5, available at *JAC* Online). Quantitative data were compared with ANOVA or Kruskal–Wallis tests, and qualitative data with chi-squared or Fisher's exact tests. Incidence was calculated as number of episodes per 1000 person-years. Incidence rate ratios (IRRs) for each integrase inhibitor were estimated considering the arbitrary reference of 1 for raltegravir. Negative binomial regression models using the likelihood ratio or Wald tests were used for IRR comparisons. Risk factors for discontinuation were assessed by multivariate Cox models.

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[28]; it was approved by the Local Institutional Review Board and informed consent was not required. The authors declare that they have been completely independent in the design, analysis and writing of this study.

Results

Population characteristics

There were 557 patients treated with raltegravir, 322 patients treated with elvitegravir and 212 patients treated with dolutegravir meeting criteria for inclusion in this analysis. Patients treated with raltegravir were also treated with emtricitabine/tenofovir disoproxil fumarate ($n = 390$, 70%), lamivudine/abacavir ($n = 139$, 25%) or with other agents ($n = 28$, 5%). All patients treated with elvitegravir in this cohort had received it as the STR containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Patients treated with dolutegravir were taking it either as the STR containing dolutegravir/lamivudine/abacavir ($n = 93$, 44%) or as the individual dolutegravir tablet together with other antiretroviral agents ($n = 119$, 56%); 36 of those taking the individual dolutegravir tablet were also taking the fixed-dose combination lamivudine/abacavir. Table 1 shows the characteristics of patients in each group. Patients on elvitegravir were younger, more commonly men who had sex with men, and with higher baseline CD4 cell count, and patients on raltegravir were less frequently males.

Incidence of early discontinuation due to any reason

There was a trend to a lower incidence of early discontinuation with elvitegravir (168 episodes per 1000 patient-years) than with raltegravir (271 episodes per 1000 patient-years) or with dolutegravir (264 episodes per 1000 patient-years) ($P = 0.0821$) (Table 2). Relative to raltegravir, unadjusted IRRs (95% CI) for elvitegravir and dolutegravir early discontinuation were 0.62 (0.39–0.97) (Bonferroni corrected P value 0.1091) and

Table 1. Baseline characteristics

Characteristic	Raltegravir ($n = 557$)	Elvitegravir ($n = 322$)	Dolutegravir ($n = 212$)	*P* value
Age (mean, SD)	45 (11)	39 (10)	46 (11)	<0.0001
Gender, *n* (%)				
men	443 (80)	283 (88)	183 (86)	0.0025
women	114 (20)	39 (12)	29 (14)	
Route of infection, *n* (%)				
heterosexual sex	127 (23)	47 (15)	40 (19)	<0.0001
MSM	292 (52)	237 (74)	143 (67)	
IDU	98 (18)	17 (5)	23 (11)	
other or unknown	40 (7)	21 (7)	6 (3)	
CD4 cells/mm^3 at HIV diagnosis, median (IQR)	343 (193–519)	404 (241–556)	370 (201–533)	0.0176
HIV RNA copies/mL at HIV diagnosis (median, IQR)	17170 (1339–138000)	24625 (2364–118800)	30773 (3055–132100)	0.2917

Table 2. Incidence of early discontinuation (≤1 year) with each of the three integrase inhibitors: overall results

Drug	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
Raltegravir	557	71 (12.7)	262.06	270.93	1	0.0821
Elvitegravir	322	26 (8.1)	155.06	167.68	0.62 (0.39–0.97)	
Dolutegravir	212	26 (12.3)	98.66	263.53	0.97 (0.62–1.52)	

0.97 (0.62–1.52) (Bonferroni corrected *P* value 1.0000) respectively; relative to elvitegravir, unadjusted IRR (95% CI) for dolutegravir was 1.57 (0.91–2.71) (Bonferroni corrected *P* value 0.3092). There were no differences in the rate of overall discontinuation between antiretroviral-naive (241 episodes per 1000 patient-years) and antiretroviral-experienced with undetectable plasma HIV-RNA (234 episodes per 1000 patient-years) ($P = 0.8897$) (Table 3). However, the rate of early discontinuation for raltegravir was higher in naive versus non-naive patients (304 versus 193 episodes per 1000 patient-years, $P = 0.1039$), for dolutegravir lower in naive versus non-naive patients (186 versus 450 episodes per 1000 patient-years, $P = 0.0329$), and for elvitegravir roughly similar in naive versus non-naive patients (158 versus 184 episodes per 1000 patient-years, $P = 0.7032$) (Table 3).

Incidence and reasons for early discontinuation not due to toxicity

The incidence of early discontinuation not attributed to toxicity was lower in patients taking elvitegravir (64 episodes per 1000 patient-years) than in patients taking raltegravir (191 episodes per 1000 patient-years) or dolutegravir (182 episodes per 1000 patient-years) ($P = 0.0003$). Incidence of overall early discontinuation not due to toxicity was not significantly different between antiretroviral-naive (137 episodes per 1000 patient-years) and antiretroviral-experienced patients with undetectable plasma HIV-RNA (180 episodes per 1000 patient-years) ($P = 0.2508$). There were no differences between antiretroviral-naive and antiretroviral-experienced patients with undetectable plasma HIV-RNA in the incidence of early discontinuation not due to toxicity in raltegravir-treated patients (206 versus 154 episodes per 1000 patient-years, $P = 0.3713$) and elvitegravir-treated patients (42 versus 100 episodes per 1000 patient-years, $P = 0.1055$), but the incidence of early discontinuation not attributed to toxicity in dolutegravir-treated patients was significantly higher in antiretroviral-experienced patients with undetectable plasma HIV-RNA (415 episodes per 1000 patient-years) than in antiretroviral-naive patients (86 episodes per 1000 patient-years) ($P = 0.0009$). Reasons for discontinuation not due to toxicity included: therapy simplification ($n = 25$), medical decision ($n = 8$), virological failure ($n = 3$) and lost to follow-up/dead ($n = 15$) for raltegravir; risk of interactions ($n = 7$), virological failure ($n = 1$) and lost/dead ($n = 2$) for elvitegravir; and therapy simplification ($n = 15$), risk of interactions ($n = 1$), medical decision ($n = 1$) and lost/dead ($n = 1$) for dolutegravir.

Incidence of early discontinuation due to toxicity

Although the incidence of early discontinuation due to adverse effects was highest for elvitegravir and lowest for raltegravir, there were no significant differences among the three drugs (Table 4). The rate of early dolutegravir discontinuation due to adverse effects was double when dolutegravir was combined with abacavir plus lamivudine than when it was not, although this difference was not significant (Table 5). Overall, the incidence of early discontinuation due to adverse effects was higher in naive (103 episodes per 1000 patient-years) than in experienced (48 episodes per 1000 patient-years) patients ($P = 0.0308$) (Table 6).

Table 3. Incidence of early discontinuation (≤1 year) with each of the three integrase inhibitors: antiretroviral-naive versus antiretroviral-experienced patients with plasma HIV-RNA below the detection level

Group	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
All naive	739	84 (11.4)	349.23	240.53	1	0.8897
All experienced	352	39 (11.1)	166.55	234.16	0.97 (0.67–1.42)	
Raltegravir						
naive	396	56 (14.1)	184.34	303.79	1	0.1039
experienced	161	15 (9.3)	77.72	192.99	0.64 (0.36–1.12)	
Elvitegravir						
naive	196	15 (7.7)	95.13	157.68	1	0.7032
experienced	126	11 (8.7)	59.93	183.55	1.16 (0.53–2.53)	
Dolutegravir						
naive	147	13 (8.8)	69.76	186.35	1	0.0329
experienced	65	13 (20.0)	28.90	449.84	3.11 (1.03–9.39)	

Table 4. Incidence of early discontinuation (≤1 year) due to adverse effects with each of the three integrase inhibitors: overall results

Drug	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
Raltegravir	557	20 (3.6)	262.06	76.32	1	0.6792
Elvitegravir	322	16 (5.0)	155.06	103.19	1.35 (0.70–2.61)	
Dolutegravir	212	8 (3.8)	98.66	81.09	1.06 (0.47–2.41)	

Table 5. Incidence of early discontinuation (≤1 year) due to adverse effects in dolutegravir-treated patients according to the accompanying drugs: abacavir/lamivudine versus other drugs

Dolutegravir	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
+Abacavir/lamivudine	129	6 (4.7)	62.06	96.69	1	0.4795
+Other drugs	83	2 (2.4)	36.60	54.64	0.47 (0.06–3.85)	

Table 6. Incidence of early discontinuation (≤1 year) due to adverse effects: antiretroviral-naive versus antiretroviral-experienced patients with plasma HIV-RNA below the detection level

Group	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
All naive	739	36 (4.9)	349.23	103.08	1	0.0308
All experienced	352	8 (2.3)	166.55	48.03	0.42 (0.16–1.05)	
Raltegravir						
naive	396	18 (4.5)	184.34	97.65	1	0.0368
experienced	161	2 (1.2)	77.72	25.73	0.19 (0.03–1.09)	
Elvitegravir						
naive	196	11 (5.6)	95.13	115.63	1	0.5376
experienced	126	5 (4.0)	59.93	83.43	0.72 (0.25–2.08)	
Dolutegravir						
naive	147	7 (4.8)	69.76	100.34	1	0.1587
experienced	65	1 (1.5)	28.90	34.60	0.16 (0.01–2.85)	

Table 7. Profile of early (≤1 year) discontinuation due to adverse effects among the three integrase inhibitors

	Raltegravir ($n = 20$, 3.6%)	Elvitegravir ($n = 16$, 5.0%)	Dolutegravir ($n = 8$, 3.8%)	*P* value
Neuropsychiatric ($n = 17$)[a]	7 (35%)	3 (19%)	7 (88%)	0.0046
Muscular ($n = 12$)	3 (15%)	6 (38%)	3 (38%)	0.2442
Digestive ($n = 11$)	7 (35%)	4 (25%)	0	0.1793
Skin/mucous membranes ($n = 6$)	4 (20%)	2 (13%)	0	0.4557
Systemic ($n = 5$)	2 (10%)	0	3 (38%)	0.0224
Respiratory ($n = 1$)	1 (5%)	0	0	1
Kidney ($n = 1$)	0	1	0	0.5455
Number of organs/systems				
1	17 (85%)	16 (100%)	5 (63%)	0.0656
>1	3 (15%)	0	3 (37%)	

All results are *n* (%).
[a]Neuropsychiatric clinical symptoms among patients discontinuing integrase inhibitors due to adverse effects: Raltegravir ($n = 7$): Patient 1: somnolence, myalgia, malaise; Patient 2: insomnia; Patient 3: dizziness; Patient 4: insomnia; Patient 5: dizziness; Patient 6: insomnia, anxiety, headache; Patient 7: headache, irritability. Elvitegravir ($n = 3$): Patient 1: insomnia, headache, vivid dreams; Patient 2: dizziness, somnolence; Patient 3: insomnia. Dolutegravir ($n = 7$): Patient 1 (+other): dizziness, myalgia, malaise; Patient 2 (+abacavir/lamivudine): insomnia; Patient 3 (+abacavir/lamivudine): insomnia, headache, confusion; Patient 4 (+other): insomnia, nightmares; Patient 5 (+abacavir/lamivudine): insomnia; Patient 6 (+abacavir/lamivudine): anxiety, arthralgia, insomnia, headache; Patient 7 (+abacavir/lamivudine): anxiety, insomnia.

Clinical manifestations of adverse effects leading to integrase inhibitor early discontinuation

Table 7 shows the profile of early discontinuation due to adverse effects among the three integrase inhibitors. The most common adverse effects were neuropsychiatric ($n = 17$), followed by osteomuscular ($n = 12$) and digestive ($n = 12$) (Table 7). Neuropsychiatric and systemic effects were significantly more common with dolutegravir than with raltegravir or elvitegravir. Almost all patients discontinuing dolutegravir due to toxicity had experienced neuropsychiatric effects ($n = 7$, 88%) in contrast to those discontinuing raltegravir ($n = 7$, 35%) or elvitegravir ($n = 3$, 19%) due to toxicity ($P = 0.0046$). Clinical manifestations of neuropsychiatric effects leading to early discontinuation, as reported in the medical database, were heterogeneous but did not substantially differ among integrase inhibitors. The most common clinical neuropsychiatric manifestations leading to early discontinuation were insomnia, dizziness or headache.

Risk factors for early discontinuation of integrase inhibitors

We were unable to find any significant factor influencing early discontinuation of integrase inhibitors in the univariate analysis (Table 8). There were, however, trends to lower discontinuation with lower age and in those taking elvitegravir. Increasing age (4% per year) was the only independent risk factor (adjusted HR 1.04, 95% CI 1.02–1.07, $P = 0.0007$) for early discontinuation of integrase inhibitors due to adverse effects (Table 9). No integrase inhibitor was significantly associated with a higher risk for early discontinuation due to adverse effects in the multivariate analysis [raltegravir, HR 1 (reference); elvitegravir, HR 1.35 (95% CI 0.70–2.61); dolutegravir, HR 1.06 (95% CI 0.47–2.41): $P = 0.06545$] (Table 9).

Discussion

In this large cohort of HIV-infected patients treated with currently available integrase inhibitors, we found rates of discontinuation due to any reason with all three integrase inhibitors in the first year of therapy ranging from 8.1% to 12.7%. There was a trend to fewer overall discontinuations and discontinuations not due to toxicity were significantly less frequent with elvitegravir compared with raltegravir or dolutegravir. In contrast to raltegravir, which is not combined into an STR, or dolutegravir, which first became available as an individual drug, elvitegravir has always been used as an STR. This fact may be responsible at least in part for the lower overall discontinuation rate not due to toxicity with elvitegravir. STRs are considered as the most convenient antiretroviral regimens,[29,30] and convenience has been reported as a major determinant for drug discontinuation in patients starting antiretroviral therapy.[31]

Only a portion of discontinuations were attributed to adverse effects. Proportions ranged from 3.6% for raltegravir, 3.8% for dolutegravir and 5.0% for elvitegravir. These figures were slightly higher than those reported in clinical trials.[4–9] Rates of early discontinuation due to adverse effects did not significantly differ among the three integrase inhibitors. There has been a huge controversy on the potential of dolutegravir for a worse tolerability in real-life settings because an unexpected high rate of discontinuation due to adverse effects has been reported in some cohorts.[12–21] The availability of increasing post-marketing information on adverse effects might have influenced the decision of drug discontinuation in the clinical setting. The data from our cohort reported here were generated before the public release of the Dutch cohort report at the Conference on Retroviruses and Opportunistic Infections (CROI) 2016. Therefore, the potential influence of the Dutch cohort report on the discontinuation of dolutegravir in our cohort should be negligible, if any. Our results do not confirm a higher rate of discontinuation due to adverse effects for

Table 8. Risk factors for early discontinuation (≤1 year) due to any reason

Characteristic	Unadjusted HR (95% CI)	*P* value
Age	1.01 (1.00–1.03)	0.0699
Gender		
men	1	0.8655
women	1.04 (0.65–1.67)	
Integrase inhibitor		
raltegravir	1	
elvitegravir	0.62 (0.39–0.97)	0.0990
dolutegravir	0.97 (0.62–1.52)	
Year of integrase inhibitor initiation		
2007–10	1	
2011–13	1.34 (0.62–2.91)	0.6056
≥2014	1.11 (0.54–2.29)	
Route of infection		
heterosexual sex	1	
MSM	0.69 (0.45–1.05)	
IDU	0.73 (0.39–1.35)	0.3841
other or unknown	0.80 (0.37–1.73)	
HIV RNA(log copies/mL) at HIV diagnosis	0.93 (0.82–1.06)	0.2852
HIV RNA (log copies/mL) immediately prior to integrase inhibitor therapy	1.02 (0.90–1.15)	0.7509
CD4 (cell/mm^3) at HIV diagnosis	1.00 (1.00–1.00)	0.9970
CD4 immediately prior to integrase inhibitor therapy	1.00 (1.00–1.00)	0.9103

dolutegravir as compared with raltegravir or elvitegravir. It is possible that differences in patients' characteristics or other not well-known factors will explain the higher rate of dolutegravir discontinuation due to adverse effects observed in some cohorts.

The most common adverse effects leading to discontinuation for each of the three integrase inhibitors in our cohort were neuropsychiatric and osteomuscular. These effects were already acknowledged in the summaries of product characteristics of raltegravir,[25] elvitegravir/cobicistat/emticitabine/tenofovir disoproxil fumarate[26] and dolutegravir.[27] Nevertheless, the frequency of neuropsychiatric effects among patients with drug discontinuation due to toxicity was significantly higher with dolutegravir compared with raltegravir or elvitegravir, suggesting that this toxicity profile might be more characteristic of dolutegravir. This contention is further supported by recent data from a German cohort study.[18] This is in contrast with data from randomized clinical trials in which the overall incidence of reported neuropsychiatric adverse effects in patients allocated to dolutegravir was similar to that of the competitors (efavirenz in SINGLE, raltegravir in SPRING-2, darunavir/ritonavir in FLAMINGO and atazanavir/ritonavir in ARIA) and very few patients discontinued dolutegravir due to neuropsychiatric adverse effects.[32] Discrepancies in dolutegravir discontinuation due to neuropsychiatric effects between clinical trials and cohort studies might be due at least in part to the promotion of patient retention in clinical trials and the generally mild and apparently transient nature of neuropsychiatric side effects.

We did not see major differences in the clinical profile of neuropsychiatric adverse effects leading to discontinuation among the three integrase inhibitors, although this comparison should be treated with caution due to the inherently subjective nature of both patients' description and physician's registration. The

Table 9. Risk factors for early discontinuation (≤1 year) due to adverse effects

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	1.04 (1.02–1.07)	0.0007	1.04 (1.02–1.07)	0.0007
Gender				
men	1	0.1360		
women	1.68 (0.85–3.33)			
Integrase inhibitor				
raltegravir	1			
elvitegravir	1.35 (0.70–2.61)	0.6545		
dolutegravir	1.06 (0.47–2.41)			
Year of integrase inhibitor initiation				
2007–10	1			
2011–13	1.34 (0.28–6.29)	0.5577		
≥2014	1.82 (0.44–7.56)			
Route of infection				
heterosexual sex	1			
MSM	0.37 (0.19–0.70)			
IDU	0.36 (0.12–1.06)	0.0170		
other or unknown	0.55 (0.16–1.87)			
HIV RNA (log copies/mL) at HIV diagnosis	0.81 (0.66–1.00)	0.0529		
HIV RNA (log copies/mL) immediately prior to integrase inhibitor therapy	0.82 (0.63–1.05)	0.1186		
CD4 (cell/mm^3) at HIV diagnosis	1.00 (1.00–1.00)	0.2815		
CD4 immediately prior to integrase inhibitor therapy	1.00 (1.00–1.00)	0.0686		

predominance of insomnia among neuropsychiatric effects may suggest a potential interference with mechanisms involved in physiological sleep.[33] Several drugs have been reported to cause insomnia as an adverse effect.[34] The coincidence of a common CNS adverse effect profile between efavirenz and integrase inhibitors has led to speculation regarding whether similar pathogenetic pathways may be involved. However, recent data argue against that contention because patients experiencing efavirenz-associated CNS adverse effects showed improvement after switching from efavirenz to dolutegravir.[23,24] Further research is needed to understand the pathogenesis and risk factors for CNS adverse effects associated with integrase inhibitors.

In our cohort, increasing age was the only factor associated with a higher risk of integrase inhibitor discontinuation due to adverse effects. The risk increased 4% per year. Increasing age has been associated with better virological response due to better adherence to antiretroviral therapy, but worse immunological response due to reduced functional reserve.[35] Discontinuation of antiretroviral therapy for reasons other than virological failure has been reported more commonly in older patients but also in younger ones as compared with middle-aged ones, but in the case of older patients the discontinuation was associated with toxicity and in younger ones with lack of adherence.[36] Increasing age is associated with higher incidence of comorbidities[37] and with increased plasma exposure to some antiretroviral drugs,[38] and both factors contribute to a higher propensity for toxicity.[39,40] These results emphasize the need for an increased awareness for potential adverse effects leading to the discontinuation of integrase inhibitors among older patients even though these drugs are preferentially recommended in them because of their better safety profiles compared with non-nucleoside reverse transcriptase inhibitors or protease inhibitors.[1–3]

In conclusion, discontinuation of available integrase inhibitors not due to toxicity was less frequent with elvitegravir than with raltegravir or dolutegravir, although discontinuation due to adverse effects was similar among the three integrase inhibitors and slightly higher than that reported in clinical trials. Neuropsychiatric and osteomuscular effects were the most common ones leading to drug discontinuation with all three available integrase inhibitors, although neuropsychiatric adverse effects were significantly more common with dolutegravir than with raltegravir or elvitegravir. Increasing age was an independent factor associated with a higher risk for discontinuation of integrase inhibitors due to adverse effects.

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Supplementary data

Tables S1–S5 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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5.8 Estudio A-TRI-WEEK *(clinicaltrials.gov: NCT01778413)*

Objetivo 3.7 Evaluar la viabilidad, seguridad y eficacia de una pauta con efavirenz/emtricitabina/tenofovir disoproxil fumarato tomada tres días por semana en adultos infectados por VIH con supresión virológica sostenida.

PDF del artículo 7:

"A maintenance 3-day-per-week schedule with the single tablet regimen efavirenz/emtricitabine/tenofovir disproxil fumarate is effective and decreases sub-clinical toxicity" J. Rojas, J.L. Blanco, S. Sánchez-Palomino, M.A. Marcos, A.C. Guardo, A. González-Cordon, et al. AIDS 2018; 32: 1633-41. FI: 4,914.

A maintenance 3-day-per-week schedule with the single tablet regimen efavirenz/emtricitabine/ tenofovir disoproxil fumarate is effective and decreases sub-clinical toxicity

Jhon Rojas, Jose L. Blanco, Sonsoles Sanchez-Palomino, Maria A. Marcos, Alberto C. Guardo, Ana Gonzalez-Cordon, Montserrat Lonca, Amparo Tricas, Ana Rodriguez, Anabel Romero, Jose M. Miro, Josep Mallolas, Jose M. Gatell, Montserrat Plana and Esteban Martinez

Background: Antiretroviral drugs contained in single tablet Atripla have pharmacokinetic properties that could allow for longer than once-daily dosing. We hypothesized that simplifying Atripla once daily to 3-day per week would be feasible, able to maintain viral suppression and less toxic.

Methods: Virologically suppressed (≥2 years) HIV+ adults on Atripla once daily, $CD4^+$ greater than 350 cells/μl at inclusion, and no prior documented virological failure or evidence of resistance mutations to efavirenz, tenofovir, or emtricitabine were randomized to maintain their once-daily (OD) regimen or to reduce it to 3 days (Mondays, Wednesdays, and Fridays) a week (3W) (A-TRI-WEEK pilot trial). Primary end-point was the proportion of patients free of treatment failure (noncompleter = failure) at 24 weeks. $CD4^+$ and $CD8^+$ cells, ultrasensitive HIV-1 RNA, Pittsburg Sleep Quality Index (PSQI), bone mineral density, plasma efavirenz levels, and fasting blood and urine chemistries were measured at baseline and 24 weeks. The study is registered at ClinicalTrials.gov, NCT01778413.

Results: Sixty-one patients were randomized. All patients in both arms remained free of treatment failure (estimated difference 0%; 95% confidence interval −14.1 to 14.1). Ultrasensitive plasma HIV-1 RNA below detection threshold showed no difference between arms (70% in the 3W arm vs. 71% in the OD arm, $P = 0.933$) at 24 weeks. Total cholesterol and femur *T*-score significantly increased, whereas PSQI, plasma efavirenz, albumin/creatinine and beta-2-microglobulin in urine significantly decreased in the 3W arm relative to OD arm.

Conclusion: The A-TRI-WEEK study represents a proof of concept for the feasibility of three-day per week Atripla maintenance that should be further confirmed in a larger, well powered clinical trial.

AIDS 2018, **32**:1633–1641

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

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Introduction

With widespread access to effective antiretroviral therapy, a majority of HIV-infected patients can nowadays achieve sustained viral suppression [1]. However, antiretroviral therapy should be indefinitely taken and the associated risk of long-term chronic toxicities and/or negative impact on aging comorbidities increases with exposure. In fact, these reasons are now the most common ones leading to changes in antiretroviral therapy in developed countries [2].

Because of suboptimal efficacy and limited number, antiretroviral drugs were usually approved at the maximum tolerated dose rather than the minimum effective dose [3]. There is a clear relationship between plasma levels of some antiretroviral drugs such as efavirenz (EFV) [4] or tenofovir [5] and their potential for developing drug-related toxicities. Reducing the daily dose of EFV from 600 to 400 mg in antiretroviral-naïve patients [6,7] and using tenofovir alafenamide (TAF) instead of tenofovir disoproxil fumarate (TDF) [8,9] are strategies decreasing exposure to EFV and tenofovir, respectively, that have shown noninferior efficacy and better safety profile.

Antiretroviral therapy has evolved to a larger number of families available and drugs with more convenient dosing schemes and better overall tolerability. The construction of fixed-drug combinations with half-lives long enough to allow for once-daily dosing established the basis for preferred antiretroviral regimens in the last decade. Atripla, a fixed-drug combination of EFV 600 mg/emtricitabine 200 mg/TDF 300 mg, was the first once-daily single-tablet combination, approved more than 10 years ago. The drugs contained in the Atripla pill are among the ones with longer half-lives, allowing for sustained viral suppression despite suboptimal adherence [10–13]. Although triple regimens based on integrase inhibitors are currently recommended as first options in most developed countries, the combination EFV with lamivudine or emtricitabine with tenofovir disoproxil fumarate remains as preferred first-line regimen according to the World Health Organization [14] and a substantial number of patients are expected to use it in low-income and middle-income countries in the next years [15,16].

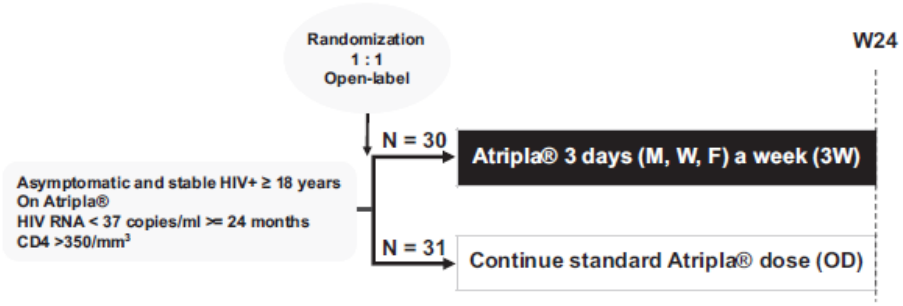
Previous small randomized controlled trials have shown that short-cycle 5 days on/2 days off intermittent treatment with either EFV/FTC/TDF [17] or a three-drug combination therapy including EFV with two nucleoside reverse transcriptase inhibitors [18,19] resulted in noninferior efficacy and improved safety profile relative to standard continuous antiretroviral therapy. These studies helped putting the rationale of our work into context and provided a strong support to test the 3-day-per-week Atripla scheme. However, those studies were not performed with either Atripla or the drugs contained in the Atripla pill, they were based on a 5 days on/2 days off schedule instead of a the 3-day-per-week schedule, and did not assess potential benefits on subclinical disease or in-depth changes in immunological and virological parameters. We hypothesized that simplifying the fixed-dose single-tablet combination EFV/FTC/TDF (Atripla) from standard once-daily dosing to a 3-day-per-week schedule would be feasible, able to maintain viral suppression and less toxic.

Methods

Study design and participants

The A-TRI-WEEK study is an open-label, pilot, unicentre, randomized clinical trial. Consecutive stable and asymptomatic HIV-infected adults (≥18 years) on Atripla once daily were invited to participate if they had plasma HIV-1 RNA less than 37 copies/ml for at least the previous 2 years and $CD4^+$ cell counts greater than 350 cells/μl at the time of consideration for the study (Fig. 1). In addition, participants were required not to have any of the following: prior virological failure to any antiretroviral regimen or documented resistance mutations to EFV, tenofovir, or emtricitabine; any diagnosis of psychiatric illness, evidence of alcohol abuse or illicit drug consumption (based on their past medical history and specific questions at the time of recruitment) or any other condition at the doctor's discretion that did not allow ensuring a correct adherence. For women of childbearing age, a negative pregnancy test at the time of consideration for the study and use of anticonceptive measures were also required. Patients who meet all inclusion criteria, none of exclusion criteria, and agreed to participate were randomized 1:1 to maintain their once-daily regimen (OD arm) or to reduce it to 3 days (Mondays, Wednesdays, and Fridays) a week (3W arm). We took into consideration time and cost for estimating a realistic sample size. Assuming less than 15% therapeutic failure (10% viral failure with 5% attrition) as a plausible target for the experimental treatment arm, with 30 patients per group we could be 68% confident that our estimate was accurate within 5% points, 90% confident that it was accurate within 8% points, and 95% confident that it was accurate within 9% points [20]. 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: NCT01778413.

Although the hypothesis of the study was based on consistent data to support its potential feasibility, we planned prior to the initiation of the study that development of virological failure in more than 10% of the patients in the 3W arm would be unacceptable and should lead to stopping the trial. Following the request of the Institutional Review Board that approved the study, if



Standard plasma viral load was measured at baseline, 12, and 24 weeks in both arms, and also intensively at 1, 2, 4, 6, and 8 weeks in the 3W arm.

- **Primary end-point:** Patients free of treatment failure (noncompleter = failure) at 24 weeks.

- **Secondary end-points:** Pittsburg Sleep Quality Index (PSQI), BMI, BMD, $CD4^+$ and $CD8^+$ cells, ultrasensitive HIV-1 RNA (2 copies/ml), plasma 25OH vitamin D levels, eGFR CPK-EPI, fasting blood lipids, and protein/creatinine, albumin/creatinine, and beta-2-microglobulin in urine

Fig. 1. The A-TRI-WEEK study design.

the 24-week trial proved to be successful an extension phase was planned in which patients in the 3W would remain with such schedule and patients in the OD arm would be invited to switch to the 3W schedule; in this extension phase, all patients would have a follow-up long enough (e.g. at least 3 years) with the 3W dosing schedule to better guarantee the efficacy and safety of the new schedule. Again, development of virological failure in more than 10% of the patients in the 3W arm would be unacceptable and should lead to stopping the extension phase. The extension phase is currently ongoing and will not be reported here.

Procedures

After inclusion, all patients had three medical visits: baseline, 12, and 24 weeks. At baseline, patients' characteristics including age, sex, ethnicity, suspected route of HIV transmission, and Centers for Disease Control (CDC) stage at the time of HIV diagnosis were collected. At baseline, 12 and 24 weeks, participants had a complete physical examination done and blood drawn for $CD4^+$ and $CD8^+$ cell counts and standard plasma HIV-1 RNA (Siemens VERSANT HIV-1 RNA 1.5 Assay, limit of detection 37 copies/ml). Patients allocated to the 3W arm had blood drawn also at 1, 2, 4, 6, and 8 weeks for standard plasma HIV-1 RNA to detect potential early viral failure. In the 3W arm, blood was drawn on Mondays following the longest period off therapy. At each follow-up visit, information on adverse events and use of drugs other than antiretroviral therapy was collected, and a simplified adherence questionnaire [21] and a pregnancy test for women of childbearing age were performed.

At baseline and at 24 weeks: weight and height were measured; the Spanish-validated version of the Pittsburg Sleep Quality Index (PSQI) [22] was self-assessed; blood was drawn after at least a 8-h fasting period to measure blood cells and chemistry including total and HDL cholesterol, triglycerides, creatinine, 25-OH vitamin D, and EFV plasma levels; urine was collected to measure protein/creatinine, albumin/creatinine, and beta-2-microglobulin; and a dual X-absorptiometry (DXA) to measure lumbar and femur bone mineral density was performed. The PSQI is an effective instrument used to measure the quality and patterns of sleep in adults in both clinical and research settings [23]. It differentiates 'poor' from 'good' sleep quality by measuring seven sleep characteristics: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. A total score of '5' or greater is indicative of poor sleep quality. BMI was calculated from weight and height. Estimated glomerular filtration rate (CKD-EPI) was calculated from plasma creatinine following a standard formula [24]. Assessment of these variables was chosen because they would reveal any potential impact of reducing the exposure of Atripla components

on their subclinical toxicity profiles. EFV plasma concentrations were categorized as suboptimal (<1 μg/ml), normal (1–4 μg/ml) or high (>4 μg/ml) [25].

In addition, at baseline and at 24 weeks, plasma and peripheral blood mononuclear cells (PBMC) samples were collected and stored at −80 °C until deferred measurement of ultrasensitive plasma HIV-1 RNA (limit of detection 2 copies/ml), total and integrated HIV-1 DNA in $CD4^+$ cells, and immunophenotyping (the last two not reported here). Ultrasensitive plasma HIV-1 RNA was measured according to Palmer *et al.* [26]. Assessment of these variables was chosen because they could provide additional evidence on the potential efficacy of the 3W arm.

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 (confirmed plasma viral load ≥37 copies/ml), 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.

Secondary outcomes were 24-week changes in plasma lipids, 25-OH vitamin D, $CD4^+$ cells, $CD4^+/CD8^+$ ratio, ultrasensitive HIV-1 RNA in plasma, PSQI score, lumbar and femur *T*-score, estimated glomerular filtration rate, and urine protein/creatinine, albumin/creatinine, and beta-2 microglobulin.

Statistical analysis

Patients were followed for the entire trial period regardless of whether they prematurely discontinued assigned study medication. 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–Witney or ANOVA tests were used for comparisons of continuous variables between groups. For comparing efficacy of the 3W arm relative to the OD arm, 95% confidence intervals were calculated by Newcombe's method [27]. Simple comparisons were made with use of a two-sided alpha level of 0.05.

Results

Baseline characteristics

Between 3 June 2013 and 30 May 2014, 68 patients were assessed for eligibility, 61 underwent randomization and received at least one dose of study drugs. Seven patients were excluded because of refusal to participate (lack of time, $n = 4$; lack of interest, $n = 1$; fear of viral failure, $n = 1$) or evidence of illicit drug consumption ($n = 1$). Out of 61 patients randomized, 30 were allocated at the 3W arm and 31 were allocated at the OD arm. Baseline epidemiological characteristics are shown in Table 1. Most participants were men ($n = 54$, 89%), of Caucasian ethnicity ($n = 40$, 66%), and infected with HIV through homosexual sex ($n = 45$, 75%). Their median age was 48 years. Although most participants in this study had a CDC stage A ($n = 48$, 80%), there was a trend to more patients with CDC stages B or C in the 3W arm than in the OD arm. Median (interquartile range) pretreatment HIV-1 RNA was 5.2 (4.7–5.6) log copies/ml in the OD arm and 5.2 (4.8–5.7) log copies/ml in the 3W arm ($P = 0.826$). HIV-1 RNA had been maintained below detection level for a median (interquartile range) of 61 (35–86) months before randomization.

Table 2 shows median (interquartile range) values of plasma and urine chemistry, plasma 25-OH vitamin D,

Table 1. Baseline characteristics.

	Total	Atripla OD ($n = 31$)	Atripla 3W ($n = 30$)	*P* value
Sex (n, %) ($n = 61$)				0.722
Men	54 (88.5)	27 (87.1)	27 (90.0)	
Women	7 (11.5)	4 (12.9)	3 (10.0)	
Ethnicity (n, %; $n = 61$)				
Hispanic	21 (34.4)	10 (32.3)	11 (36.7)	0.717
Caucasian	40 (65.6)	21 (67.7)	19 (63.3)	
Age (median, interquatile range) ($n = 61$)	48.2 (38.0–54.6)	48.5 (38.1–58.3)	47.8 (37.4–53.8)	0.554
BMI, kg/m^2 (median, interquatile range) ($n = 59$)	24.2 (36.2–27.1)	24.8 (23.0–27.1)	24.2 (22.0–26.9)	0.295
Route of HIV transmission (n, %; $n = 60$)				0.552
Homosexual men	45 (75.0)	24 (80.0)	21 (70.0)	
Heterosexual	14 (23.3)	6 (20.0)	8 (26.7)	
Intravenous drug addiction	1 (1.7)	0 (0.0)	1 (3.3)	
CDC stage (n, %; $n = 60$)				0.078
A	48 (80.0)	28 (90.3)	20 (69.0)	
B	2 (3.3)	0 (0.0)	2 (6.9)	
C	10 (16.7)	3 (9.7)	7 (24.1)	

CDC, Centers for Disease Control; OD, once daily; 3W, 3 days a week.

Table 2. Baseline laboratory and other tests.

	Total	Atripla OD ($n=31$)	Atripla 3W ($n=30$)	P value
Chemistry				
Creatinine (mg/dl; $N=61$)	0.86 (0.78–0.94)	0.86 (0.78–0.93)	0.87 (0.79–0.96)	0.868
Total cholesterol (mg/dl; $N=60$)	194 (168–218)	207 (179–220)	189 (158–217)	0.160
HDL-cholesterol (mg/dl; $N=60$)	47 (40–55)	46 (40–52)	49 (38–58)	0.733
Total/HDL cholesterol ratio ($N=60$)	4.2 (3.3–5.1)	4.5 (3.6–5.4)	4.0 (3.2–4.7)	0.231
Triglycerides (mg/dl; $N=60$)	99 (67–151)	109 (68–156)	86 (65–136)	0.287
Estimated glomerular filtration rate (CPK-EPI) (ml/min/1.73 m^2; $N=61$)	101 (91–111)	99 (89–112)	101 (92–108)	0.603
25-OH Vitamin D (ng/ml; $N=61$)	18.0 (12.5–25.2)	18.1 (13.8–28.9)	16.9 (12.2–24.2)	0.306
Immunology				
$CD4^+$ cells (per μl. $N=61$)	563 (457–697)	576 (491–666)	545 (402–738)	0.202
$CD8^+$ cells (per μl) ($N=61$)	569 (447–703)	486 (430–746)	598 (475–694)	0.493
$CD4^+/CD8^+$ ratio	1.1 (0.8–1.3)	1.2 (0.8–1.4)	1.0 (0.8–1.2)	0.334
Ultrasensitive HIV-1 RNA ($N=57$)	1.0 (1.0–3.7)	1.0 (1.0–4.5)	1.0 (1.0–1.0)	0.290
≥2 copies/ml	16 (28.1)	10 (33.3)	6 (22.2)	
<2 copies/ml	41 (71.9)	20 (66.7)	21 (77.8)	0.351
Efavirenz plasma levels (μg/ml; $N=61$)	2.1 (1.6–2.8)	2.1 (1.5–2.6)	2.2 (1.6–3.1)	0.511
Pittsburg Sleep Quality Index ($N=61$)	4.0 (2.0–7.0)	4.0 (3.0–9.0)	4.0 (2.0–5.3)	0.318
Bone mineral density (DXA)				
Lumbar T-score ($N=60$)	−1.3 (−1.9–−0.3)	−1.3 (−1.9–−0.9)	−1.1 (−1.95–−0.2)	0.437
Femur T-score ($N=60$)	−1.3 (−1.8–−0.7)	−1.3 (−1.9–−0.7)	−1.3 (−1.8–−0.45)	0.773
Urine				
Protein/creatinine (mg/g)	75 (52–100)	74 (49–102)	76 (58–101)	0.613
Albumin/creatinine (mg/g)	4 (2–7)	3 (2–5)	4 (3–8)	0.175
Beta-2 microglobulin (mg/g)	194 (105–431)	165 (102–393)	217 (115–439)	0.787

Data are median (interquartile range). DXA, dual X-absorptiometry; OD, once daily; 3W, 3 days a week

immunology, ultrasensitive HIV-1 RNA in plasma, efavirenz plasma concentration, PSQI, and bone mineral density (lumbar and femur T-scores) at baseline. In general, most chemistry values and PSQI score were within normal values. $CD4^+$ cells and $CD4^+/CD8^+$ ratio were well preserved. As it often occurs, plasma 25-OH vitamin D values were usually lower than normal. Median lumbar and femur T-scores were indicative of mild osteopenia. A substantial number of patients ($n=41$, 72%) had ultrasensitive plasma HIV-1 RNA below detection threshold at baseline. At baseline, efavirenz plasma concentrations were: suboptimal (<1 μg/ml) in four (13%) OD patients and two (7%) 3W patients; normal (1–4 μg/ml) in 26 (84%) OD patients and 27 (90%) 3W patients; and high (>4 μg/ml) in one (3%) OD patient and one (3%) 3W patient.

Efficacy

At 24 weeks, 30 out of 30 (100%) patients in the 3W arm and 31 out of 31 (100%) patients in the OD arm completed the study and remained free of treatment failure (estimated difference 0%; 95% confidence interval −14.1 to 14.1). Out of 333 plasma samples for standard HIV-1 RNA measurement during the study, none had at least 37 copies/ml.

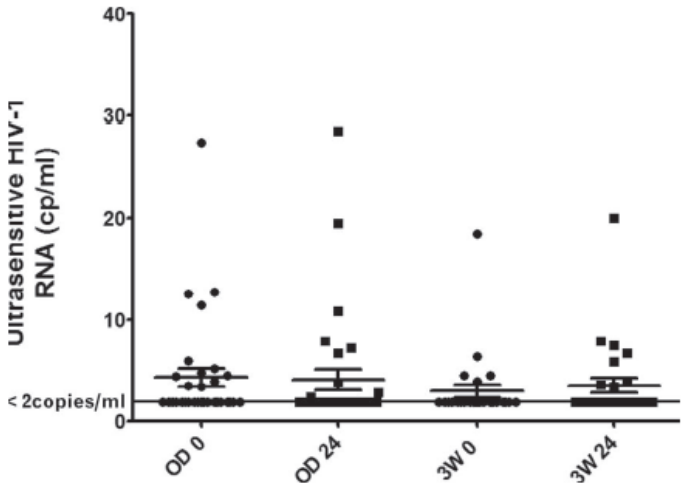
Figure 2 shows plasma ultrasensitive HIV-1 RNA at baseline and at 24 weeks in both arms. The number of patients with ultrasensitive plasma HIV-1 RNA below detection threshold at 24 weeks was roughly similar to that at baseline and it showed no difference between arms (70% in the 3W arm vs. 71% in the OD arm, $P=0.933$). In the OD arm, three (15%) patients went from less than 2 copies/ml at baseline to at least 2 copies/ml at 24 weeks and four (40%) patients from at least 2 copies/ml at baseline to less than 2 copies/ml at 24 weeks; in the 3W arm, three (14%) patients went from less than 2 copies/ml at baseline to at least 2 copies/ml at 24 weeks and one (17%) patient from at least 2 copies/ml at baseline to less than 2 copies/ml at 24 weeks.

Safety

Eleven (36%) patients in the OD arm and 13 (43%) in the 3W arm reported at least one adverse effect ($P=0.530$). All adverse effects reported were grade 1 or 2 and none of them was considered to be drug-related. No patient discontinued therapy because of adverse effects. Adherence in both arms was excellent; two (6%) patients in the OD arm and no patient in the 3W arm missed at least one dose during the study period. Patients allocated to the 3W arm overwhelmingly reported that they were more comfortable with this schedule than with the daily one.

Ten (33%) patients in the 3W arm and 12 (39%) patients in the OD arm used new drugs other antiretroviral therapy at some time being the most common ones nonsteroid anti-inflammatory agents and antibiotics. No patient used psychotropic drugs during the study.

Table 3 shows the 24-week minus baseline changes in plasma lipids, 25-OH vitamin D, $CD4^+$ cells, $CD4^+/CD8^+$ ratio, PSQI score, lumbar and femur T-scores, and urine parameters. In the 3W arm, total cholesterol



	Atripla® OD		Atripla® 3W	
	Baseline (*n* = 30)	24 weeks (*n* = 31)	Baseline (*n* = 27)	24 weeks (*n* = 27)
≥ 2 copies/ml	10 (33%)	9 (29%)	6 (22%)	8 (30%)
<2 copies/ml	20 (67%)	22 (71%)	21 (78%)	19 (70%)

Fig. 2. Ultrasensitive HIV RNA in plasma.

significantly increased whereas PSQI score significantly decreased, femur *T*-score significantly increased, and both urine albumin/creatinin ratio and urine β-2-microglobulin significantly decreased relative to the OD arm.

Although EFV plasma levels remained relatively stable in the OD arm [median (interquartile range) 24-week minus baseline absolute change 0.2 μg/ml (−0.1; 0.5), $P = 0.051$], there was a significant decrease in the 3W arm [median (interquartile range) 24-week minus baseline absolute change −1.3 μg/ml (−1.8; −0.6), $P < 0.005$]. At week 24, EFV plasma concentrations were: suboptimal (<1 μg/ml) in two (7%) OD patients and 17 (63%) 3W patients; normal (1–4 μg/ml) in 28 (90%) OD patients and 10 (37%) 3W patients; and high (>4 μg/ml) in one (3%) OD patient and no (0%) 3W patients.

Table 3. 24-week minus baseline changes in laboratory and other tests.

	Atripla OD (*n* = 31)	Atripla 3W (*n* = 30)	*P* value for the difference between arms
Total cholesterol (mg/dl)	−5 (−14 to +4)	+4 (0 to +16)	0.019
HDL cholesterol (mg/dl)	−3 (−4 to +1)	−4 (−6 to +3)	0.636
Triglycerides (mg/dl)	+5.5 (−11 to +21)	+1 (−7 to +27)	0.575
25OH vitamin D (ng/ml)	+0.1 (−7.7 to +3.7)	0 (−6.3 to +5.7)	0.630
$CD4^+$ cells (per mm^3)	−15 (−73 to +50)	+5 (−52 to +116)	0.132
$CD4^+/CD8^+$ ratio	0 (−0.085 to +0.103)	+0.03 (−0.11 to +0.10)	0.414
Pittsburg Sleep Quality Index (PSQI) score	−0.5 (−1.3 to 0)	−1 (−2 to −1)	0.038
Lumbar *T*-score	0.0 (−0.1 to 0)	0 (−0.2 to +0.1)	0.815
Femur *T*-score	0.0 (−0.2 to +0.1)	0.1 (0 to +0.1)	0.010
Urine protein/creatinine (mg/g)	−6 (−17 to +4)	−16 (−33 to −3)	0.144
Urine albumin/creatinine (mg/g)	0 (−1 to +1)	−1 (−3 to 0)	0.047
Urine phosphorus (mg/dl)	−10 (−22 to +6)	−1.5 (14 to +12)	0.180
Urine β-2-microglobulin (μg/g)	+312 (−45 to +1300)	−158 (−474 to −61)	0.003

Data are median (interquartile range). OD, Once daily; 3W, 3 days a week.

Discussion

This pilot study is a proof of concept confirming the feasibility of a 3-day-per-week Atripla schedule. In otherwise healthy HIV-infected adults with sustained viral suppression, 3-day-per-week Atripla was able to maintain efficacy and to improve subclinical toxicity parameters. Despite Atripla being dosed as just one pill a day, patients were enthusiastic on the prospect of decreasing the burden of their chronic medication to three pills a week. Patients allocated to the 3W arm were specifically asked on their follow-up visits on how they managed to comply with their new nonstandard regimen. We did not design any special intervention to facilitate adherence in the 3W arm. At the beginning, some patients in the 3W arm confessed having developed reminders on their smartphones or wall calendars to help them to comply with the new nonstandard dosing schedule, but after a few weeks, the new regimen became their routine regimen and they felt comfortable and managed excellently with it. We were unable to find a single patient showing adherence problems with the new 3-day-per-week regimen. Despite having no neuropsychiatric complaints and showing normal kidney function and mild osteopenia, patients allocated to the 3W schedule had improvements on markers of subclinical toxicities associated with both EFV and tenofovir. These improvements were evident despite the relatively short study period and were presumably because of decreased drug exposure. It is difficult to extrapolate these significant subclinical changes into clinical meaningful long-term benefits. Nevertheless, we should acknowledge that these changes were not for worse. Moreover, some of these 24-week changes show comparable favourable trends as those seen after 96 weeks with the reduction of EFV daily dose from 600 to 400 mg or the use of TAF instead of TDF. Reduction in the exposure to some antiretroviral drugs such as EFV or tenofovir to decrease toxicity while preserving efficacy is a strategy actively investigated. EFV 400 mg once-daily has been approved by the 2015 World Health Organization (WHO) Guidelines following the results of ENCORE1 Study [6,7] and, where available, TAF is being increasingly used instead of TDF to decrease the risk of tenofovir-related kidney and bone toxicities [28–30]. As it was not preplanned, we did not include any economic analysis in our study. Nevertheless, it is obvious that reducing the Atripla dose from 7 days a week to 3 days a week has a 57% reduction effect in direct antiretroviral therapy cost and this may have important implications in resource-limited settings [31].

Efficacy of the 3W arm was demonstrated in this intensive study, with frequent plasma HIV RNA monitoring particularly at the beginning of the study. Not only no patient had any viral failure but also there were no blips detected either. In addition, results from ultrasensitive plasma viral load measurements further confirmed the efficacy of the 3W arm. Safety of the 3W arm was excellent. Participants were already taking Atripla at standard OD dosing and the 3W arm only decreased drug exposure without further changes in therapy. This reason may explain in great part the excellent tolerability of the 3W arm. In addition to proving efficacy, any therapy simplification strategy has to offer additional advantages [32]. In the A-TRI-WEEK study, reduction of drug exposure had a significant positive impact on parameters reflecting toxicities related with efavirenz or tenofovir such as sleep quality, bone mineral density, and proteinuria. It should be also noted that there was an increase in total cholesterol in patients allocated to the 3W arm; as tenofovir has a cholesterol-lowering effect [33], the decrease in total cholesterol may be related to less exposure to tenofovir. These changes, despite being significant, were of small magnitude and they occurred in stable patients, with no evidence of clinical disease, and as previously said its real clinical importance is unknown. Nevertheless, because toxicity of antiretroviral agents is directly associated with the duration of exposure, it is reasonable to assume that the long-term impact of those small changes may have clinical relevance. As expected, EFV plasma levels were reduced in the 3W arm at 24 weeks. Therapeutic concentrations of EFV have been reported between 1 and 4 μg/ml [25]. In the 3W arm, 63% of the patients had less than 1 μg/ml at 24 weeks. However, despite this decrease in EFV plasma concentration, no patient in the 3W arm experienced viral failure not only as defined by detectable standard plasma viral load but also considering ultrasensitive viral load results. Some studies assessing pharmacokinetics of EFV in patients taking rifampin, an inducer of EFV metabolism, have shown that a proportion of patients taking both drugs may have EFV trough levels below 1 μg/ml yet not developing viral failure [34,35]. In addition, a novel method to assess antiretroviral target trough concentrations using in-vitro susceptibility data estimated that the protein-bound 95% inhibitory concentration of EFV was 126 ng/ml [36], which is well below the average C_{trough} of 1.800 ng/ml in patients receiving 600 mg once daily and below the proposed EFV lower concentration threshold (1.000 ng/ml) [25].

This study had several 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 done (total and integrated HIV-1 DNA in $CD4^+$ cells and immunophenotyping have been reported elsewhere [37]) and the results obtained are confirmatory of the ones reported here. In addition, a 3-year extension phase is currently ongoing. All participants agreed participating in the extension phase of the A-TRI-WEEK study and so far after more than 2 years of follow-up, no patient has discontinued therapy or been lost, and there have not been any viral failure or any other major

incidences obliging to stop it. Another limitation is that, by design, all participants came from a stable standard regimen consisting of Atripla. Therefore, the conclusions of the A-TRI-WEEK study cannot be generalized to HIV-infected patients taking antiretroviral regimens other than Atripla.

In conclusion, 3-day-per-week Atripla in patients with sustained viral suppression was a feasible option that maintained efficacy and improved subclinical toxicity parameters after 24 weeks of follow-up. A 3-year extension phase to support the long-term efficacy and safety of the new schedule is currently ongoing. The A-TRI-WEEK study represents a proof of concept for the feasibility of 3-day-per-week Atripla maintenance that should be further confirmed in a larger, adequately powered clinical trial.

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Conflicts of interest

None of the authors had conflicts of interes twith this study.

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6. DISCUSIÓN

6. Discusión

6.1 Discusión acerca de los resultados del Estudio LIPOKAL *(ClinicalTrials.gov NCT00978237)*

El cambio de los ITIAN de timidina ha sido la única intervención basada en la evidencia para mejorar la lipoatrofia [33]. Este ensayo clínico piloto aleatorizado demostró la prueba de concepto de que el cambio de fármacos antirretrovirales distintos de los ITIAN de timidina puede mejorar aún más la distribución de la grasa corporal en pacientes infectados por VIH con lipoatrofia persistente a pesar de haber suspendido los ITIAN de timidina. Los aumentos de la grasa de las extremidades en los pacientes que pasaron de EFV a LPV/r fueron progresivos durante 96 semanas de seguimiento. Los cambios en las puntuaciones de percepción subjetiva estuvieron de acuerdo con la de los cambios objetivos de grasa en las extremidades.

Dado que los subestudios de composición corporal son más frecuentes en los ensayos clínicos que comparan regímenes antirretrovirales y los ITIAN de timidina que ya no se utilizan en estos estudios, ha sido posible saber que los regímenes que contienen fármacos antirretrovirales distintos de los ITIAN de timidina pueden mostrar efectos diferenciales sobre la grasa corporal. El estudio ALTAIR **[133]** y el subestudio ACTG A5224S [134], en el que pacientes infectados por el VIH iniciaron un tratamiento antirretroviral basado en TDF/3TC, han demostrado que el atazanavir/ritonavir puede provocar un aumento de grasa en las extremidades mayor que el EFV después de 96 semanas. En el ACTG 5142 [31], los pacientes tratados con los ITIAN, TDF más emtricitabina (FTC) mostraron el doble de sujetos con pérdida de grasa en las

extremidades ≥ 20% en la rama de EFV (12%) comparado con la rama de LPV/r (6%) después de 96 semanas, aunque esta diferencia no fue estadísticamente significativa.

Los datos de composición corporal de estudios anteriores en pacientes con antirretrovirales-naive como BMS089 y COL100758 mostraron un mayor aumento de la grasa en las extremidades cuando el atazanavir fue potenciado con ritonavir que cuando no lo fue [**135**] y cuando el fosamprenavir fue potenciado con ritonavir 200 mg en lugar de 100 mg [**136**], respectivamente.

En conjunto, todos estos datos sugieren que al menos algunos inhibidores de la proteasa (en relación con EFV), cuando se administran con ritonavir (en relación con ritonavir-no potenciado) y con una dosis más alta de ritonavir (en relación con una dosis más baja), conducirán a un mayor aumento de la grasa de las extremidades en los pacientes infectados con VIH naive que inician el tratamiento antirretroviral. El cambio de los ITINN a LPV/r manteniendo los ITIN (mayormente ITINs de timidina, estavudina 48% y zidovudina 34%) en pacientes que fracasaron a un tratamiento de primera línea basado en ITINN también condujo a un aumento de la grasa en las extremidades a las 48 semanas [**137**], en concordancia con nuestros resultados. Si el efecto del cambio de LPV/r en la promoción de la ganancia de grasa en las extremidades puede compartirse con el cambio a inhibidores de la proteasa distintos del LPV/r es plausible, pero actualmente se desconoce.

Nuestro estudio también sugiere una tendencia diferencial entre EFV y LPV/r con respecto a la grasa en el tronco por DXA y VAT por TAC. Los depósitos de grasa subcutánea e intraabdominal muestran diferencias biológicas y genéticas tanto en la

población general [138] como en los pacientes infectados por VIH con lipodistrofia [139]. En los pacientes infectados por el VIH, la lipoatrofia y la lipohipertrofia no se presentan necesariamente simultáneamente [140, 141]. Se informó que el indinavir promueve el aumento de grasa visceral (el llamado'crixbelly') [142]. Se ha descrito comúnmente un aumento del VAT tras el inicio de la terapia antirretroviral; el aumento del VAT suele estar correlacionado con el aumento de la grasa de las extremidades y ambos cambios serian el reflejo del fenómeno del "retorno a la salud" en lugar de los efectos directos de las drogas [143]. Sin embargo, en el estudio MITOX, en el que a los pacientes infectados por el VIH con lipoatrofia se les cambió el régimen antirretroviral con el objetivo de aumentar la grasa de las extremidades, es notable que el VAT también tendió a disminuir en el brazo experimental durante un período de 96 semanas [144] en concordancia con nuestros resultados.

Datos recientes in vitro han revelado datos sobre los efectos tóxicos potenciales del EFV sobre las células adiposas y hepáticas humanas. En comparación con LPV/r [147], nevirapina [145] o rilpivirina [146], EFV mostró más efectos en el deterioro de la adipogénesis humana y el aumento de la expresión y liberación de citocinas. También se ha demostrado que el EFV (pero no la nevirapina) induce toxicidad mitocondrial al inhibir agudamente el complejo I de la cadena respiratoria, lo que a su vez conduce a una rápida acumulación de lípidos en el citoplasma hepatocitario mediada por la activación de la 5' adenosin monofosfato protein quinasa [148, 149]; la esteatosis hepática se ha asociado con resistencia a la insulina, dislipidemia y obesidad abdominal visceral [150].

Aunque estos efectos tóxicos in vitro de EFV podrían ser compensados in vivo por mecanismos de regulación, podrían tener un papel en el mantenimiento de las anomalías de grasa corporal en pacientes con lipoatrofia al prevenir el aumento de grasa en las extremidades y promover la acumulación visceral de grasa. En un estudio reciente no aleatorizado que evaluó cambios a 48 semanas en los marcadores moleculares de la biología y función de los adipocitos en biopsias de tejido adiposo subcutáneo a partir de biopsias de pacientes infectados por el VIH en primera línea de TAR que comienzan con EFV o LPV/r con TDF/FTC [151], EFV se asoció con un aumento de la expresión de los genes que codifican las citoquinas de inflamación en relación con LPV/r. En nuestro estudio, la expresión de CEBP/A, ADIPOQ, GLUT4, LPL y COXIV en el tejido adiposo subcutáneo fue significativamente mayor con LPV/r que con EFV después de 96 semanas, aunque no hubo diferencias entre las ramas en la expresión génica de inflamación. Estas tendencias fueron similares a las observadas en un ensayo clínico aleatorizado de 48 semanas realizado por nuestro grupo en pacientes infectados con VIH que iniciaron EFV o LPV/r [152], aunque en este último estudio los cambios de grasa corporal entre brazos no fueron significativos. Debido a que los ARNm de los genes CEBP/A, ADIPOQ, GLUT4, LPL y COXIV y sus correspondientes niveles de proteínas disminuyen en pacientes infectados por VIH con lipodistrofia [153], nuestros resultados podrían sugerir un impacto potencial de la estrategia de cambio sobre el tejido adiposo lipoatrófico. Sin embargo, el aumento de la transcripción de GLUT4 en pacientes que cambian a LPV/r podría alternativamente reflejar un mecanismo compensatorio para la conocida inhibición mediada por IP de GLUT4, un mecanismo que conduce a la

resistencia a la insulina [154]. Desafortunadamente, los marcadores plasmáticos de sensibilidad a la insulina no se midieron en este estudio.

El cambio de EFV a LPV/r redujo el colesterol HDL. No se observaron efectos en otros lípidos además del colesterol HDL, aunque esto puede deberse al menos en parte al pequeño tamaño de la muestra. Nuestro grupo informó hace años que la lipodistrofia clínicamente evidente era un factor de riesgo independiente para desarrollar dislipidemia temprana en pacientes infectados por VIH experimentados que iniciaban una terapia basada en LPV/r [155].

Aunque el aumento de la grasa en las extremidades y la disminución de la grasa en el tronco observados después del cambio a LPV/r en este estudio podrían contribuir a una distribución más saludable de la grasa corporal y, por lo tanto, a un perfil lipídico más favorable, el uso de LPV/r se ha asociado sistemáticamente con dislipidemia [156] y el infarto de miocardio [157, 158].

Nuestro estudio tuvo limitaciones importantes. Los participantes fueron seleccionados sin intención, y sólo 33 de los 125 pacientes examinados aceptaron ser aleatorizados, aunque no pudimos encontrar diferencias epidemiológicas importantes ni en los antecedentes de VIH entre los pacientes que rechazaron o aceptaron el ingreso al estudio. Debido a una tasa de perdida inferior a la esperada, pudimos mantener el tamaño de la muestra estimado para detectar diferencias en el criterio de valoración primario. La administración abierta de medicamentos antirretrovirales podría haber inducido algún sesgo en hacer que los pacientes a los que se les cambió la terapia adoptaran medidas dietéticas o de estilo de vida diferentes a las de los que se les

continuó la terapia. Sin embargo, estos factores usualmente ejercen impacto a través del cambio de peso y encontramos diferencias en los cambios de grasa corporal entre los brazos a pesar de no haber diferencias en el índice de masa corporal. No se evaluaron los marcadores de resistencia a la insulina en plasma y, por lo tanto, no se sabe si los cambios en la grasa corporal al cambiar a LPV/r finalmente condujeron a un estado de sensibilidad a la insulina mejor o peor. Hemos observado anteriormente que los cambios en la grasa corporal, incluso en el compartimento de la grasa subcutánea, en pacientes naive al antirretroviral tratados con algunos inhibidores de la proteasa potenciados con ritonavir pueden estar asociados con la resistencia a la insulina [142].

Debido al pequeño tamaño de la muestra, no fue posible evaluar con más detalle información sobre los factores influencia en los cambios en la grasa corporal. Los hallazgos se restringieron a los pacientes lipotróficos con criterios de inclusión y exclusión claramente definidos que habían cambiado el EFV por LPV/r y no pueden extrapolarse a otros tipos de pacientes o terapias antirretrovirales. La mayoría de los participantes eran hombres y no pueden generalizarse a las mujeres. Encontramos que es extremadamente difícil inscribir a los pacientes porque simplemente no aceptaron cambiarse a un régimen más complejo a pesar de cumplir todos los criterios de inclusión y exclusión; el advenimiento de nuevas combinaciones de tabletas únicas basadas en IP/r una vez al día podría mejorar esta limitación.

Aunque los resultados de nuestro estudio sugieren una mejora en la lipoatrofia y la distribución de la grasa corporal al cambiar de EFV a LPV/r, esta estrategia debe

valorarse frente a los inconvenientes bien establecidos de un régimen más complejo y también los riesgos potenciales de efectos adversos asociados con LPV/r [156-158].
La lipoatrofia sigue siendo un problema frecuente en los países en vías de desarrollo, a pesar de la disminución del uso de los ITINs de timidina.

Nuestro estudio sugiere que el cambio de EFV a LPV/r en pacientes infectados por VIH con lipoatrofia clínicamente aparente puede ofrecer una mejora adicional en el aumento de la grasa de las extremidades además de la interrupción del ITIN de timidina, aunque también puede estar acompañado de efectos adversos bien conocidos relacionados con el LPV/r, como resistencia a la insulina, dislipidemia y enfermedades cardiovasculares. Se necesitarán estudios adicionales que consideren cambiar a otros regímenes basados en IP/r más convenientes y mejor tolerados para confirmar esta estrategia y determinar su relevancia clínica.

6.2 Discusión acerca de los resultados de los Estudio KiRilNa y KIVI

Respecto al **estudio KiRiNa**, hemos observado que, en la práctica clínica, en un grupo seleccionado de pacientes con infección VIH naive, un régimen con abacavir/lamivudina + rilpivirina es efectivo y seguro.

Existen pocos datos en la literatura que utilicen esta combinación. En el estudio THRIVE sólo el 10% (n= 35) de los pacientes incluidos recibieron abacavir/lamivudina + rilpivirina. La eficacia global fue del 86%, sin diferencias aparentes en función de ITIN de base [38]. Recientemente, se presentó un estudio que evalúo esta combinación en 33 pacientes durante 12 meses. Sólo se observó un FV en un paciente con adherencia

intermitente (con resistencia a los ITIN y a los ITINN) y siete pacientes discontinuaron el tratamiento (en cuatro por toxicidad/intolerancia) [159].

En pacientes con ARN-VIH indetectable, este régimen se ha utilizado como estrategia de cambio. Imaz y cols. [160] presentaron una serie de 80 pacientes con eficacia a los 6 meses de 85% (ITT) y 92% (en tratamiento) mejoría en el perfil lipídico y dos discontinuaciones debidas a eventos adversos. En el estudio SIMKE, 85 pacientes se cambiaron a abacavir/lamivudina + rilpivirina. Después de 12 meses la eficacia fue del 96%; hubo un FV y cuatro discontinuaciones debido a eventos adversos [161]. En el estudio SIMRIKI, la eficacia a los 12 meses, en 205 pacientes, fue del 91% (ITT) y el 97% (en-tratamiento), con cinco FV y cuatro discontinuaciones debidas a toxicidad [162].

Existen varios argumentos a favor del uso de esta combinación en pacientes seleccionados. Uno es evitar los posibles efectos secundarios renales y óseos del tenofovir. Incluso cuando esté disponible el tenofovir alafenamida (una pro-droga con menos toxicidad renal y ósea que el tenofovir disoproxil fumarato), será más caro que el abacavir [163]. Otra razón para usar esta combinación es la buena tolerabilidad [164].

Además, observamos un buen perfil metabólico, con un incremento significativo en el HDL sin cambios en el colesterol total o el LDL, generando una pequeña, pero significativa disminución de la proporción de colesterol total/HDL. Estos incrementos en el HDL también se han observado con abacavir/lamivudina en grandes ensayos aleatorizados, pero sin la disminución en la proporción colesterol total/HDL [165,166].
La rilpivirina es un inhibidor débil de los transportadores de OCT2 en la célula tubular proximal y puede incrementar ligeramente la creatinina sérica debido a la inhibición de

la secreción tubular renal activa, como se observa en nuestros pacientes, sin afectar la tasa real de filtrado glomerular (FG) [167].

También es un régimen conveniente, de sólo dos comprimidos (la rilpivirina es el comprimido más pequeño disponible) tomadas una vez al día. El potencial de interacciones de la rilpivirina es bajo. Por último, pero no menos importante, es un régimen relativamente barato [164].

Por supuesto, se deben considerar algunas precauciones, todas inherentes a los fármacos que forman la combinación. La rilpivirina sólo está aprobada para pacientes con ARN VIH < 100.000 copias/mL3 y probablemente no se recomienda para pacientes hospitalizados con CD4+ < 200 células/mm3. Debe tomarse con alimentos y el paciente no puede tomar inhibidores de la bomba de protones [36], pero estas precauciones son aplicables independientemente de los fármacos que acompañan a la rilpivirina. Con respecto al uso del abacavir en pacientes con alto riesgo cardiovascular, la evidencia en la literatura es inconsistente, con una asociación observada en algunas cohortes pero no en otras ni en un meta-análisis realizado por la FDA [168]. Sin embargo, algunas guías recomiendan precaución cuando se use abacavir en este tipo de pacientes [42]. Además, se debe tener un HLA B5701 negativo previo a su uso.

La naturaleza retrospectiva y observacional de este estudio es una clara limitación que puede implicar un sesgo de selección y no permite controlar factores como la adherencia o los eventos adversos que podrían no haber sido reportados. Además, no todos los pacientes tienen el mismo seguimiento. Una evaluación más

prolongada de estos pacientes será muy útil para determinar la eficacia y seguridad reales de este régimen en el ámbito clínico.

Respecto al **estudio KiVi,** a pesar de que una considerable proporción de pacientes tuvieron que discontinuar el tratamiento debido a toxicidad (la mayoría asociada con la NVP), los que inicialmente toleraron este régimen presentaron una alta respuesta virológica e inmunológica a las 96 semanas, así como un perfil lipídico favorable.

6.3 Discusión acerca de los resultados del Estudio ZEST

En este ensayo aleatorizado, controlado y de carácter estratégico, la administración anual de ácido zoledrónico resulto en un incremento mayor en la DMO a los 24 meses en comparación con el cambio de TDF en adultos infectados por el VIH virológicamente suprimidos en tratamiento antirretroviral con TDF y osteopenia. El tratamiento con ácido zoledrónico intravenoso también se asoció con una reducción significativa de la proporción de personas con osteoporosis. El mayor incremento en la DMO se produjo en los primeros 12 meses en la rama del ácido zoledrónico, con una desaceleración del aumento posteriormente. En la rama del cambio de TDF, todo el incremento en la DMO ocurrió en los primeros 12 meses, con una estabilización de la DMO en los siguientes 12 meses. Ambas estrategias fueron bien toleradas.

Los resultados de nuestro estudio están en consonancia con el aumento de la DMO a 1-2 años observado en seis ensayos aleatorizados de tratamiento con bifosfonatos en pacientes seropositivos; cuatro usaron alendronato 70 mg semanal y dos, ácido zoledrónico intravenoso 5 mg al año, además todos los participantes

recibieron suplementos de calcio y vitamina D (generalmente 1000 mg/día y 400 UI/día, respectivamente). En estos ensayos, la DMO fue mayor a los dos años que al año, y los aumentos en la DMO fueron similares o mayores en la columna lumbar que en el cuello femoral y parecieron similares o mayores con el ácido zoledrónico (3,7-8,9% en la columna vertebral y 3,2-3,8% en la cadera) que con el alendronato (3,4-5,2% en la columna vertebral y 1,8-4% en la cadera) [57 - 60, 131, 132]).

El aumento del 7,4% en la DMO de la columna vertebral en nuestro estudio fue similar al aumento aproximado del 6% en la DMO con ácido zoledrónico en relación con los controles a 2 años en pacientes seropositivos que se observó en grandes ensayos en fase 3 en mujeres posmenopáusicas con osteoporosis [167, 168].

En un ensayo con alendronato hubo una tendencia a mayor incremento en la DMO en aquellos que recibieron TDF Vs TAR sin TDF, pero no fue significativo. [58]. El aumento medio del 2,9% en la DMO en la columna y la cadera en nuestro estudio es ligeramente mayor al observado en otros estudios con cambio de TDF en los que se evaluó el cambio en la DMO con una mejoría que fue generalmente del 1-2,5% [62, 63].

La mayor magnitud de cambio en la DMO en nuestro estudio puede deberse a la suplementación con vitamina D para los individuos insuficientes y deficientes de vitamina D y a la suplementación con calcio.

La vitamina D con o sin calcio ha mostrado en varios estudios que mejora la DMO en aquellos que reciben tratamiento con TDF. [169-171]. Aunque tanto el alendronato como el ácido zoledrónico fueron bien tolerados en los ensayos anteriores, el ácido zoledrónico podría ser preferible al alendronato semanal por varias razones: el principal

efecto secundario del alendronato son las náuseas, que son una razón común de la deficiente adherencia a este régimen. Las náuseas también son un efecto secundario común del TAR y los efectos secundarios del TAR son los que más probabilidades tienden a causar la no adherencia y el cese de la terapia antirretroviral [172]. Además, el ZOL no aumentaría la carga de comprimidos ni dificultaría el cumplimiento de la terapia antirretroviral.

Sólo un individuo experimentó un fracaso virológico en la rama del cambio y necesitó un nuevo esquema de tratamiento. El cambio de TAR en individuos con supresión virológica siempre está asociado con un riesgo de nuevos eventos adversos o pérdida de control virológico y de opciones de tratamiento futuro [173].

En este estudio, un participante en la rama del cambio de TDF presentó un FV debido a mala adherencia a su nuevo régimen de TAR y cuatro participantes presentaron nuevos efectos adversos y reiniciaron el TDF al mismo tiempo que mantuvieron la supresión virológica. Un participante en la rama de ZOL presentó viremia de bajo nivel, con un cambio en el régimen de TAR (cambio del TDF). Otros dos participantes en la rama de ZOL dejaron de usar TDF debido a la disminución de la función renal. Se observó una disminución continua del FG en la rama del ZOL, en comparación con un aumento del FG en la rama del cambio de TDF, muy probablemente debido al uso concomitante del TDF en aquellos asignados al uso de ZOL.

Nuestro estudio tiene limitaciones. Hubo muy pocas mujeres reclutadas y la población del estudio era predominantemente caucásica, hombres adultos. El seguimiento actual es corto a los 24 meses; el seguimiento está en curso a los 36 meses.

Aunque se produjeron significativamente más fracturas en el grupo con cambio de TDF, no hubo diferencias en el número de participantes que experimentaron una fractura entre las dos ramas del estudio. El estudio no tuvo poder estadístico para los eventos de fractura y se necesitarán estudios mucho más grandes y de mayor duración para determinar el impacto sobre los resultados en la fractura. Finalmente, el estudio se inició antes de que se dispusiera del TAF, el cual ha demostrado que está asociado con una menor pérdida ósea que con el TDF, y una menor toxicidad renal. Sin embargo, el aumento de la DMO observado después de cambiar de TDF a TAF es similar al observado después de cambiar de TDF a ABC o a un INI, [61 - 64] por lo que, aunque es probable que ambas estrategias sean efectivas para aumentar la DMO, también es probable que el tratamiento con ácido zoledrónico IV sea superior al cambio de TDF a TAF en adultos con VIH y baja masa ósea.

Aunque el cambio de TDF es un enfoque razonable para mejorar la DMO baja en adultos con infección por VIH que toman TDF, hemos demostrado que el tratamiento con ácido zoledrónico es una estrategia superior a 24 meses. El seguimiento continuo al mes 36 será importante para establecer si el efecto del ácido zoledrónico es duradero (los participantes solo recibieron una infusión de 5 mg al inicio del estudio y en el mes 12), y si hay un aumento continuo en la DMO después del mes 24 en cualquiera de los dos grupos. Aunque es probable que se prefiera el uso de ZOL para las personas con osteoporosis, la importancia clínica de esta estrategia también dependerá del riesgo absoluto subyacente de fractura, que, tanto para la población con VIH como para la población general, aumenta con la edad.

6.4 Discusión acerca de los resultados del Estudio Dolutegravir monoterapia

Este estudio surgió de la coincidencia de dos factores en una gran cohorte de adultos infectados con VIH. Por un lado, las numerosas dificultades que experimentaron una serie de pacientes para mantener satisfactoriamente su TAR, a pesar de haber logrado una supresión viral sostenida [174]. Las características de los pacientes incluidos en esta cohorte (múltiples: toxicidades a regímenes de TAR, mutaciones de resistencias, comorbilidades y polifarmacia) ponen de manifiesto las múltiples limitaciones que tenían y la necesidad de seguir mejorando sus regímenes antirretrovirales. Por otro lado, la disponibilidad de antirretrovirales como el dolutegravir con características que permitían considerar la posibilidad de una monoterapia [69].

Dolutegravir se ha comparado favorablemente con efavirenz [175] y darunavir / ritonavir [176] y de forma similar con raltegravir [177] en pacientes naive; actualmente se recomienda como una primera opción en pacientes naive. Dolutegravir también se comparó favorablemente con raltegravir en pacientes con FV, pero sin exposición previa a inhibidores de la integrasa [178]. Además de su excelente eficacia, dolutegravir también se caracteriza por su alta barrera genética y su robustez en la prevención de la resistencia viral. En pacientes naive, [175 - 177] los tratados con dolutegravir con FV no mostraron mutaciones de resistencia tanto a dolutegravir como a los ITIAN, una característica conocida de los IP potenciados, pero no de otra clase de antirretrovirales ni incluso otros inhibidores de la integrasa disponibles actualmente, raltegravir y elvitegravir. Esta característica también está respaldada por los datos clínicos en

pacientes experimentados, pero naive a INI con FV [178] y por datos de laboratorio [179].

Dolutegravir también mostró menos discontinuaciones que otros fármacos y no tuvo efecto sobre los lípidos ni las enzimas hepáticas en pacientes naive, aunque se puede esperar un aumento de la creatinina por bloqueo tubular que no se considera un efecto tóxico. Dolutegravir se administra cómodamente como un comprimido pequeño una vez al día y sin restricciones alimenticias. Dolutegravir no requiere potenciación y se ha informado que los niveles plasmáticos están por encima de la IC90 24 h después de la administración [180]. Dolutegravir no tiene interacciones importantes con otras drogas, una característica que también comparte con raltegravir. Todos estos factores en conjunto hacen que el dolutegravir sea diferente de los otros antirretrovirales disponibles y puede ser particularmente importante para los pacientes con limitaciones al tratamiento antirretroviral preexistente.

Los resultados en esta cohorte de pacientes que recibieron monoterapia con dolutegravir son notables, ya que casi todos fueron capaces de mantener la supresión viral después de 24 semanas, con mejoras en las razones inmediatas que hicieron que se cambiaran sus terapias y no se produjeran efectos perjudiciales sobre la función inmunológica o eventos adversos importantes. Todos los pacientes de la cohorte, excepto el que tuvo FV, han mantenido la monoterapia con dolutegravir durante casi 1 año de seguimiento en el momento de redactar este informe y el ARN del VIH en plasma ha permanecido suprimido en todos ellos. Estos resultados son sorprendentes porque no habrían sido posibles con ningún otro fármaco único. Durante los últimos 30 años, la

vulnerabilidad al desarrollo de resistencia ha sido una seria limitación para todos los antirretrovirales. Esta fue la razón por la que los primeros estudios que utilizaron combinaciones simples y dobles produjeron solo beneficios a muy corto plazo.

Observamos que un paciente desarrolló un FV en nuestra cohorte. Este paciente tuvo un FV previo a un régimen con raltegravir, si bien no se encontraron mutaciones de resistencia a los inhibidores de la integrasa inicialmente cuando se detectó el FV a la monoterapia con dolutegravir. Aunque este paciente negó haber omitido dosis de dolutegravir, había razones para sospechar que su adherencia a la terapia no era óptima. Este paciente tuvo una viremia persistente de bajo nivel y desarrolló la mutación 118 en el gen de la integrasa, que le confiere resistencia intermedia a raltegravir y elvitegravir y resistencia de bajo nivel a dolutegravir según la Base de datos de resistencia al VIH de la Universidad de Stanford *(http: //sierra2.stanford .edu / sierra / servlet / JSierra).* En otro estudio una cohorte francesa a 24 semanas que incluyó pacientes con características epidemiológicas similares a nuestra cohorte, 3 (11%) de los 28 pacientes que cambiaron a dolutegravir en monoterapia experimentaron un FV con el desarrollo de mutaciones de resistencia a los inhibidores de la integrasa [181]. Al igual que el paciente con FV de nuestra cohorte, los tres pacientes con FV en el estudio francés habían estado expuestos previamente a inhibidores de la integrasa. Estos pacientes tenían niveles plasmáticos de dolutegravir medidos en varios puntos del tiempo durante el seguimiento; aunque estaban muy por encima de la IC90 y dentro de los niveles terapéuticos en el momento del FV, no se midieron en las semanas o últimos meses antes del FV y, por lo tanto, no podemos confirmar si se había mantenido una

adherencia óptima a la terapia en estos tres pacientes que fracasaron. Lo que es evidente apartir del estudio francés y del nuestro es que el FV a la monoterapia con dolutegravir puede llevar a la aparición de mutaciones de resistencia a los inhibidores de la integrasa y esto es algo muy distinto de lo que sabíamos acerca de la monoterapia con IP potenciados. La existencia de mutaciones de resistencia a raltegravir podría causar resistencia cruzada a dolutegravir, lo que puede provocar resultados menos positivos cuando el dolutegravir se emplea como un régimen de mantenimiento de segunda línea [182]. Aunque dolutegravir tiene una alta barrera genética contra la resistencia, es inferior a la de los IP potenciados. Tanto R263K como G118R como mutaciones únicas pueden conferir resistencia a dolutegravir [183] y la resistencia puede ser aún mayor cuando también hay mutaciones secundarias presentes [184]. La monoterapia y la terapia dual con dolutegravir [181, 185 - 187] son estrategias no estándar y se necesitan más investigaciones antes de que puedan generalizarse en el ámbito clínico.

Nuestro estudio no fue controlado, incluyo pocos pacientes y tuvo un seguimiento corto. Reconocemos que las razones para cambiar de tratamiento difirieron entre los participantes y que se podrían haber utilizado otros regímenes no estándar en lugar de la monoterapia con dolutegravir. Las limitaciones de la terapia antirretroviral en nuestra cohorte están ejemplificadas en el uso común de tratamientos no estándar (p.ej. monoterapia con IP aumentados) en un número considerable de pacientes. De este modo, los pacientes de nuestra cohorte fueron altamente seleccionados y es posible que sus resultados no se puedan aplicar a otros pacientes. Al igual que con

cualquier estudio retrospectivo, no tuvimos información precisa de los efectos adversos potenciales al iniciar el tratamiento con dolutegravir, pero no se identificó ningún paciente que discontinuara el tratamiento.

La principal fortaleza de nuestro estudio es que el cambio permitió que los pacientes se liberaran de las limitaciones de sus regímenes antirretrovirales anteriores, a la vez que podían mantener los beneficios de la supresión viral sostenida [188].

En resumen, estos datos sugieren la eficacia de la monoterapia con dolutegravir como estrategia de mantenimiento debe ser confirmada en ensayos clínicos aleatorios. Varios estudios con monoterapia o terapia dual con dolutegravir ya se han registrado o se están planificando, estos nos aportaran más datos para determinar si la monoterapia con dolutegravir o la terapia dual pueden desafiar el paradigma de la terapia triple estándar.

6.5 Discusión acerca de los resultados del Estudio DOLAM

Hasta donde sabemos, DOLAM es el único estudio que ha comparado directamente la terapia dual con dolutegravir / lamivudina Vs monoterapia con dolutegravir como posibles estrategias de simplificación basadas en dolutegravir en un ensayo clínico aleatorizado cara a cara. En la fase A del estudio DOLAM reportado aquí, encontramos que la incidencia de FV en la rama de monoterapia con dolutegravir excedió el umbral preestablecido del protocolo del 5% a las 24 semanas. Los FV en pacientes de la rama de monoterapia con dolutegravir no ocurrieron de forma temprana, sino al final del período de 24 semanas. Además, los dos pacientes que

presentaron FV bajo la monoterapia con dolutegravir desarrollaron mutaciones de novo, lo que implica resistencia cruzada a todos los inhibidores de la integrasa actualmente autorizados. [189].

En ambos pacientes, se desarrollaron múltiples mutaciones en presencia de viremia de bajo nivel y a pesar de niveles adecuados de dolutegravir en plasma y adherencia a la terapia. Estos resultados concuerdan con los de un ensayo clínico aleatorizado recientemente publicado que comparó la monoterapia con dolutegravir de mantenimiento con la terapia antirretroviral combinada. [190]. En ese ensayo, ocho (8%) pacientes tratados con monoterapia con dolutegravir presentaron FV y tres de ellos desarrollaron una mutación de resistencia cada uno (S230R, R263K y N155H) a pesar de los niveles adecuados de dolutegravir en plasma y de la adherencia reportada por cada uno de ellos. Además, una revisión sistemática reciente y un meta-análisis de la terapias simplificadas basadas en dolutegravir en pacientes infectados con VIH [191] proporcionaron estimaciones precisas de la tasa de FV en el mantenimiento con monoterapia y la terapia dual basada en dolutegravir (que incluía no sólo el dolutegravir/lamivudina, sino también el dolutegravir/rilpivirina) mostraron que la tasa de FV era 10 veces más elevada con la monoterapia (3,18%) que con el tratamiento dual (0,32%) a 24 semanas, pero la diferencia se incrementó aún más, hasta 20 veces mayor a las 48 semanas (8,91% versus 0,41%), lo que sugiere que el riesgo de FV y el desarrollo de mutaciones de resistencia con la monoterapia con dolutegravir puede ser mayor después de las primeras 24 semanas. En conjunto, estos datos sugieren que el dolutegravir utilizado como monoterapia no es lo suficientemente potente y/o que su

barrera genética a la resistencia es insuficiente para prevenir el desarrollo de resistencias a pesar de una adherencia óptima y, por lo tanto, no se debe utilizar esta estrategia.

En resumen, en el análisis planificado a 24 semanas de dos estrategias de simplificación basadas en dolutegravir (Estudio DOLAM), la rama de monoterapia con dolutegravir mostró un riesgo inaceptable de FV con el desarrollo de mutaciones con resistencia cruzada a inhibidores de la integrasa y esta rama se interrumpió y no se recomendó; por su parte la rama de terapia doble con dolutegravir + lamivudina no mostró signos de alarma. Con base en los resultados de esta fase A, el protocolo del estudio DOLAM se modificó a solo dos ramas (terapia dual con dolutegravir / lamivudina versus control), el tamaño de la muestra se recalculo y se invitó a otros centros a completar la fase B del estudio.

6.6 Discusión acerca de los resultados del Estudio tolerabilidad de los inhibidores de la integrasa en la vida real

En esta gran cohorte de pacientes infectados por VIH tratados con los inhibidores de la integrasa actualmente disponibles, encontramos tasas de discontinuación por cualquier motivo en el primer año de tratamiento en un rango del 8,1% al 12,7%. Con elvitegravir hubo una tendencia a menos discontinuaciones en general y las interrupciones no debidas a toxicidad fueron signficativamente menos frecuentes que con raltegravir o dolutegravir.

En contraste con el raltegravir, que no se combina en un STR, o el dolutegravir, que first se hizo disponible como un medicamento individual, el elvitegravir siempre se ha utilizado como un STR. Este hecho puede ser responsable, al menos en parte, de la menor tasa de interrupción general que no se debe a la toxicidad con el elvitegravir. Los STR se consideran los regímenes antirretrovirales más convenientes [192, 193] y se ha informado de que la conveniencia es un factor determinante para la interrupción del tratamiento antirretroviral en los pacientes que inician el tratamiento [194].

Sólo una parte de las discontinuaciones se atribuyó a efectos adversos. Las proporciones oscilaron entre el 3,6% para raltegravir, el 3,8% para dolutegravir y el 5,0% para elvitegravir [76–81]. Estas cifras fueron ligeramente superiores a las reportadas en los ensayos clínicos. La tasa de discontinuación temprana debido a efectos adversos no difirió significativamente entre los tres inhibidores de la integrasa. Ha habido una enorme controversia sobre el potencial del dolutegravir en cuanto a una peor tolerabilidad en el entorno de la vida real, debido a que en algunas cohortes se ha reportado una tasa inesperadamente alta de discontinuación debida a efectos adversos [84 – 93]. La disponibilidad de información cada vez mayor sobre los efectos adversos después de la comercialización podría tener influencia en la decisión de discontinuar un medicamento en el ámbito clínico. Los datos de nuestra cohorte reportados aquí fueron generados antes de la publicación del informe de la cohorte holandesa en la Conferencia sobre Retrovirus e Infecciones Oportunistas de 2016. Por lo tanto, el potencial de influencia del informe de la cohorte holandesa sobre la discontinuación del dolutegravir en nuestra cohorte debería ser insignificante, si es que existe.

Nuestros resultados no muestran una mayor tasa de discontinuación debida a efectos adversos por dolutegravir en comparación con raltegravir o elvitegravir. Es posible que diferencias en las características de los pacientes u otros factores no bien conocidos expliquen la mayor tasa de discontinuación de dolutegravir debido a efectos adversos observados en algunas cohortes.

Los efectos adversos más frecuentes que llevaron a la discontinuación de cada uno de los tres inhibidores de la integrasa en nuestra cohorte fueron neuropsiquiátricos y osteomusculares. Estos efectos ya están reconocidos en los resúmenes de las características del producto de raltegravir [97], elvitegravir / cobicistat /emticitabina/tenofovir disoproxil fumarato [98] y dolutegravir [99]. Sin embargo, la frecuencia de efectos neuropsiquiátricos entre los pacientes con discontinuación debida a toxicidad fue significativamente mayor con dolutegravir en comparación con raltegravir o elvitegravir, sugiriendo que este perfil de toxicidad podría ser más característico del dolutegravir. Esta afirmación está respaldada por datos recientes de un estudio de cohorte alemán [90].

Esto contrasta con los datos de los ensayos clínicos aleatorizados en los que la incidencia general de efectos adversos neuropsiquiátricos reportados en pacientes asignados a dolutegravir fue similar a la de los competidores (efavirenz en SINGLE, raltegravir en SPRING-2, darunavir/ritonavir en FLAMINGO y atazanavir/ritonavir en ARIA) siendo muy pocos los pacientes que discontinuaron el dolutegravir debido a efectos adversos neuropsiquiátricos [195].

Las discrepancias en la discontinuación del dolutegravir debido a efectos neuropsiquiátricos entre los ensayos clínicos y los estudios de cohorte podrían deberse, al menos en parte, a la propensión hacía la retención de pacientes en los ensayos clínicos y a la naturaleza generalmente leve y aparentemente transitoria de los efectos secundarios neuropsiquiátricos.

No se observaron diferencias importantes en el perfil clínico de los efectos adversos neuropsiquiátricos que llevaron a la discontinuación entre los tres inhibidores de la integrasa, aunque esta comparación debe tomarse con cautela debido a la naturaleza inherentemente subjetiva tanto de la descripción de los pacientes como del registro del médico.

El predominio del insomnio entre los efectos neuropsiquiátricos puede sugerir una interferencia potencial con los mecanismos implicados en la fisiología del sueño [196]. Se ha notificado varios fármacos que causan insomnio como efecto adverso [197]. La coincidencia de un efecto adverso común en el perfil del SNC entre efavirenz y los inhibidores de la integrasa ha llevado a especular sobre si pueden estar involucradas vías patogénicas similares. Sin embargo, datos recientes argumentan en contra de esta afirmación debido a que los pacientes que experimentaron efectos adversos asociados con el efavirenz en el SNC mostraron mejoría después de cambiar de efavirenz a dolutegravir [95, 96]. Se necesita más investigación para comprender la patogénesis y los factores de riesgo de los efectos adversos del SNC asociados con los inhibidores de la integrasa.

En nuestra cohorte, el aumento de la edad fue el único factor asociado con un más alto riesgo de discontinuación del inhibidor de la integrasa debido a efectos adversos. El riesgo aumenta un 4% por año. El aumento de la edad se ha asociado con una mejor respuesta virológica debido a una mejor adherencia a la terapia antirretroviral, pero una peor respuesta inmunológica debido a la reducción de la reserva funcional [198]. La discontinuación del TAR por razones distintas del FV se ha informado con mayor frecuencia en pacientes mayores, pero también en pacientes más jóvenes en comparación con los de mediana edad, sin embargo, en el caso de los pacientes mayores la discontinuación se asoció con toxicidad y en los más jóvenes con falta de adherencia [199]. El aumento de la edad se asocia a una mayor incidencia de comorbilidades [200] y a una mayor exposición plasmática a algunos fármacos antirretrovirales, [201] y ambos factores contribuyen a una mayor propensión a la toxicidad [202, 203].

Estos resultados subrayan la necesidad de una mayor conciencia de los efectos adversos potenciales que llevan a la discontinuación de los inhibidores de la integrasa entre los pacientes mayores, a pesar de que estos fármacos se recomiendan preferentemente en ellos debido a su mejor perfil de seguridad, en comparación con los ITINAN o los IPs [73–75].

En conclusión, la discontinuación de los inhibidores de la integrasa disponibles no debida a toxicidad fue menos frecuente con elvitegravir que con raltegravir o dolutegravir, aunque la discontinuación debido a efectos adversos fue similar entre los tres y ligeramente superior a la que se informó en los ensayos clínicos. Los efectos neuropsiquiátricos y osteomusculares fueron los más comunes que llevaron a la

discontinuación del fármaco con los tres inhibidores de la integrasa, aunque los efectos adversos neuropsiquiátricos fueron más frecuentes con dolutegravir que con raltegravir o elvitegravir. El aumento de la edad fue un factor independiente asociado con un mayor riesgo de discontinuación de los inhibidores de la integrasa debido a los efectos adversos.

6.7 Discusión acerca de los resultados del Estudio A-TRI-WEEK *(ClinicalTrials.gov: NCT01778413)*

Este estudio piloto es una prueba de concepto que confirma la viabilidad de Atripla 3 días por semana. En los adultos VIH + estables Atripla 3 días por semana mantiene la eficacia y mejora parámetros de toxicidad subclínica. A pesar de Atripla tiene una dosificación de solo 1 vez al día los pacientes mostraron entusiasmo en poder reducir el número de comprimidos a 3 por semana. A los pacientes de la rama con Atripla 3 días por semana (3W) se les interrogo específicamente en cada una de las visitas acerca del cumplimiento/adherencia al esquema no estándar. No diseñamos ninguna intervención especial para facilitar la adherencia en la rama 3W. Al inicio del estudio algunos pacientes refirieron haberse ayuda de herramientas para recordar las tomas (smartphones, calendarios de pared…) en la rama 3W pero después de algunas semanas el régimen se convirtió en rutinario sintiéndose cómodos y con un manejo excelente del nuevo esquema sin encontrar ninguno que tuviese problemas de adherencia. A pesar de que estos pacientes no tenían problemas a nivel neuropsiquiátrico y mostraban una función renal normal con leve osteopenia se observaron mejorías en la rama 3W en

marcadores de toxicidad subclínica asociados con EFV y TDF. Estas mejorías fueron evidentes a pesar del relativo corto periodo de estudio y debieron presumiblemente debido a la disminución de la carga de exposición al TAR. Es difícil extrapolar estos cambios subclínicos significativos en beneficios clínicos significativos a largo plazo; sin embargo, debemos reconocer que estos cambios no fueron malos. Además, algunos de estos cambios a 24 semanas fueron comparables a los observados después de 96 semanas de reducción de 600 a 400 mgs diarios de EFV o del uso de TAF en lugar de TDF.

La reducción de la exposición a algunos fármacos antirretrovirales como EFV o TDF para disminuir la toxicidad, manteniendo la eficacia es una estrategia investigada activamente. EFV 400 mgs 1 vez al día se aprobó en las guías de la OMS en 2015 por los resultados del estudio ENCORE 1 [103, 104], así mismo se está incrementando el uso de TAF en lugar de TDF para disminuir toxicidad ósea y renal [204-206].

Debido a que no fue planeado previamente no podemos realizar un análisis económico. Sin embargo, es obvio que con la reducción de la dosis de ATP de 7 días a la semana a 3 se obtiene una reducción del 57% lo cual tiene un efecto directo en el coste y por lo tanto tiene importantes implicaciones en sitios con recursos limitados [207].

La eficacia del esquema 3W fue demostrada en este estudio intensivo con una monitorización frecuente del ARN-VIH particularmente al inicio del estudio. No solo no hubo ningún paciente con FV, sino que tampoco se detectaron blips. Además, los resultados de la medida de la CV ultrasensible confirmaron la eficacia de la rama 3W. La seguridad y tolerabilidad de la rama 3W fue excelente. Además de mantener la eficacia algunas estrategias de simplificación han ofrecido ventajas [208].

En el estudio A-TRI-WEEK la reducción de la exposición a la medicación tuvo un significativo impacto en los parámetros que reflejan toxicidad relacionada con EFV o TDF tales como calidad del sueño, DMO y proteinuria. Debemos también destacar que se presentó un aumento del colesterol total en la rama 3W; debido a que tenofovir tiene un efecto lipídico protector este cambio observado en el colesterol puede estar relacionado con la menor exposición al fármaco; este cambio a pesar de ser significativo es de pequeña magnitud e importancia en la clínica real es desconocido; sin embargo debido a que la toxicidad a los agentes antirretrovirales esta asociada directamente con la duración de la exposición se asume que a largo plazo pequeños cambios pueden tener relevancia clínica.

Como era esperado los niveles de EFV en plasma descendieron en la rama 3W a las 24 semanas. Concentraciones terapéuticas de EFV entre 1 y 4 ug/ml han sido reportadas [209]. En la rama 3W el 63% de los pacientes tenían menos de 1ug/ml a las 24 semanas; sin embargo, a pesar de estos datos ningún paciente experimento FV medido tanto de forma estándar en plasma como considerando los resultados en CV ultrasensible. Algunos estudios de evaluación farmacocinética de EFV en pacientes que toman de forma concomitante rifampicina (un inductor del metabolismo del EFV) ha mostrado que una proporción de pacientes que toman ambos pueden tener niveles de EFV por debajo de 1 ug/ml y no desarrollan FV [210-211].

Este estudio tuvo varias limitaciones. Hubo pocos pacientes y el seguimiento fue corto. Sin embargo, esta fue una forma apropiada de planificar un estudio piloto tan intensivo sobre una nueva estrategia terapéutica. Para compensar estas limitaciones, se

realizaron estudios virológicos e inmunológicos intensivos (estos últimos no descritos en este artículo) y los resultados obtenidos hasta ahora son muy tranquilizadores. Además, hubo una fase de extensión después de las primeras 24 semanas. Por indicación de la Junta de Revisión Institucional, los pacientes en la rama QD fueron invitados a cambiar su régimen de QD al de 3W y los pacientes en el brazo de 3W fueron invitados a continuar con este programa, y el seguimiento con la estrategia de 3W se extendió hasta tres años consecutivos. Todos los participantes estuvieron de acuerdo en participar en la fase de extensión del estudio ATRIWEEK, que actualmente se encuentra en curso y hasta el momento no se han producido fallos virales ni ninguna otra incidencia que haya obligado a detenerlo o a replanteárselo. Otra limitación es que, por diseño, todos los participantes provenían de un régimen estándar estable consistente en Atripla. Por lo tanto, las conclusiones del estudio ATRIWEEK no pueden generalizarse a los pacientes infectados por el VIH que toman regímenes antirretrovirales distintos de Atripla QD.

En resumen, Atripla® tres días a la semana en pacientes con supresión viral sostenida es una opción factible que mantiene la eficacia y mejora los parámetros de toxicidad subclínica. Este estudio representa una prueba de concepto que debería ser confirmada en ensayos clínicos más grandes.

7. CONCLUSIONES

7. CONCLUSIONES

I. El cambio de efavirenz a lopinavir/ritonavir en pacientes infectados por VIH con lipoatrofia y no tratados actualmente con análogos de timidina mejoró la grasa de las extremidades, aunque también se acompañó de efectos adversos como resistencia a la insulina y dislipidemia.

II. Abacavir/lamivudina+rilpivirina es una opción efectiva y segura en pacientes infectados con VIH-1 que no habían recibido tratamiento previo.

III. ABC/3TC/NVP es un régimen efectivo, con buen perfil lipídico y una toxicidad temprana limitada en pacientes infectados con VIH-1 que no habían recibido tratamiento previo.

IV. El tratamiento con ácido zoledrónico es una estrategia más eficaz que el cambio de tenofovir para mejorar la densidad mineral ósea en pacientes VIH tratados con una pauta que contiene tenofovir disoproxil fumarato con carga viral suprimida y densidad mineral ósea baja.

V. La monoterapia con dolutegravir se asocia a un riesgo potencial de fracaso virológico acompañado de desarrollo de mutaciones de resistencia a los inhibidores de integrasa.

VI. La simplificación del tratamiento antirretroviral triple estándar a la terapia dual dolutegravir más lamivudina es una opción viable, pero no así la monoterapia con dolutegravir. En un análisis planificado al cabo de 24 semanas de dos estrategias de simplificación basadas en dolutegravir, la pauta de dolutegravir en monoterapia mostró un riesgo inaceptable de fracaso virológico con desarrollo de mutaciones de resistencia cruzada a los inhibidores de la integrasa, mientras que la terapia dual dolutegravir más lamivudina no mostró señales de alarma.

VII. Los efectos neuropsiquiátricos y osteomusculares fueron los que más frecuentemente llevaron a la interrupción del tratamiento con cualquiera de los tres inhibidores de la integrasa actualmente disponibles en la cohorte de pacientes infectados por VIH del Hospital Clínic de Barcelona, aunque los efectos adversos neuropsiquiátricos fueron significativamente más frecuentes con dolutegravir que con raltegravir o elvitegravir. El aumento de la edad fue el único factor independiente identificado que se asoció a un mayor riesgo de discontinuación de los inhibidores de la integrasa debido a efectos adversos.

VIII. Un estudio piloto sobre la simplificación del tratamiento en pastilla única efavirenz/lamivudina/tenofovir isoproxil fumarato (Atripla®) de una vez al día a 3 días por semana mostró no ser inferior virologicamente y redujo la toxicidad subclínica.

8. REFERENCIAS

8. Referencias

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