UNIVERSIDADE DA CORUÑA

inibic
instituto de
investigación biomédica
de a coruña

SERVIZO
GALEGO
de SAÚDE | Xerencia Xestión Integrada
A Coruña

IMPACTO DEL VIRUS DE LA HEPATITIS C EN LA EVOLUCION DE LAS COMORBILIDADES EN PACIENTES INFECTADOS POR EL VIH (1993-2014)

TESIS DOCTORAL

Héctor Manuel Meijide Míguez

A Coruña, 2017

IMPACTO DEL VIRUS DE LA HEPATITIS C EN LA EVOLUCION DE LAS COMORBILIDADES EN PACIENTES INFECTADOS POR EL VIH (1993-2014)

Esta memoria ha sido presentada para optar al grado de Doctor en Ciencias de la Salud por la Universidad de A Coruña por el licenciado:

Héctor Manuel Meijide Míguez

Directores de Tesis:

Dra. María Ángeles Castro Iglesias
Doctora en Medicina y Cirugía. Médico Facultativo de área del Servicio de Medicina Interna (CHUAC). Titular de Universidad del departamento de Medicina de la Facultad de Ciencias de la Salud de la Universidad de A Coruña.

Dra. Eva Poveda López
Doctora en Microbiología Médica. Grupo de Virología Clínica Instituto Investigación Biomédica de A Coruña.

Los directores de esta tesis doctoral, Dña. María Ángeles Castro Iglesias y Dña. Eva Poveda López

CERTIFICAN:

Que D. Héctor Manuel Meijide Míguez, Licenciado en Medicina y Cirugía por la Universidad de Santiago de Compostela, ha realizado en la Unidad de VIH y Hepatitis del Servicio de Medicina Interna del Complejo Hospitalario Universitario de A Coruña, y en el Grupo de Virología Clínica del Instituto de Investigación Biomédica de A Coruña, y bajo su dirección, el trabajo "Impacto del virus de la Hepatitis C en la evolución de las comorbilidades en pacientes infectados por el VIH (1993-2014)", el cual reúne todas las condiciones para ser presentado como Tesis Doctoral, en la modalidad compendio por artículos de investigación.

Y para que así conste, firman el presente certificado en A Coruña, a 12 de Junio de 2017.

Dra. María Angeles Castro Iglesias   Dra. Eva Poveda López

Directora   Directora

AGRADECIMIENTOS

Al finalizar un trabajo arduo como el desarrollo de una tesis doctoral te asalta un sentimiento de éxito personal por el aporte que has hecho. Sin embargo , el análisis de tal logro te demuestra inmediatamente que hubiese sido imposible sin la participación de determinadas personas que me han facilitado el camino para que este trabajo llegase a buen puerto. Por ello, es para mí un verdadero placer utlizar este espacio para ser justo y consecuente con ellas, expresándoles mis agradecimientos.

Debo agradecer en primer lugar a las directoras de esta tesis por aceptarme para realizar este trabajo bajo su dirección. Destaco por encima de todo su apoyo y confianza en mi, su disponibilidad absoluta y su paciencia para conmigo. A la Dra Castro, por enseñarme desde la etapa de residente el camino de la investigación y hacerme partícipe de muchos proyectos de la Unidad. A la Dra Poveda, por impulsar la relación de los clinicos y los básicos con la formación del Grupo de Virología Clínica y hacerme formar parte del mismo. Todo un honor. A todos sus integrantes por su ilusion y compromiso para seguir creciendo.

Es justo y necesario agradecer la función desempeñada por el personal dedicado a la Unidad de VIH y Hepatitis del Servicio de Medicina Interna del CHUAC a lo largo de todos estos años, desde los inicios difíciles hasta la actualidad en la que se ha convertido en un centro de referencia. Al Dr Pedreira, al Dr Juega, a la Dra Castro, a la Dra Lopez-Calvo, a la Dra Vázquez, a Fina y al personal de Enfermería, a los más recientes que han continuado la labor, el Dr Mena, la Dra Rodriguez-Osorio, la Dra Pernas y a todos los que han hecho de esta Unidad un sitio mejor. De ellos es el mérito y yo solo traté de expresarlo con este trabajo.

ÍNDICE

RESUMEN

Resumen

La introducción del tratamiento antirretroviral (TAR) de alta eficacia ha disminuido de manera significativa la morbimortalidad de los pacientes con infección por el virus de la inmunodeficiencia adquirida (VIH) convirtiendo a la infección por VIH en una patología crónica y al paciente VIH+ en un paciente cada vez más mayor, no exento de otras comorbilidades médicas o eventos no SIDA. En este nuevo escenario, se hace indispensable mejorar el conocimiento acerca de las diferentes comorbilidades y los factores de riesgo que las condicionan con el propósito de establecer estrategias en el ámbito de la prevención, del diagnóstico y del tratamiento específicas para la población con infección por VIH. Una de las principales comorbilidades en las personas infectadas por VIH es la coinfección por el virus de la hepatitis C (VHC), que condiciona en gran medida el desarrollo de enfermedad hepática y también extrahepática.

En base a lo anteriormente expuesto, es importante conocer las características epidemiológicas y clínicas de los pacientes VIH+ de nuestra área sanitaria, sus comorbilidades y los eventos que condicionan su vida como las hospitalizaciones y la mortalidad. Además, es pertinente analizar el impacto que supone la coinfección en términos de morbimortalidad de causa hepática y no hepática.

En la presente tesis se desarrollaron tres estudios:

- **ESTUDIO 1.** Analizó todas las hospitalizaciones de pacientes VIH en el CHUAC en el periodo 1993-2013. Se incluyeron 6917 hospitalizaciones que correspondieron a 1937 pacientes (37% coinfectados VIH/VHC). La tasa de hospitalización mostró una reducción progresiva desde 30,7/100 pacientes

(IC95%:27,7-33,8) en 1993 a 19,9/100 pacientes (17,7-22,2) en 2013, siendo esta reducción más significativa después de 1996 (4,9% anual), pero este descenso fue menos acusado en los pacientes coinfectados VIH/VHC (1,7% anual). Las hospitalizaciones motivadas por enfermedades infecciosas y trastornos psiquiátricos disminuyeron significativamente en el segundo periodo de estudio (2003-2013), mientras que aumentaron aquellas relacionadas con neoplasias, enfermedad cardiovascular, gastrointestinal y enfermedades respiratorias crónicas. En los pacientes coinfectados VIH/VHC, buena parte de las hospitalizaciones y de las muertes fueron motivadas por enfermedad hepática.

- **ESTUDIO 2.** Comparó la mortalidad relacionada con enfermedad hepática y las hospitalizaciones motivadas por causa hepática en pacientes con infección por VIH que han sido expuestos o no al VHC. Se incluyeron resultados de 2379 pacientes VIH (1390 VIH monoinfectados, 146 aclaradores espontáneos de VHC y 843 con coinfección crónica VIH/VHC) en el periodo 1993-2014. La tasa de mortalidad relacionada con enfermedad hepática en los pacientes coinfectados VIH/VHC fue de 10,01 por 1000 paciente-años frente al 3,84 por 1000 paciente-años en el grupo de VIH monoinfectados (p<0.001). La fracción de mortalidad y hospitalización atribuíble a la infección crónica por VHC fue 0.61 y 0.74, respectivamente. No se encontraron diferencias en eventos relacionados con hígado entre pacientes VIH monoinfectados frente a los que aclararon espontanánemente el VHC.

- **ESTUDIO 3**. Evaluó la incidencia de cáncer en pacientes con infección por VIH en el área sanitaria de A Coruña en el periodo 1993-2014 y permitió su comparación con la población coinfectada VIH/VHC y con la observada en la población general (utilizando la herramienta GLOBOCAN 2012), calculando la razón de incidencia estandarizada (RIE). 185 pacientes (117 VIH monoinfectados y 68 coinfectados VIH/VHC) desarrollaron cáncer en una cohorte de 26580 paciente-años, con una tasa de incidencia cruda de 696 neoplasias por 100000 persona-años, mayor que en la población general (RIE=3,8). La tasa de incidencia cruda de NNDS en pacientes coinfectados VIH/VHC fue 415.0 (RIE=3,4), significativamente mayor que en VIH monoinfectados (377,3; RIE=1,8). Tras el ajuste, los pacientes coinfectados VIH/VHC tenía una mayor incidencia acumulada de NNDS que los pacientes VIH monoinfectados (HR=1,80), incluso después de excluír del análisis el hepatocarcinoma (HR=1,26).

Resumo

A introducción do tratamiento antirretroviral (TAR) de alta eficacia disminui de maneira significativa a morbimortalidade dos doentes con infección polo virus da inmunodeficiencia humana (VIH) convertindo a infección por VIH nunha patoloxía crónica e ó doente nun doente cada vez máis maior, non exento de outras comorbilidades médicas ou eventos non SIDA. Neste novo escenario, faise indispensable mellorar o coñecemento acerca das diferentes comorbilidades e os factores de risco que as condicionan co propósito de establecer estratexias no ámbito da prevención, do diagnóstico e do tratamento específicas para a poboación con infección por VIH. Unha das principais comorbilidades nas persoas infectadas é a coinfección polo virus da hepatite C (VHC), que condiciona en gran medida o desenvolvemento de enfermidade hepática e tamén extrahepática.

En base ó anteriormente exposto, é importante coñecer as características epidemiolóxicas e clínicas dos doentes VIH+ da nosa área sanitaria, as súas comorbilidades e os eventos que condicionan a súa vida, como as hospitalizacións e a mortalidade. Ademáis, e pertinente analizar o impacto que supón a coinfección en termos de morbimortalidade de causa hepática e extrahepática.

Na presente tese desenvolvéronse tres estudos:

- **ESTUDO 1**. Analizou todas as hospitalizacións does doentes VIH no CHUAC no periodo 1993-2013. Incluíronse 6917 hospitalizacións que corresponderon a 1937 doentes (37% coinfectados VIH/VHC). A tasa de hospitalización mostrou unha reducción progresiva dende 30,7/100 doentes (IC 95%:27,7-33,8) en 1993 a 19,9/100 doentes (IC 95%:17,7-22,2) en 2013, sendo esta reducción máis significativa despóis de 1996 (4,9% anual), pero

6

este descenso foi máis acusado nos doentes coinfectados VIH/VHC. As hospitalizacións motivadas por enfermidades infecciosas e trastornos psiquiátricos diminuíron significativamente no segundo periodo do estudo (2003-2013), mentras que aumentaron aquelas relacionadas con neoplasias, enfermidades cardiovasculares, gastrointestinales e enfermidades respiratorias crónicas. Nos doentes coinfectados VIH/VHC, boa parte das hospitalizacións e das mortes foron motivadas por enfermidade hepática.

- **ESTUDO 2**. Comparou a mortalidade relacionada con enfermidade hepática e as hospitalizacións motivadas por causa hepática nos doentes con infección por VIH que foron expostos ou non ó VHC. Incluíronse resultados de 2379 doentes VIH (1390 VIH monoinfectados, 146 aclaradores espontáneos do VHC e 843 con coinfección crónica por VHC) no periodo 1993-2014. A tasa de mortalidade relacionada con enfermidade hepática nos doentes coinfectados VIH/VHC foi de 10,01 por 1000 doentes-anos fronte ó 3,84 por 1000 doentes-anos propio dos VIH monoinfectados (p<0,001). A fracción de mortalidade e hospitalización atribuíble á infección crónica por VHC foi 0.61 e 0.74, respectivamente. Non se atoparon diferencias nos eventos relacionados con enfermidade hepática entre doentes VIH monoinfectados fronte ós que aclararon espontáneamente o VHC.

- **ESTUDO 3.** Evaluou a incidencia de cáncer en doentes con infección por VIH na área sanitaria de A Coruña no periodo 1993-2014 e permitiu a súa comparativa coa poboación coinfectada VIH/VHC e coa observada na

poboación xeral (utilizando a ferramenta GLOBOCAN 2012), calculando a razón de incidencia estandarizada (RIE). 185 doentes (117 VIH monoinfectados e 68 coinfectados VIH/VHC) desenvolveron cáncer nunha cohorte de 26580 doentes-anos, cunha tasa de incidencia cruda de 696 neoplasias por 100000 persoa-anos, maior que na poboación xeral (RIE=3,8). A tasa de incidencia cruda de neoplasia non definitoria de SIDA (NNDS) nos pacientes coinfectados VIH/VHC foi 415.0 (RIE=3,4), significativamente maior que en VIH monoinfectados (377,3;RIE=1,8). Tras ser axustado, os doentes coinfectados VIH/VHC tiñan unha maior incidencia acumulada de NNDS que os doentes monoinfectados (HR=1,80), incluso despóis de excluír do análise o hepatocarcinoma (HR=1,26).

Abstract

High efficacy antiretroviral treatment (ART) introduction has significantly decreased the morbidity and mortality of HIV+ patients, making HIV infection a chronic disease. and HIV+ patient an older patient with other medical comorbidities or non-AIDS events. In this new scenario, it is essential to improve knowledge about the different comorbidities and risk factors with the purpose of perfom new strategies in the area of prevention, diagnosis and treatment specific to HIV population . One of the main comorbidities in people infected with HIV is HCV coinfection, which could modified liver and extrahepatic disease.

Therefore, it is important to know the epidemiological and clinical characteristics of HIV + patients in our health area, their comorbidities and the events such as hospitalizations and mortality. In addition, it is necessary to analyze the impact of coinfection in terms of hepatic and non-hepatic morbidity and mortality.

In this thesis, three studies has been developed:

- **STUDY 1**. All the hospitalizations of HIV patients in the CHUAC in the period 1993-2013 were analysed. We included 6917 hospitalizations corresponding to 1937 patients (37% HIV/HCV coinfected). The hospitalization rate showed a progressive reduction from 30.7/100 patients (IC95%: 27.7-33.8) in 1993 to 19.9/100 patients (17.7-22.2) in 2013; a higher reduction was seen after 1996 (4.9% per year), but this decrease was less pronounced in HIV / HCV coinfected patients (1.7% per year). Hospitalizations motivated by infectious diseases and psychiatric disorders decreased significantly in the second period (2003-2013), while those related to malignancies, cardiovascular diseases,

gastrointestinal diseases and chronic respiratory diseases increased. In HIV/HCV coinfected patients, a large proportion of hospitalizations and deaths were due to liver disease.

- **STUDY 2**. Liver disease related mortality and hospitalizations due to hepatic causes were compared in patients with HIV infection who have been exposed to HCV or not. 2,379 HIV patients (1390 HIV monoinfected, 146 with HCV spontaneous clearence and 843 HCV / HCV coinfected) were included between 1993-2014. Liver disease related mortality rate in coinfected HIV/HCV patients were 10.01 per 1000 patient-years versus 3.84 per 1000 patient-years in the HIV monoinfected group (p <0.001). The fractions of liver related mortality and liver-related hospitalizations attributable to chronic HCV coinfection were 0.61 and 0.74, respectively. There were no differences in   liver-related events between   HIVmonoinfected   individuals   and those who   spontaneously cleared HCV.

- **STUDY 3**. Cancer incidence in HIV infected patients between 1993 and 2014 In La Coruña was assessed and compared with the HIV/HCV coinfected population and with the general population (with GLOBOCAN 2012 Tool), using the standardized incidence ratio (SIR). 185 patients (117 HIV monoinfected and 68 HIV / HCV coinfected) developed cancer in a cohort of 26,580 patient-years, with a crude incidence rate of 696 malignancies per 100,000 person-years, higher than in the general population (SIR = 3, 8). The crude incidence rate of NNDS in HIV / HCV coinfected patients was 415.0 (SIR = 3.4), significantly higher than in   monoinfected HIV (377.3; SIR = 1.8). After adjustment, HIV / HCV coinfected   patients had a higher cumulative incidence of NNDS than

monoinfected HIV   patients (adjusted   hazard   ratio=1.80),   even   when

excluding hepatocellular carcinomas (adjusted hazard ratio=1.26).

INTRODUCCIÓN

1.1 Infección por el virus de la inmunodeficiencia humana (VIH). Aspectos generales.

El VIH pertenece a la familia retroviridae, del género lentivirus, y fue identificado en 1983 como el agente etiológico del síndrome de inmunodeficiencia adquirida (SIDA) [Barré-Sinoussi *et al*. 1983; Gallo *et al*. 1983]. La infección por VIH se caracteriza por un deterioro progresivo del sistema inmunológico como consecuencia de un descenso paulatino del nivel de linfocitos T CD4+, principal diana del virus [Barré-Sinoussi *et al*. 1983; Popovic *et al*. 1983]. A medida que evoluciona la infección, el progresivo deterioro del sistema inmunológico favorece la aparición de infecciones por microorganismos patógenos u oportunistas.

Existen dos tipos de VIH, el VIH-1 y el VIH-2, originados por transmisiones zoonóticas independientes. La infección por VIH-2 es más prevalente en África occidental y a nivel mundial afecta aproximadamente a un millón de personas [Rowland-Joness *et al*. 2007; Luft *et al*. 2011]. Se caracteriza por presentar una menor carga viral y una caída de linfocitos T CD4+ más lenta de manera que, los sujetos infectados por VIH-2 se mantienen asintomáticos durante períodos de tiempo muy prolongados.

La fisiopatología del SIDA es un proceso extraordinariamente complejo en el que se encuentran implicados mecanismos patgénicos muy diferentes, algunos de los cuales todavía no son completamente comprendidos. Una vez tiene lugar la entrada del virus en el organismo, se inicia una infección en la que se pueden diferenciar distintas fases o estadios evolutivos relativamente bien definidos, aunque no siempre identificados clinicamente, con una duración variable que depende de distintos factores

_____

relacionados tanto con el virus como con el huésped. Las distintas fases en que se

divide la historia natural de la infección son: la infección aguda, desde el momento de

la infección hasta que se produce la seroconversión; la fase crónica, de duración

variable y más o menos sintomática, y una fase final a partir del diagnóstico de SIDA.

Así, el estadío avanzado de la infección o SIDA se caracteriza por ser una fase con

recuento de células CD4+ inferiores a 200 cél/μL, aumento en la tasa de replicación

viral, descenso de la actividad de los linfocitos T citotóxicos anti-VIH, destrucción de la

arquitectura linfática, síntomas constitucionales y desarrollo de infecciones

oportunistas. Afortunadamente, la aparición del tratamiento antirretroviral de alta

eficacia (TARGA) en 1996 [Gulick RM et al,1997] ha modificado de forma espectacular

la evolución natural de estas fases, lo que ha producido un cambio notable en la

morbi-mortalidad de estos pacientes, de manera que actualmente buena parte de los

pacientes infectados por VIH que fallecen lo hacen por causas sin relación directa con

la infección, por comorbilidades no relacionadas con SIDA, destacando entre ellas las

complicaciones hepáticas asociadas al virus de la hepatitis C (VHC).

1.2 Epidemiología de la Infección por VIH.

La vigilancia epidemiológica de la infección por el VIH y del SIDA tiene como

objetivo cuantificar la magnitud de la epidemia y definir las características de la

población afectada, en particular en relación con las formas de contagio del virus. La

epidemia ha evolucionado de forma diferente y con distinta intensidad en las diversas

áreas geográficas, en función de los factores sociodemográficos, culturales,

económicos y políticos de cada zona. Por todo ello, el conocimiento y la monitorización

de la distribución de la epidemia de VIH/SIDA en una comunidad determinada

_____

constituye una herramienta básica para establecer y evaluar las intervenciones preventivas necesarias, que influirán en el futuro desarrollo de la epidemia.

La infección por VIH continúa siendo un problema de salud pública a nivel mundial, cada año se diagnostican más de 2 millones de nuevas infecciones, y más de 36 millones de personas conviven con esta infección, de los cuales, más de 2,5 millones son niños menores de 15 años [WHO/UNAIDS 2015]. Según la Organización Mundial de la Salud (OMS), la tasa de infecciones por VIH para la Unión Europea se sitúa en 5,7 por cada 100000 habitantes. En España, más de 39000 nuevos pacientes se han diagnosticado de infección por VIH desde el año 2003 y en el 2015 se notificaron 3428 nuevos diagnósticos, lo que supone una tasa de 7,39 por cada 100000 habitantes sin corregir por retraso en la notificación. Tras corregir por este retraso, se estima que la tasa para 2015 será de 9,44 por 100.000 habitantes cuando se haya completado la notificación de todos los diagnósticos realizados ese año.[Ministerio de Sanidad-España, 2016].

La vía de transmisión, varía en función del área geográfica, lo que refleja la diversidad en la epidemiología del VIH en Europa. En España en el año 2015, la transmisión entre hombres que tienes sexo con hombres (HSH) fue la vía de transmisión más frecuente (53,9%) seguida de la heterosexual (26,0%) y los usuarios de drogas vía parenteral (UDVP) (4,4%); siendo el 32.1% de los nuevos diagnósticos de infección por VIH de origen extranjero [Ministerio de Sanidad-España, 2016]. A pesar de los esfuerzos preventivos realizados en la última década en Europa, el número de nuevos diagnósticos entre HSH se ha incrementado en un 33% desde el año 2004, representando los jóvenes entre 15 y 24 años el 11% de todos los diagnósticos registrados. No obstante, las medidas preventivas sí han conseguido disminuir el

_____

número de nuevas infecciones entre usuarios a drogas por vía parenteral en un 36%, así como la transmisión vertical y por transfusión sanguínea, siendo actualmente su prevalencia inferior al 1% [HIV/AIDS Surveillance in Europe, 2013].

En Europa, se estima que hasta el 30% de las personas infectadas por VIH desconocen su estado serológico, con una incidencia de diagnóstico tardío (recuento de CD4 inferior a 350 cél/µL y/o la presencia de una enfermedad definitoria de SIDA al diagnóstico) cercana al 50% de todos los nuevos casos de infección por VIH [Sabin *et al*. 2010]. La alta prevalencia de diagnóstico tardío tiene repercusiones negativas ya que se asocia a mayores tasas de transmisión de la infección, peor respuesta al TARGA y mayor riesgo de toxicidad al mismo, menor supervivencia, e incremento de los costes sanitarios [Moreno *et al*. 2010; Sabin *et al*. 2010; Camoni *et al*. 2013]. En España, el 46,2% de las nuevas infecciones por VIH ocurrieron en el contexto de un diagnóstico tardío. Durante el periodo 2009-2014 la tasa de diagnóstico tardío no ha disminuido en ninguna categoría de transmisión, aunque entre HSH es menor que en el resto [Ministerio de Sanidad-España, 2016]. Es importante, por tanto, asegurar un acceso igualitario a todos los grupos de población para la prevención, diagnóstico y tratamiento de la infección por VIH, para así poder alcanzar los objetivos del 90% de las personas con infección por VIH diagnosticadas, 90% de las personas diagnosticadas con acceso a los cuidados sanitarios y al tratamiento, y 90% de las personas tratadas con supresión virológica [HIV/AIDS Surveillance in Europe, 2013].

Estudios recientes en nuestro medio [Pernas *et al*. 2015] han confirmado no solo una incremento de nuevas infecciones en los ultimos años sino también del cambio de perfil del paciente diagnosticado de infección por VIH, predominando en ese nuevo perfil el varón joven cuya ruta de transmisión ha sido la sexual, con un

_____

predominio de hombres que tiene sexo con hombres (HSH); además, y a pesar de que la reducción del diagnóstico tardío se considera una prioridad de salud pública, en dicha cohorte el porcentaje ascendió al 53%.

1.3 Comorbilidades asociadas a la infección por VIH.

La alta eficacia del tratamiento antirretroviral (TAR) actual ha permitido convertir a la infección por VIH en una infección crónica en países con acceso al tratamiento [Mocroft *et al*. 1998; Palella *et al*. 1998; Cohen *et al*. 2011]. Consecuentemente, como resultado, se ha observado de manera progresiva una disminución de la mortalidad derivada de eventos definitorios de SIDA y un aumento notorio de la esperanza de vida [Mocroft et al, 2003, Sackoff et al, 2006]. En la figura 1 se muestra gráficamente el envejecimiento progresivo de la población americana con infección por VIH, según los Centers for Prevention and Disease Control (CDC), con una estimación de hasta el 70% de pacientes VIH mayores de 50 años prevista para el año 2020. Es por ello que la incidencia de otras comorbilidades inicialmente no relacionadas con SIDA han aumentado, entre ellas, las enfermedades cardiovasculares, las neoplasias no definitorias de SIDA (NNDS), las enfermedades respiratorias crónicas, etc., entendiendo como razones capitales no solo la mayor esperanza de vida y el envejecimiento *per se*, sino también la sobrerrepresentación de factores de riesgo clásicos inherentes al periodo de senectud, la toxicidad relacionada con el TAR de larga evolución, la coinfección con otras enfermedades virales, la inflamación y la inmunoactivación persistente relacionadas con el propio virus e incluso tras la supresión virológica del mismo.

Personas con VIH

Edad>50 en 2011

Edad>50 en 2015

Edad >50 en 2020

1,25 mill

37%

50%

70%

Figura 1. Envejecimiento de la población con infección por VIH en USA. Adaptado de Centers for Disease and Prevention Control Surveillance Data, 2017.

Este cambio en el espectro de enfermedades en el paciente VIH va a tener implicaciones en el cuidado de este colectivo, entre ellas, unas mayores y nuevas demandas en el sistema de salud, y una necesidad de garantizar estudios para poder conocer los factores de riesgo relacionados y la carga de la enfermedad en esta población. Así, las enfermedades cardiovasculares ya son una de las principales causas de morbi-mortalidad en población VIH [Smith et al, 2014; Morlat et al,2014], siendo el propio virus un factor de riesgo independiente cuando se controlan los factores de riesgo clásicos. Aunque la comorbilidad respiratoria no SIDA ha recibido menos atenciones, los estudios han demostrado que el propio virus puede aumentar la susceptibilidad a los daños del tabaco y la inflamación derivada deteriora más precozmente la función pulmonar [Collini et al, 2016; Drummond et al, 2014].

Especial consideración tiene la morbi-mortalidad relacionada con enfermedad hepática en este colectivo. Si bien suele ir de la mano de la coinfección por otros virus hepatotropos (VHC, VHB), puede también ocurrir en ausencia de hepatitis crónicas virales [Smith et al, 2010]. Otras comorbilidades asociadas a progresión de la fibrosis y deterioro de la función hepatocelular son más prevalentes en las personas infectadas por VIH, como son el consumo de alcohol, el síndrome metabólico o la toxicidad por algunos fármacos. La enfermedad hepática por depósito graso no alcohólico es especialmente prevalente entre las personas infectadas por VIH y se ha relacionado, entre otras cosas, con la duración de la infección por VIH [Handigan et al, 2007]

Desde una perspectiva de salud pública es importante conocer las tendencias y características de las hospitalizaciones, reingresos y tasa de mortalidad intrahospitalaria en personas con infección por VIH. La tasa de reingreso a los 30 días es un indicador de calidad asistencial [Berry et al, 2013]. Las razones del ingreso hospitalario se han ido modficando en la era TAR. Así, las enfermedades definitorias de SIDA están menos representadas en la actualidad en detrimento de patologías más habituales en población general, en relación al cambio de perfil del paciente con VIH, más envejecido y con mayor número de comorbilidades, y el mejor control de la infección por VIH [Kim et al, 2013;Crowell et al, 2014].

A pesar de un mejor cuidado y manejo de estos pacientes, la tasa de hospitalizaciones sigue siendo mayor que la de la población general [Buchaczk et al, 2008; Crum-Cianflone et al, 2010]. Un estudio trasnsversal americano llevado a cabo en año 2009 estimó una tasa de 26,6 por 100 persona-años (P_A) en pacientes con infección por VIH frente a un 11,9 por 100 P_A en población general. Así mismo, la mortalidad intrahospitalaria ha disminuido respecto a la era pre-TAR, pero continúa

_____

siendo elevada, mayor que en población general, y a expensas (casi tres cuartas partes) de eventos no definitorios de SIDA [Kim et al, 2013].

Un estudio de cohortes danés [Obel et al, 2011] demostró el impacto que suponía en la supervivencia de pacientes con infección por el VIH, determinados factores relacionados con el VIH (carga viral indetectable o situación inmunológica con CD4> 200 cel/uL), factores no relacionados con el VIH (como el abuso de alcohol y otras drogas), así como la presencia de enfermedades concomitantes (entre ellas la coinfección VIH/VHC). La supervivencia fue inferior respecto a la población general en el subgrupo de pacientes VIH con exposición al abuso de sustancias tóxicas, seguido por aquellos con mayor comorbilidad y los que tan solo tenían mala situación inmunológica. Por otro lado, los pacientes VIH en tratamiento con buena situación inmunovirológica se aproximaban razonablemente a términos de supervivencia a la población general, tal y como se refleja en la Figura 2.

Teniendo en cuenta el cambio de perfil de paciente VIH y la continua mejora en términos de mejor adherencia y tolerabiliad del TAR, con el subsiguiente impacto en una mejor situación inmuno-virológica, es razonable destacar el papel que van a desarrollar las comorbilidades en la evolución de estos pacientes, y muy especialmente, el papel que juegue la coinfección por VHC en todo ello.

_____
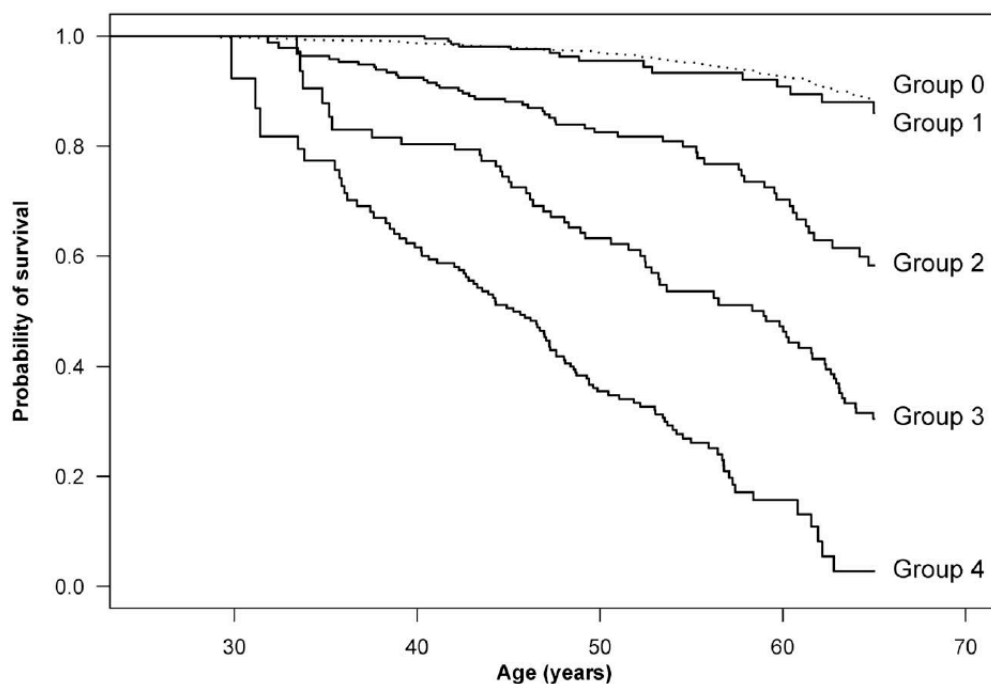
Figura 2. Impacto de los factores de riesgo en la supervivencia de pacientes VIH. Adaptado de Obel et al, 2011. Grupo 0: población general. Grupo 1: pacientes VIH sin factores de riesgo de VIH (carga viral detectable y/o CD4 < 200 cel/ul), sin comorbilidad ni consumo de tóxicos. Grupo 2: pacientes VIH con FR pero sin comorbilidad ni consumo de tóxicos. Grupo 3: pacientes VIH con comorbilidad, sin consumo de tóxicos. Grupo 4: pacientes VIH con consumo de tóxicos.

A pesar de estas evidencias, quedan numerosas cuestiones por resolver, como el impacto de estos eventos no-SIDA en la era de TAR actual, cual es su óptimo manejo clínico, las medidas de screening, cómo hacer el seguimiento de este nuevo perfil de paciente, su tolerancia al TAR con el condicionante de más añoso y con más comorbilidad, entre otras. Se estima que para el año 2030 los pacientes con infección por VIH presentarán tres o más comorbilidades y más de la mitad tendrá polifarmacia.

En este contexto, se necestian estudios para dar respuesta a estas incógnitas, algunas de ellas ya en marcha, como la cohorte danesa incluida en el COCOMO study [Ronit et al, 2016], la cohorte holandesa de Age_HIV study [Schouten et al, 2014], entre otras.

1.4 Coinfección VIH/VHC.

La infección por VHC es frecuente entre las personas infectadas por VIH; se estima que, aproximadamente, a nivel mundial hay unos 7 millones de personas que están co-infectadas por ambos virus [Kim et al, 2009]. De hecho, la infección por VHC se encuentra en hasta un 10-30% de los pacientes con VIH y en casi hasta el 90% de los pacientes VIH que son UDVP [Sherman et al, 2012; Mena et al, 2014].

El VIH y el VHC tienen efectos deletéreos sinérgicos que aceleran la inmunopatogénesis de cada virus y por tanto modifican la historia natural de cada uno. El VHC *per se* ha sido relacionado con aumento de hospitalizaciones por cualquier causa e incremento de la morbimortalidad [Soriano et al, 2015]. Se estima que al menos un 30% de los pacientes con VHC desarrollarán cirrosis y alrededor del 1-4% de ellos sufrirán un hepatocarcinoma.

La historia natural de la enfermedad hepática por VHC está acelerada en los pacientes VIH. Esto condiciona una mayor progresión de fibrosis hepática comparada con los pacientes VHC monoinfectados, según algunas series hasta 2-6 veces mayor en el paciente coinfectado VIH/VHC [Brau et al, 2007, Salmon-Ceron et al, 2009, Weber et al, 2006, Castellanos et al, 2008], lo que supone un aumento de las complicaciones derivadas de la fibrosis, entre ellas, las descompensaciones hepáticas; además, una vez ocurre una descompensación hepática es sabido que los pacientes coinfectados

_____

VIH/VHC se morirán más precozmente que aquellos VHC monoinfectados [Pineda et al, 2007].

El papel del VHC en la progresión del daño hepático es incuestionable. Sin embargo, hay otros muchos factores que contribuyen al desarrollo de enfermedad hepática en pacientes con infección por VIH, entre otros, la propia replicación del VIH, la inmunoactivación e inflamación, la disfunción inmune, las infecciones oportunistas, la exposición a factores de riesgo (alcohol y otras drogas), las enfermedades metabólicas, los agentes antirretrovirales, etc… [Krooij et al, 2016; Fernandez-Montero et al, 2014]. Estos factores suelen quedar enmascarados o pasados por alto debido al principal papel que tiene la infección por el VHC en la progresión de la enfermedad hepática en pacientes coinfectados VIH/VHC.

Estudios previos en poblacion VHC monoinfectada demostraron que alcanzar la respuesta viral sostenida tras el tratamiento se asociaba a menor riesgo de fracaso hepático, menor riesgos de desarrollo de hepatocarcinoma y menor riesgo de mortalidad de causa hepática y extrahepática [Lee et al, 2014]. En pacientes VIH/VHC coinfectados el impacto del tratamiento del VHC a largo plazo no ha sido bien evaluado mediante estudios prospectivos. Sí hay estudios retrospectivos [Berenguer et al, 2009] que demuestran que los pacientes no respondedores al tratamiento tenían al menos nueve veces más riesgo de eventos relacionados con el hígado que aquellos que alcanzaban la RVS, así como una reducción de mortalidad relacionada con hígado y mortalidad por cualquier causa [Shermman et al 2012; Giordano et al 2004]. Todos estos estudios están realizados en la época en que se utilizaban tratamientos basados en interferón, donde un importante número de pacientes no eran elegibles para el tratamiento, suponiendo en muchos casos un sesgo de selección (especialmente

_____

marcado en pacientes coinfectados por el VIH, con menor acceso al tratamiento basado en interferón), lo que puede magnificar el efecto beneficioso de la RVS. No existen de momento datos en la nueva era de los antivirales de acción directa frente al VHC, que han supuesto un acceso masivo al tratamiento de todos los grupos de pacientes, con altas tasas de RVS.

En un estudio multicéntrico europeo publicado recientemente [Peters et al, 2016] se comparó el riesgo de muerte por cualquier causa y muerte relacionada con hígado según respuesta al tratamiento de VHC basado en regímenes con interferón en población coinfectada VIH/VHC; aquellos pacientes con respuesta viral sostenida (RVS) tenían una significativa mejora en términos de mortalidad comparado con los pacientes no respondedores, aunque de una forma modesta (HR 1,53). Cuando compararon la mortalidad no relacionada con enfermedad hepática, no encontraron diferencias entre respondedores y no respondedores, a diferencia de estudios previos [Berenguer et al, 2012] en los que sí observaban asociación, lo que denota incertidumbre y controversia a la hora de interpretar trabajos en los que se relacionaba la infección crónica por VHC con enfermedades cardiovasculares, desórdenes linfoproliferativos, enfermedades extrahepáticas o enfermedades autoinmunes sistémicas. De ser cierta esta aseveración, se podría esperar que la mortalidad no relacionada con hígado también se reduciría con la RVS. En este sentido, también podrían tener importancia los factores ambientales y de estilo de vida en los pacientes que alcanzan la curación respecto a los que no [Innes et al, 2015]. Es posible que todos estos datos de estudios pasados no apliquen al escenario actual, en el que el acceso masivo a los nuevos antivirales de acción directa, de elevada eficacia y tolerabilidad, podrían prevenir no sólo las complicaciones relacionadas con el hígado

_____

sino también aquellas no relacionadas, así como la mortalidad por cualquier causa, pero se necesitan todavía estudios prospectivos que lo demuestren.

En una gran cohorte española de pacientes con infección por VIH controladores de élite y controladores con viremia detectable con un largo seguimiento, se observó una tasa no despreciable de eventos no definitorios de SIDA, si bien en menor medida que en aquellos pacientes sin un control espontáneo de la infección [Dominguez-Molina et al, 2016]. La coinfección VIH/VHC fue el pincipal factor asociado al desarrollo de eventos no definitorios. Aunque los eventos relacionados con hígado fueron los más prevalentes, éstos sólo representaban el 30% de todos los eventos en los controladores de la infección por VIH, lo que sugiere un daño extrahepático atribuído a la infección por VHC. Estos resultados ponen de manifiesto la importancia de un tratamiento temprano frente al VHC en pacientes VIH tanto controladores como no, así como apoyar el reto de la erradicación del VHC en población infectada por el VIH.

1.5 Neoplasias en pacientes con infección por VIH.

El cáncer ha emergido como una de las principales causas de morbi-mortalidad en la actualidad en los pacientes con infección por VIH. La incidencia de cáncer en esta población se espera que aumente de manera notoria dado el aumento de la esperanza de vida y el envejecimiento de la población, unido a otras cuestiones inherentes a la propia infección por VIH. Son muchas las razones postuladas, entre ellas, los avances en el tratamiento antiviral, los cambios demográficos de la población, la mayor prevalencia de factores de riesgo oncogénicos más clásicos, la coinfección por otros virus oncogénicos, los efectos directos del propio VIH, la inmunoactivación de factores que conlleva un estado proinflamatorio, la inmunodepresión, la reconstitución inmune

y el hecho de un mayor tiempo de exposición a carcinógenos [Silverberg et al, 2009; Worm et al, 2013; Borges et al,2013].

Históricamente, la infección por VIH se ha asociado con determinadas neoplasias características llamadas oportunistas por su relación con el mayor estado de inmunodeficiencia, entre ellas, el sarcoma de Kaposi, algunos linfomas no hodgkin y el cáncer de cérvix, tal y como se refleja en la Figura 4. Sin embargo, desde la introducción del TAR la incidencia de estas neoplasias ha disminuido acorde con un mejor control de la infección y una mayor esperanza de vida. Como resultado, se ha observado un aumento en la incidencia de neoplasias no definitorias de SIDA (NNDS) [Meijide et al, 2013]. Es sabido que estas neoplasias se presentan a una edad más temprana, y habitualmente llevan un curso evolutivo más agresivo [Nguyen et al, 2010]. Numerosos estudios han demostrado no solo la asociación sino incluso la mayor prevalencia de NNDS comparado con la población general (cáncer de colon, cáncer de pulmón, etc…). Este incremento de NNDS se ha observado en población VIH y también en población coinfectada VIH/VHC [Hurtado-Cordovi et al,2016] . La relación entre infección crónica por VHC y el hepatocarcinoma está bien establecida, pero en trabajos previos también se ha constatado la relacion con otras neoplasias, como el cáncer de colon y el LNH, entre otros [Rustagi T et al, 2014], si bien se necesitan más datos consistentes en población coinfectada VIH/VHC que relacionen el papel oncogénico del VHC en el desarrollo de neoplasias más alla del hepatocarcinoma.

Con el cambio en la epidemiología del cáncer durante la infección por VIH se ha propuesto una nueva clasificación en detrimento de la anteriormente mencionada que dividía los tipos de cancer en NDS y NNDS. Así, teniendo en cuenta la interrelación

_____

entre el propio VIH, la inmunosupresión y las coinfecciones virales en el desarrollo de

la carcinogénesis, se puede diferenciar entre cáncer relacionado con agentes

infecciosos y cáncer no relacionado.
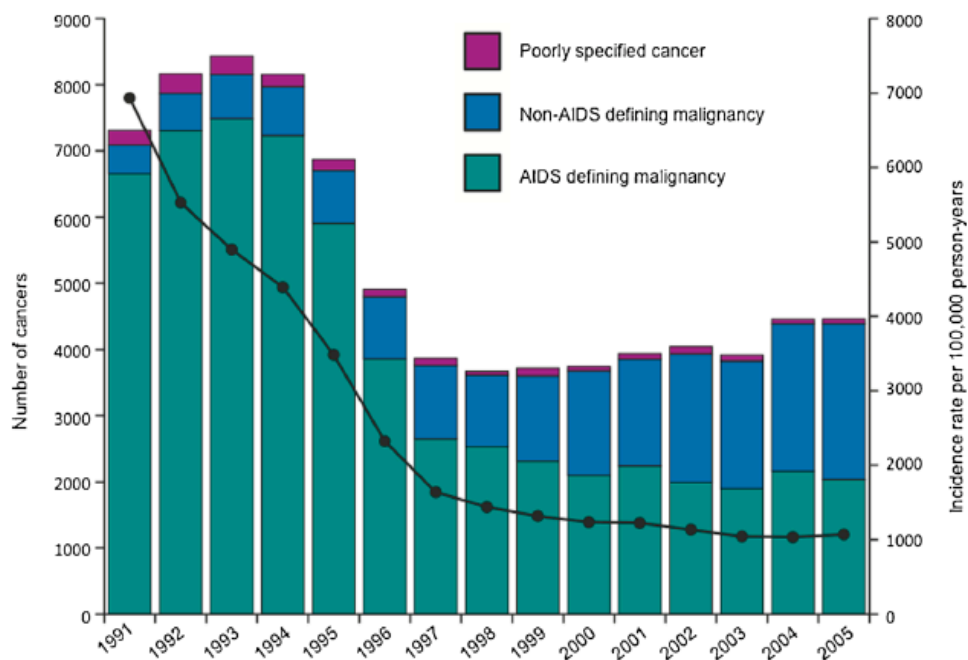
Figura 3: Tasa de incidencia de cáncer en pacientes VIH. Adaptado de Brickman C et al, 2015. Las barras señalan los casos estimados de cáncer y la línea de puntos la tasa de incidencia estandarizada de la población americana ajustada por edad, sexo y raza. Se diferencian tumores definitorios (verde) y no definitorios (azul) de SIDA.

Estudios recientes han demostrado que el inicio inmediato del TAR reduce

significativamente el riesgo de desarrollo de cáncer, especialmente a expensas de

aquellas neoplasias relacionadas con agentes infecciosos. Sin embargo, tras el ajuste

por la situación inmunovirológica, esa significación estadística se atenuaba en las

_____

neoplasias no relacionadas con agentes infecciosos, en principio, en probable relación

con el escaso tiempo de seguimiento evolutivo de la cohorte [Borges et al, 2016].

OBJETIVOS

La introducción del TAR de alta eficacia ha disminuido de manera significativa la morbimortalidad de los pacientes VIH+ convirtiendo a la infección por VIH en una patología crónica. Uno de los mayores retos en el cuidado del paciente con infección por VIH será conocer el óptimo manejo de los eventos no SIDA, teniendo en cuenta que el continuo envejecimiento de esta población. En este escenario, es necesaria más información acerca de las diferentes comorbilidades, los factores de riesgo que condicionan estos eventos y establecer las estrategias preventivas, diagnósticas y terapéuticas específicas para la población con infección por VIH. Una de las principales comorbilidades en esta población es la coinfección por el VHC, que dado el sinergismo entre ambas infecciones en la inmunopatogénesis de cada virus, no solo condiciona un papel a nivel hepático sino tambien a expensas de efectos extrahepáticos.

En base a lo anteriormente expuesto, es importante conocer las características epidemiológicas, clínicas y virológicas de los pacientes VIH+ de nuestra área sanitaria, así como las comorbilidades que condicionen la necesidad de hospitalización a lo largo del seguimiento clínico, con el objetivo de optimizar las estrategias de diagnóstico y manejo clínico de los pacientes con infección por VIH en general y de los pacientes con coinfección VIH/VHC en particular. Además, es importante analizar el impacto que supone la coinfección en términos de morbimortalidad no solo de causa hepatica sino también extrahepática. En este contexto se desarrolló esta tesis con los siguientes objetivos:

1. Evaluar las tendencias en las hospitalizaciones, reingresos y mortalidad en pacientes con infección por VIH seguidos en el área sanitaria de A Coruña en el periodo 1993-2014, analizando en particular el papel de la coinfección por el VHC en esta población.

2. Comparar la mortalidad relacionada con enfermedad hepática y las hospitalizaciones relacionadas con enfermedad hepática en pacientes con infección por VIH con o sin exposición al VHC, y estimar la fracción atribuible a enfermedad hepática debido a la coinfección por el VHC.

3. Analizar la incidencia de cáncer, una de las principales causas de morbi-mortalidad de los pacientes con infección por VIH en la era TAR, y determinar el riesgo de cáncer añadido en población VIH y VIH/VHC respecto a la población general.

PACIENTES Y MÉTODOS

3.1 Tipo y ámbito de estudio.

Estudio de cohortes observacional longitudinal retrospectivo realizado en el Complejo Hospitalario Universitario de A Coruña (CHUAC). El CHUAC es un hospital terciario universitario de 1422 camas. La población de influencia es de aproximadamente 550.000 habitantes. La Unidad de VIH y Hepatitis del Servicio de Medicina Interna es Unidad de referencia para el paciente con infección por VIH en el Área Sanitaria de A Coruña y por tanto, ofrece atención médica a todos los pacientes con infección por VIH dado que no son atendidos en otros hospitales del área.

3.2 Periodo de estudio y fuentes de información.

El estudio incluyó todos los pacientes con infección por VIH mayores de 18 años en seguimiento en consultas externas de la Unidad VIH y Hepatitis durante el periodo 1993-2014, así como aquellos pacientes sin seguimiento activo pero que precisaron hospitalización en el mismo centro durante el periodo 1993-2013. Las fuentes de información que posibilitaron la recogida de datos fueron la base de datos propia de la Unidad de VIH y Hepatitis de los pacientes en seguimiento, el sistema de codificación del propio centro para aquellos pacientes que fueron hospitalizados, la historia clínica convencional y la historia clínica electrónica (ofrecida inicialmente por el programa de Gestion Documental y posteriormente por el programa IANUS). Este ultimo programa de gestion de la historia clínica electrónica está implementado en toda la Comunidad Autónoma de Galicia, con acceso al paciente independientemente de donde sea atendido, lo que permite minimizar los sesgos de pacientes desplazados o que fallecen en otros centros gallegos.

3.3 . Variables analizadas. Definiciones de parámetros evaluados.

*Variables***:** Se recogieron variables demográficas, epidemiológicas, clínicas e inmunonológicas relacionadas con la hospitalización. Se consideró coinfección VIH/VHC sólo si la carga viral de VHC era detectable. Se registratron aquellos pacientes que fueron tratados frente al VHC, así como si alcanzaron o no la respuesta viral sostenida (RVS). Se evaluó la estancia media, la tasa de reingreso, definido por la necesidad de nueva hospitalización antes de los 30 días después del alta previa, y la tasa de hospitalización programadas (aquellos ingresos que no proceden del Servicio de Urgencias). El seguimiento activo fue definido como aquel paciente con al menos dos visitas a la consulta y una determinación de recuento de CD4. La pérdida de seguimiento como la no comparecencia a la clínica por razones distintas a la muerte.

*Causa de hospitalizacion***:** Recogida siguiendo las directrices de la Clasificación Internancional de Enfermeades, 9º revisión (CIE_9). Se desestimaron como causas de ingreso los códigos indicadores de VIH y VHC. Siguiendo las indicaciones de trabajos previos, y tomando como referencia la Clasificación Internacional CCS que determina 18 causas de hospitalización [Elixhauser A et al, 2008], posteriormente se agruparon esas 18 categorías en grandes síndromes con el objetivo de facilitar el análisis final.

Causa de muerte: Diferenciamos mortalidad asociada o no a SIDA. Así, la mortalidad relacionada con SIDA fue definida como aquella atribuída a una de la entidades de la categoría C de la clasificación CDC (Tabla 1). La mortalidad no relacionada con SIDA fue clasificada siguiendo el protocolo CoDe ("Coding of Death in HIV"), www.cphiv.dk/CoDe.

Tabla 1. **Enfermedades definitorias de SIDA según Centers for Disease Control and Prevention (CDC).**

Etiología infecciosa
Candidiasis traqueal, bronquial o pulmonar. Candidiasis esofágica.
Coccidiomicosis diseminada (en una localización diferente o además de los pulmones y los ganglios linfáticos cervicales o hiliares).
Criptococosis extrapulmonar.
Criptosporidiasis, con diarrea de más de un mes.
Infección por citomegalovirus de un órgano diferente del hígado, bazo o ganglios linfáticos en un paciente de más de un mes de edad. Retinitis por citomegalovirus.
Infección por virus del herpes simple que cause una úlcera mucocutánea de más de un mes de evolución, o bronquitis, neumonitis o esofagitis de cualquier duración que afecten a pacientes de más de un mes de edad.
Histoplasmosis diseminada (en una localización diferente o además de los pulmones y los ganglios linfáticos cervicales o hiliares).
Isosporidiasis crónica (más de un mes).
Infección por Micobacterium avium-intracelulare o kansasii, diseminada o extrapulmonar. Infección por otras micobacterias, diseminada o extrapulmonar.
Tuberculosis pulmonar. Tuberculosis extrapulmonar o diseminada.
Neumonía por Pneumocystis jiroveci.
Neumonía recurrente.
Leucoencefalopatía multifocal progresiva.
Sepsis recurrente por especies de Salmonella diferente a Salmonella tiphy.
Toxoplasmosis cerebral en un paciente de más de un mes de edad.
Etiología neoplásica
Carcinoma de cérvix invasivo.
Sarcoma de Kaposi.
Linfoma de Burkitt o equivalente.
Linfoma Inmunoblástico o equivalente.
Linfoma cerebral primario.
Otros
Encefalopatía por VIH.
Wasting syndrome.

3.4. Análisis estadístico.

Las variables cualitativas se expresaron como número de casos y porcentaje, y fueron comparadas con el test X^2 o test exacto de Fisher, según fuese apropiado. Las variables continuas se expresaron como media ± desviación estándar o mediana (rango intercuartíleo) y fueron comparadas con el test T-student o los test no paramétricos, según fuese apropiado, tras evaluar la distribución normal de las distintas variables cuantitativas mediante el test de Kolmogorov-Smirnov. Un valor de p inferior a 0.05 fue considerando estadísticamente significativo para todos los análisis.

El estudio fue dividido en 2 periodos de tiempo (1993-2002 y 2003-2013) con el objetivo de poder compararlos mediante un análisis transversal.

Se llevó a cabo un análisis de regresión de tendencias (joinpoint), que proporciona el cambio porcentual estimado anual (APC) y permite detectar puntos en el tiempo con cambios de tendencias signifcativos. Para cada APC estimado, se calculó un intervalo de confianza del 95%.

El análisis estadístico se llevó a cabo con el Paquete estadístico Social Sciences Software para Windows, versión 19.0 (SPSS 19.0, Chicago, IL, USA).

3.5 Consideraciones éticas y legales.

El presente estudio de investigación y tesis doctoral ha sido revisado y aprobado por el Comité ético de investigación clínica de Galicia (código de registro 2015/164). Cumple con las directrices señaladas por las buenas prácticas clínicas en investigación y con la declaración de Helsinki y revisiones sucesivas. Se respeta la confidencialidad de los datos de los pacientes, en cumplimiento con la Ley Orgánica de Protección de Datos (Ley15/1999,LOPD).

ESTUDIO 1:

Tendencias en hospitalizaciones, reingresos y mortalidad hospitalaria en pacientes con infección por VIH (1993-2013). Impacto de la coinfección VIH/VHC

Resumen:

El objetivo principal del estudio fue evaluar las tendencias en hospitalización, reingreso y mortalidad en pacientes con infección por VIH a lo largo de 21 años de seguimiento, divididos en 2 periodos para ser comparados. El objetivo secundario consistió en analizar el papel de la coinfección VIH/VHC en dichas tendencias.

Se identificaron retrospectivamente a través del Servicio de Codificación del centro todas las hospitalizaciones de pacientes VIH en el CHUAC en el periodo establecido entre el 1 de enero 1993 y el 31 de diciembre de 2013. Se definió tasa de hospitalización como el número de hospitalizaciones por cada 100 pacientes; para el denominador, se utilizó el número de pacientes en seguimiento cada año en la Unidad de VIH-Hepatitis. El estudio fue dividido en 2 periodos de tiempo (1993-2002 y 2003-2013) para ser comparados. Se incluyeron 22901 paciente-años, que presentaron 6917 hospitalizaciones que correspondieron a 1937 pacientes (75% varones, edad media 36±11 años, 37% coinfectados VIH/VHC). La mediana de estancia hospitalaria fue de 8 días (5-16), y la tasa de reingreso a los 30 días del 20,1%. La tasa de hospitalización mostró una reducción progresiva desde 30,7/100 pacientes (IC95%: 27,7-33,8) en 1993 a 19,9/100 pacientes (17,7-22,2) en 2013, siendo esta reducción más significativa después de 1996 (4,9% anual), pero este descenso fue menos acusado en los pacientes coinfectados VIH/VHC (1,7% anual). La estancia media de los pacientes coinfectados VIH/VHC fue similar a la de los pacientes VIH monoinfectados (10,1 vs 11 días, p=0,24); sin embargo los pacientes coinfectados tuvieron más hospitalizaciones por paciente (en mediana, 3 vs 2, p<0,001) y mayor tasa de reingreso (21,5% vs 19,1%, p<0,01). En

_____

consecuencia, un mayor numero de días de estancia totales y el impacto en términos económicos que ello implica.

Se observó un descenso significativo en el segundo periodo (2003-2013) de las hospitalizaciones motivadas por enfermedades infecciosas y trastornos psiquiátricos, y un incremento de aquellas relacionadas con neoplasias, enfermedad cardiovascular, gastrointestinal y enfermedades respiratorias crónicas. La mortalidad intrahospitalaria permanece elevada (6,8% en el primer periodo vs 6,3% en el segundo), con un aumento progresivo de las muertes por enfermedades no definitorias de SIDA (37,9 vs 68,3%; p <0,001). En los pacientes coinfectados VIH/VHC, especialmente en el segundo periodo del estudio, buena parte de las hospitalizaciones y de las muertes fueron motivadas por enfermedad hepática.

_____

Original article

Trends in hospital admissions, re-admissions, and in-hospital mortality among HIV-infected patients between 1993 and 2013: Impact of hepatitis C co-infection

Héctor Meijide [a,b,◊], Álvaro Mena [a,*,◊], Iria Rodríguez-Osorio [a], Sonia Pértega [c], Ángeles Castro-Iglesias [a], Guillermo Rodríguez-Martínez [d], José Pedreira [a], Eva Poveda [a]

[a] Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña (INIBIC)-Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), Spain
[b] Servicio de Medicina Interna, Hospital Quiron, A Coruña, Spain
[c] Unidad de Epidemiología Clínica y Bioestadística, Instituto de Investigación Biomédica de A Coruña (INIBIC)-Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), Spain
[d] Unidad de Admisión y Documentación Clínica, Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, A Coruña, Spain

A B S T R A C T

Background: New patterns in epidemiological characteristics of people living with HIV infection (PLWH) and the introduction of Highly Active Antiretroviral Therapy (HAART) have changed the profile of hospital admissions in this population. The aim of this study was to evaluate trends in hospital admissions, re-admissions, and mortality rates in HIV patients and to analyze the role of HCV co-infection.
Methods: A retrospective cohort study conducted on all hospital admissions of HIV patients between 1993 and 2013. The study time was divided in two periods (1993–2002 and 2003–2013) to be compared by conducting a comparative cross-sectional analysis.
Results: A total of 22,901 patient-years were included in the analysis, with 6917 hospital admissions, corresponding to 1937 subjects (75% male, mean age 36 ± 11 years, 37% HIV/HCV co-infected patients). The median length of hospital stay was 8 days (5–16), and the 30-day hospital re-admission rate was 20.1%. A significant decrease in hospital admissions related with infectious and psychiatric diseases was observed in the last period (2003–2013), but there was an increase in those related with malignancies, cardiovascular, gastrointestinal, and chronic respiratory diseases. In-hospital mortality remained high (6.8% in the first period vs. 6.3% in the second one), with a progressive increase of non-AIDS-defining illness deaths (37.9% vs. 68.3%, *P* < .001). The admission rate significantly dropped after 1996 (4.9% yearly), but it was less pronounced in HCV co-infected patients (1.7% yearly).
Conclusions: Hospital admissions due to infectious and psychiatric disorders have decreased, with a significant increase in non-AIDS-defining malignancies, cardiovascular, and chronic respiratory diseases. In-hospital mortality is currently still high, but mainly because of non-AIDS-defining illnesses. HCV co-infection increased the hospital stay and re-admissions during the study period.

Tendencia de las hospitalizaciones, reingresos y mortalidad intrahospitalaria en los pacientes infectados por VIH entre 1993-2013: impacto de la coinfección por el virus de la hepatitis C

R E S U M E N

Introducción: Los cambios en las características epidemiológicas de los pacientes con infección por el VIH, y la introducción del tratamiento antirretroviral de alta eficacia, han modificado el perfil de las

* Corresponding author.
 E-mail address: alvaro.mena.de.cea@sergas.es (Á. Mena).
 ◊ These authors contributed equally in this work.

2   *H. Meijide et al. / Enferm Infecc Microbiol Clin. 2016;**xxx(xx)**:xxx–xxx*

Hospitalización
Reingreso

hospitalizaciones en esta población. El objetivo del estudio fue evaluar las tendencias en hospitalización, reingreso y mortalidad en pacientes VIH, y analizar el papel de la coinfección por el VHC.

Métodos: Estudio de cohortes retrospectivo, que incluyó todas las hospitalizaciones de pacientes VIH entre 1993-2013. El estudio fue dividido en 2 periodos (1993-2002 y 2003-2013) para ser comparados mediante un análisis transversal.

Resultados: Se analizaron 22.901 pacientes/años, que presentaron 6.917 hospitalizaciones que correspondieron a 1.937 pacientes (75% varones, edad media 36 ± 11 años, 37% coinfectados VIH/VHC). La mediana de estancia hospitalaria fue de 8 días (5-16), y la tasa de reingreso a los 30 días del 20,1%. Se observó un descenso significativo en el segundo periodo (2003-2013) de las hospitalizaciones motivadas por enfermedades infecciosas y trastornos psiquiátricos, y un incremento de aquellas relacionadas con neoplasias, enfermedad cardiovascular, gastrointestinal y enfermedades respiratorias crónicas. La mortalidad intrahospitalaria permanece elevada (6,8% en el primer periodo vs. 6,3% en el segundo), con un aumento progresivo de las muertes por enfermedades no definitorias de sida (37,9 vs. 68,3%; p < 0,001). La tasa de hospitalización disminuyó de manera significativa después de 1996 (4,9% anual), pero este descenso fue menos acusado en los pacientes coinfectados VIH/VHC (1,7% anual).

Conclusiones: Las hospitalizaciones motivadas por enfermedades infecciosas y trastornos psiquiátricos han descendido; por el contrario, se observó un aumento significativo de aquellas relacionadas con neoplasias no definitorias de sida, enfermedad cardiovascular y enfermedades respiratorias crónicas. La mortalidad intrahospitalaria permanece a día de hoy elevada, pero a expensas fundamentalmente de enfermedades no definitorias de sida. La coinfección VIH/VHC incrementó los días de hospitalización y los reingresos durante el periodo de estudio.

Background

Since the introduction of Highly Active Antiretroviral Therapy (HAART) in 1996, the profile of people living with HIV infection (PLWH) has changed significantly; with an appreciable decline of mortality related to AIDS-defining diseases and an improvement in life expectancy. However, the incidence of other comorbidities, mainly cardiovascular diseases and non-AIDS tumors has increased, due to the longer life expectancy, aging and persistent inflammation related to the HIV-infection, even in a context of long-term suppression of viremia.[1–5]

From a public health perspective, it is important to understand trends and characteristics of hospitalizations, re-admissions and mortality rates among PLWH. However, there are few available data among too heterogeneous study populations in different socioeconomic contexts and Health Care systems. In the general population, 30-days readmission rates are increasingly becoming a benchmark for hospital quality of care and costs, also for PLWH.[6]

The causes of hospitalizations have been changing in the HAART era. AIDS defining illnesses are less represented nowadays, but patients are older with more comorbidities. Therefore, the reasons for hospitalizations incidence, mortality and readmission rates might be changing.[6–10]

Chronic hepatitis C virus (HCV) coinfection is common in PLWH (30–50% according to different series).[11] It is estimated that at least 30% of patients with HCV develop cirrhosis and around 1–4% of these will develop hepatocellular carcinoma. The risk of progression of liver disease is 2–6 times higher in HIV/HCV coinfected than in HCV mono-infected patients, which involves a high-related morbidity and mortality.[12–16] However, the risk of hepatic decompensation and progression of liver fibrosis is drastically reduced with treatment and cure of HCV infection.[17,18]

In this context, the aim of this study was to analyze trends in hospitalization, re-admission and mortality rates in PLWH followed in a reference hospital in Northwest Spain in the last 20 years. Moreover, the impact of HCV coinfection in the dynamic of all these parameters was also evaluated.

Methods

The Complexo Hospitalario Universitario de A Coruña (CHUAC) is a 1422-bed, full service, 24 h ICU availability, tertiary acute university care hospital, serving in the Northwest of Spain. The influence population in 2013 was 547,776 citizens, and that year reported 40,869 admissions (21% scheduled). The HIV and Hepatitis Viral Unit offers outpatient and inpatient medical care to all PLWH in this reference area, attending more than 1400 PLWH by HIV-trained doctors. PLWH are not attended in other hospitals in this area.

Data collection

All hospital admissions of HIV-infected patients at CHUAC between 1993 and 2013 were obtained through the Hospital-coding Department. Hospitalization reasons were collected following the International Classification of Diseases, Ninth Revision (ICD-9). Several steps were taken in assigning each hospitalization to a single diagnostic category. To determine the reliably ICD-9 code the first listed referring to neither HIV (042, V08, 795.71, V01.79) nor chronic hepatitis C (070.44, 070.54, 070.70, 070.71) nor oral candidiasis (120.0) was defined as the primary code for hospitalization. These codes represent comorbidities that are not, by themselves, sufficient to justify hospitalization. Recurrent bacterial pneumonia was defined as a bacterial pneumonia admission occurring within >30 but <365 days of a previous such admission. Hospitalizations whose first ICD-9 code was chemotherapeutic treatment were assigned to the first code based on the type of cancer. Clinical Classification Software (CCS), developed by the Agency for Healthcare Research and Quality[19] was used to assign primary ICD-9 code into one of 18 first-level categories. Finally, using a method similar to one it has previously employed,[7] CCS classification was modified and categories were pooled together at major syndromes for further analysis.

Epidemiological and clinical data related to hospitalizations and mortality were recorded. HIV/HCV coinfection was considered if
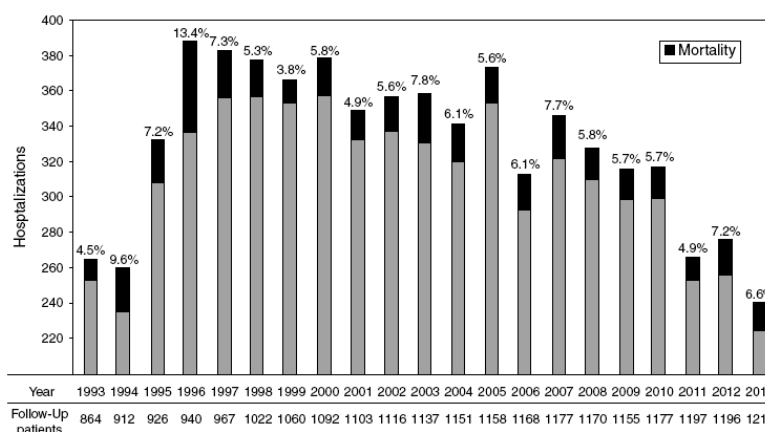
Fig. 1. Hospitalization in PLWH between 1993 and 2013; black area indicates mortality (%). Patients on follow-up each year.

RNA-HCV viral load was detectable. Mean length of hospital stay was evaluated by subtracting the date of discharge – the date of admission and adding 1. For patients that were discharged the day of admission, it was considered 1. Re-admission was defined as hospitalization occurred before 30 days after discharge. Years of active outpatient care were defined by having at least one HIV clinician visit and one measured CD4 cell count. Scheduled admissions were considered if the patient were not in the Emergency Department prior to hospitalization. Death due to an AIDS-defining illness was defined as death attributable to one of the Centers for Disease Control Prevention (CDC) category C diseases. Death due to non AIDS-defining illness was classified according to CoDe protocol ("Coding of Death in HIV", in www.cphiv.dk/CoDe).

The study is in accordance with the community standards and approved by the ethics committee. The study's protocol was reviewed and approved by the Medical Ethics Committee of the University Hospital of Galicia. All clinical data were anonymous and de-identified prior to analyze, the identification numbers of the patients were recorded blindly.

Statistical analyses

Hospitalization rate was evaluated as number of hospitalizations per 100 patients. For the denominator, the number of patients in care each year in the HIV clinic, was used; it was collected from medical records and electronic database of patients in follow up. The study was divided in two periods of time (1993–2002 and 2003–2013) to be compared with a comparative cross-sectional analysis.

Quantitative data were reported using means ± standard deviations (SD) or median (range), as indicated. For qualitative variables, absolute numbers and percentages were computed. The comparison of quantitative parameters was carried out using Student's t test. The association of qualitative variables was carried out using Chi-squared statistic; the relative risk (RR) was calculated. A two-sided type I error of 5% was considered statistically significant.

A time-trend joinpoint regression analysis was performed. This technique provides the estimated annual percent change (APC) and allows detecting points in time at which significant changes in the trends occur. For each APC estimate, 95% confidence interval was also calculated. Statistical analysis was performed using SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL).

Results

Demographic characteristics and hospitalization parameters

A total of 2498 PLWH were followed during the period study, contributing to 22,901 patient-years (PY). In the study period 6917 hospital admissions were recorded, corresponding to 1937 subjects. Of them, 75.0% were male, mean age (at first hospitalization) was 36.4 ± 10.6 years, and 37.2% were HIV/HCV coinfected. Among those PLWH hospitalized, 789 (40.7%) have one admission; the median number of admission was 2 (IQR: 1–4). The hospitalization rate showed a reduction from 30.7/100 patients (CI95%: 27.7–33.8) in 1993 to 19.9/100 patients (17.7–22.2) in 2013 (*P*<.001); Fig. 1 shows the hospitalization and mortality each year and the number of patients on follow-up.

In the comparative analysis between both periods (1993–2002 vs. 2003–2013), differences in hospitalization reasons were recognized among periods (Table 1). The main 5 reasons for hospitalization were: pneumonia (10.5%), chronic pulmonary disease/respiratory failure (8.3%), tuberculosis (7.4%), hepatic decompensation (6.3%) and psychiatric disorder/drug-abuse (5.3%). Overall, 23.1% of the total of 6917 hospitalizations was AIDS-defining illnesses, with differences between first (28.0%) and second period (16.2%), *P*<.001.

Re-admissions and mortality rates by clinical units

Overall, 5759 (83.3%) were considered primary hospitalizations, 998 (14.4%) were first re-admissions and 160 (2.3%) were subsequent re-admissions in a chain. The median length of hospital stay was 8.0 days (5.0–16.0).

The re-admission rate was 20.1% (CI95%: 19.1–21.2) without differences by gender (20.3% in men vs. 19.7% in women, *P*=.21). Mean age of patients in hospitalizations without a re-admission (37.4±10.4) was similar than those re-admitted (37.9±10.9 years). A higher rate of re-admissions was observed for some services such as Onco-Hematology (68.5%), Gynecology–Obstetrics (24.2%), Internal Medicine-Infectious Diseases (20.0%) or Pediatric Unit (16.3%). Those with lower rate were: surgery units (13.2%) or Psychiatry Unit (8.2%). Main reasons for hospital admission have different re-admission rates: tumoral diseases 33.8%, hepatic decompensations 23.5%, chronic pulmonary diseases 20.8%,

Table 1
Baseline characteristics of 6917 hospital admissions between periods (1993–2002 and 2003–2013).

	1993–2002 (N = 3463)	2003–2013 (N = 3454)	Relative change (%) (CI 95%)
Scheduled admissions (%)	42.1	26.8	**−36.3 (−40.5; −31.9)**
Length of stay (median, IQR)	9.0 (5.0–16.0)	8.0 (4.0–15.0)	−9.9 (−18.7; 2.8)
Re-admission (%)	19.8	20.4	3.0 (−9.2; 13.2)
Mortality (%)	6.8	6.3	−7.0 (−22.1; 18.1)
Hospitalization reasons (%)			
Infectious diseases	49.1	35.3	**−28.1 (−32.0; −23.9)**
Aids-defining infections	52.3	36.5	**−30.2 (−36.0; −23.9)**
Psyquiatric illness	9.1	5.2	**−42.7 (−52.0; −31.6)**
Malignancies	3.6	7.8	**115.8 (75.4; 165.3)**
Aids-defining tumors	65.2	42.6	**−34.8 (−46.0; −21.2)**
Cardiac diseases	1.2	3.7	**205.6 (116.3; 331.6)**
Digestive system diseases	9.2	16.1	**74.8 (53.6; 98.9)**
Hepatic decompensations	4.2	8.5	**103.3 (67.6; 146.6)**
Chronic respiratory diseases	5.6	11.0	**96.4 (66.3; 131.9)**
Hospitalization units (%)			
Internal medicine/infectious diseases	85.0	70.8	**−16.7 (−18.9; −14.5)**
Surgical units	5.0	10.4	**108.0 (74.6; 147.9)**
Onco-hematology	2.0	4.3	**116.5 (63.4; 186.9)**
Gynecology/obstetrics	2.7	4.3	**58.9 (23.3; 104.9)**
Pediatrics	1.5	0.3	**−80.7 (−90.2; −62.1)**
Intensive care unit	2.0	6.0	**200.8 (130.0; 293.4)**
Cause of in-hospital death (%)	**235/453**	**218/453**	
AIDS related illness:	62.1	31.7	**−49.0 (−59.1; −36.6)**
Aids related encephalopaty[a]	17.0	5.0	**−70.4 (−84.4; −43.7)**
MAI-MTB infection[b]	15.3	6.0	**−61.1 (−78.8; −28.6)**
Pneumocistis jirovecci pneumonia	11.5	6.0	**−48.1 (−72.5; −2.0)**
Aids related malignancy	8.5	11.0	29.4 (−26.4; 127.4)
Disseminated candidiasis	3.8	0.5	**−88.0 (−98.5; −6.2)**
Recurrent bacterial pneumoniae	3.4	1.8	−46.1 (−83.5; 76.5)
Wasting syndrome	2.6	1.4	46.1 (−86.3; 112.9)
Non-AIDS related illness:	37.9	68.3	**80.5 (49.7; 117.6)**
(02.1) Bacterial infection[c]	10.2	17.0	**66.2 (2.9; 168.4)**
(02.1.1) Bacterial infection with sepsis	6.8	12.8	**88.6 (5.0; 238.9)**
(03.1.1) HCV with cirrhosis	5.1	11.0	**115.6 (10.5; 320.5)**
(04) Malignancy[d]	2.6	9.6	**277.3 (55.2; 817.3)**
(16)Violent death/(19)substance abuse	3.4	1.4	−59.6 (−89.1; 50.4)
(9) Stroke and (23) other CNS disease	3.4	5.5	61.7 (−32.6; 288.0)
(13) Chronic obstructive lung disease[e]	2.6	7.8	**205.4 (22.7; 660.5)**
(08) MI and other heart disease	0.4	1.4	223.4 (−66.1; 2985.6)
(90) Other causes	3.4	1.8	−46.1 (−83.5; 76.5)

Main causes of in-hospital mortality.
Statistically significant results (P<.05) are shown in bold.

  [a] Including progressive multifocal leukoencephalopathy, cryptococcal meningitis and cerebral toxoplasmosis.
  [b] Micobacterium Avium Intracellulare and Micobacterium Tuberculosis.
  [c] Only due to pneumonia.
  [d] Including hepatocarcinoma.
  [e] Including other chronic respiratory diseases.

infectious diseases 18.9%, cardiovascular diseases 14.9%, and psychiatric disorders 12.8%.

Between 1993–2013, 453 in-hospital deaths were identified, with an overall inpatient mortality rate of 6.5% (CI95%: 6.0–7.1). Globally, the mortality of hospitalizations for males was higher than for women (7.4% vs. 4.4%, RR: 1.7 [1.3–2.1], P<.001). Mean age of patients who died during the hospitalizations was 40.1 ± 11.3 years, significantly higher (P<.001) than that of those who did not die (37.3 ± 10.4 years). Mortality of primary hospitalizations was 5.7% vs. 11.0% among re-admissions (RR 1.93 [1.59–2.35], P<.001). AIDS-defining illnesses hospitalizations presented a mortality of 13.4%, while in non AIDS-defining diseases was 4.5% (RR: 3.0 [2.5–3.6], P<.001).

There were differences in mortality rate by Units (P=.005): Onco-Hematology (12.4%), Internal Medicine-Infectious Diseases (6.7%), Surgery (3.6%) and Pediatric (3.5%). No patient's death in Gynecology–Obstetrics or Psychiatry Unit. There were 24 hospitalizations admitted in ICU directly from the Emergency Department, 21 of them (87.5%), died during the ICU stay. Hospitalizations that were admitted in ICU (whenever during the hospitalization) had

higher mortality rate (35.5%) than those without ICU care (5.3%) (RR 6.6 [5.5–8.0], P<.001). The main causes of in-patient death and the change between both periods are detailed in Table 1.

HIV/HCV coinfection

A total of 716 HIV/HCV coinfected patients were hospitalized at least once during the study period, giving a total of 3525 hospitalizations (1408 between 1993–2002 and 2117 between 2003–2013). Fig. 2 depicts the changes in incidence during the follow up. In the joinpoint regression analysis, two different trends were observed. Hospitalizations rate increased between 1993 and 1996 in all cohort (APC = 11.8%). Between 1997 and 2013, hospitalizations rate decreased much more in HIV mono-infected (APC = −4.9%) than in HIV/HCV coinfected (APC = −1.7%), P<.001.

Overall, the mean length of stay in HCV coinfected patients was similar than in mono-infected (median: 10.1 days [6.3–15.9] vs. 11.0 [6.0–19.5], P=.24); but coinfected had more hospitalizations per patient (median: 3.0 [1.0–6.0] vs. 2.0 [1.0–3.0], P<.001) and higher readmission rates (21.5% vs. 19.1%, RR: 1.1 [1.0–1.2],

_____

	Period	APC	Period	APC
Total	1993-1996	11.8 (0.9; 23.9)	1996-2013	−3.4 (−4.0; −2.7)
HIV/HCV coinfected	1993-1996	12.3 (−3.0; 29.9)	1996-2013	−1.7 (−2.5; −0.8)
HIV monoinfected	1993-1996	10.8 (−2.9; 26.4)	1996-2013	−4.9 (−5.8; −4.0)
APC=Annual percent change				
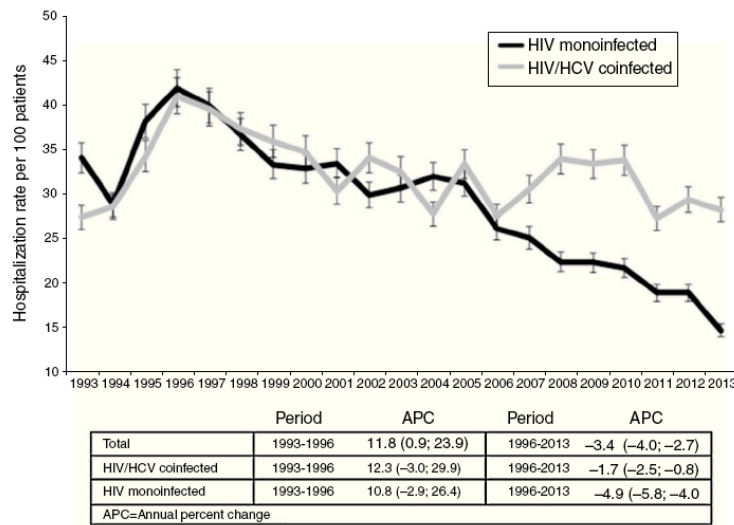
Fig. 2. Hospitalization rate in HIV/HCV coinfected and HIV monoinfected patients. Joinpoint regression analysis: trends in hospitalizations in HIV/HCV coinfected and HIV monoinfected patients. Estimated Annual percent change (bold if statistically significant, $P < .001$ in all cases). In comparison between HIV/HCV coinfected and HIV monoinfected patients, $P = .65$ in the first period (1993–1996) and $P < .001$ in the second (1996–2013).

$P < .001$). The sum of total days of hospitalization per patient during the follow-up was higher among HIV/HCV coinfected than in HIV mono-infected (median: 36.0 days [14.0–77.5] vs. 23.0 days [9.0–51.0], respectively; $P < .001$).

The main causes of hospitalization in coinfected patients, comparatively with HIV-monoinfected, are illustrated in Fig. 3.

A decrease of infectious diseases and psychiatric disorders was evidenced. On the other hand, an important increase in hospitalizations due to hepatic decompensations was found (from 5.8% to 11.5%, RR: 2.0 [CI95%: 1.5–2.6], $P < .001$).

Mortality rate of hospitalizations in HIV/HCV coinfected increases from 4.0% (1993–2002) to 6.2% (2003–2013), RR = 1.5
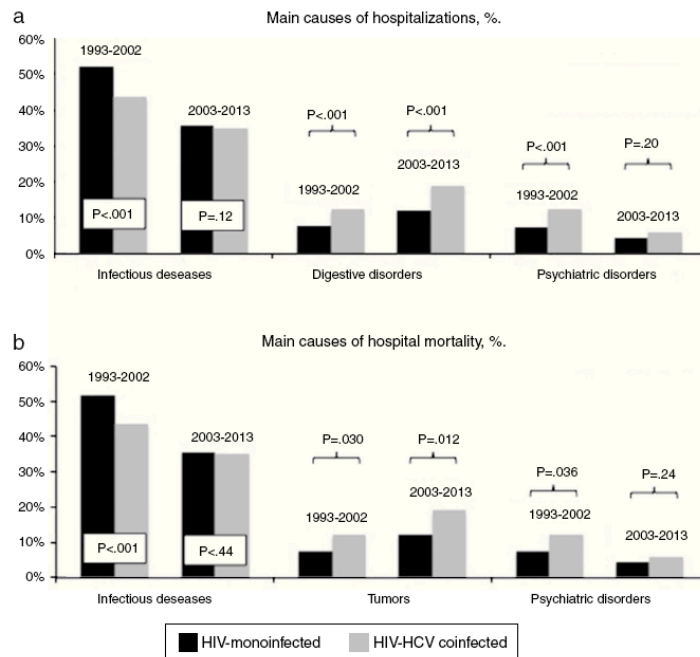
Fig. 3. Main reasons of hospital admission (a) and in-hospital mortality (b) in HIV-mono and HIV/HCV-coinfected patients during 1993–2002 and 2003–2013.

_____

(1.1–2.1, *P* < .001). There were also differences in mortality reasons: infectious diseases mortality decreased significantly (RR = .6 [.4–.9], *P* < .001), tumors increased (RR = 2.1 [.5–8.8], *P* = .01) and hepatic decompensations also increased from 15.6% to 21.2% (RR: 1.4 [.6–3.3], *P* = .005) (Fig. 3).

Discussion

This study evaluates trends in hospitalizations among PLWH in a medical reference area of Northwest Spain. Overall, the hospitalizations rate showed a decline from 31/100 patients in 1993 to 20/100 patients in 2013, but remains higher than in the general population. These results are concordant with other previously published in different countries and different Health Care Systems.[6,21] The joinpoint analysis established a point of change in 1996. This behavior is related with the introduction of HAART and its rapid impact in AIDS-defining illnesses. In this year, the trend of hospitalization incidence changed from a yearly growing of 11.8% toward a yearly decreasing of 3.4%.

Changes in the reasons of hospital admission were also observed between the two periods evaluated. Thus, a significant decrease in hospitalizations due to infectious (mainly AIDS-defining diseases) and psychiatric disease or drugs abuse was recognized in contrast to a progressive increase of malignancies specially those non AIDS-defining, chronic respiratory, cardiovascular and liver related diseases. Overall, hospitalizations due to AIDS-defining diseases dropped (from 28.0% to 16.2%) in our cohort, but their mortality did not change significantly (15.0% in 1993–2003 and 12.3% in 2004–2013). AIDS-defining diseases and their high mortality remain a current problem worldwide; this problem must be addressed from the universalization of HAART and improving the diagnostic strategies.[7]

Accordingly, changes in hospitalization units were also observed. Thus, in the second period there was an increase in hospitalizations in surgical areas and onco-haematologic units, likely due to an increase in the life expectancy among HIV-infected patients in the second period because the access to specific treatments as for the general population. The rates of ICU admissions increased up to 3-times, probably caused by the same reasons.

However, the average length of stay and re-admission rates remain high, similar to those reflected in other studies,[10,20] probably due to an increase in the comorbidities associated with HIV infection, that involve greater complexity of clinical management in this group of patients.

Despite the improvement in the care of PLWH, the in-hospital mortality remains high; in this cohort the mortality in men is 1.7 times higher than in women, according to data published previously.[21,22] Non-AIDS deaths increased significantly during the ART era and nowadays are the main cause of in-hospital mortality in PLWH. Non-AIDS infections, cirrhosis and its complications, and malignancies were major contributors to mortality. Non-AIDS mortality increased by 80.5% between first and second period; consequently, AIDS mortality decreased by 49.0%. Cowell et al., reported similar trends recently, in a huge American cohort.[23]

The 30 days re-admission rate in our cohort was 20.1%, similar to data recently reported by Berry et al. (19.3%).[6] The re-admission rate has an important impact on long-term health and mortality rate of PLWH. Indeed, some mathematical models are developed to predict re-admission, but they need to be validated in other populations.[24]

Within this cohort, nearly 40% were HIV/HCV coinfected patients. They had more hospitalizations, re-admissions and the sum of the total stays were significantly greater than for HIV mono-infected, similarly to that previously published.[16] Interestingly, the incidence of hospitalizations in 2013 was double in coinfected

compared to HIV mono-infected. Indeed, although the hospitalization rate decreases since 1996, the APC is near to three times higher in mono-infected than in coinfected. Therefore, in terms of hospitalizations and in-hospital mortality, HCV coinfection seems to mask the beneficial effect of HAART and improvements in HIV care, although other factors such IDU or alcohol could also play a significant role. Hospitalizations due to hepatic decompensation are double in the last ten years (2003–2013) compared with the first period (1993–2002). Moreover, Meyers et al. described recently that HCV mortality appears to be relatively stable while total HIV/AIDS deaths are on a decline across the state of Massachusetts in a trend analysis of HIV and HCV using multiple cause of death.[25] All these data suggest that hospitalizations, decompensations and mortality will increase in the next years if HCV infection is not eradicated. The impact of a wide access to new anti-HCV therapies in HIV-infected patients must be evaluated in the near future.[26-28]

There are some limitations in our study that merit discussion. This is a retrospective observational study, using data recorded from a single hospital that it could affect the generalizability of our finding. However, this is a reference hospital with more than 1000-beds and a large cohort of HIV- and HCV-infected patients in follow-up in this institution since the beginning of both epidemics. Although there are not other HIV outpatient clinics in our area, some patients had an admission without any follow up in our clinic; it could overestimate hospitalization rates. Moreover, there are some variables that might be also associated with mortality that were not collected (i.e. smoking, or years under HAART exposure) and therefore its specific impact in hospitalizations and rates of mortality could not be analyzed. Data of CD4 count, HAART and viral suppression were not available, the effect of this important factors in PLWH was not analyzed. Patients admitted in Onco-Hematology Units to receive scheduled chemotherapy (12%) could overestimate the hospitalization rate in these Units and underestimate the in-hospital mortality in them. The study did not include HCV-infected patients treated with new DAAs based therapies, neither a control group of hospitalized HIV-negative patients. Finally, it is possible that the use of the ICD-9 coding system might introduce coding errors, although minority.

In summary, in this large cohort of PLWH, followed during 20 years, a decrease in the hospitalizations rate and a progressive decline of AIDS defining illnesses have been recognized. Consequently, chronic comorbidities and malignancies have been increasing within the last ten years. However, the length of stay, re-admission and the mortality rate remains high. HCV coinfection has a negative impact in these parameters and is associated with increases in the morbidity and mortality and therefore in the resource consumption among PLWH. These findings are essential to improve and optimize the clinical management of PLWH and to pay special attention in those comorbidities that favor the hospitalization and mortality rates nowadays.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgements

_____

References

1. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003;362:22–9.
2. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antirretroviral therapy: New York City. Ann Intern Med. 2006;145:397–406.
3. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis. 2010;50:1387–96.
4. Cunningham WE, Tisnado DM, Lui HH, Nakazono TT, Carlisle DM. The effect of hospital experience on mortality among patients hospitalized with acquired immunodeficiency syndrome in California. Am J Med. 1999;107: 137–43.
5. Pernas B, Mena A, Cañizares A, Grandal M, Castro-Iglesias A, Pértega S, et al. Trends on epidemiological, virological, and clinical features among newly diagnosed HIV-1 persons in Northwest Spain over the last 10 years. J Med Virol. 2015;87:1319–26.
6. Berry SA, Fleishman JA, Yehia BR, Korthuis PT, Agwu AL, Moore RD, et al. Thirty-day hospital readmission rate among adults living with HIV. AIDS. 2013;27:2059–68.
7. Berry SA, Fleishman JA, Moore RD, Gebo KA, HIV Research Network. Trends in reasons for hospitalization in a multisite united states cohort of persons living with HIV, 2001–2008. J Acquir Immune Defic Syndr. 2012;59: 368–75.
8. Kim JH, Psevdos G, Gonzalez E, Singh S, Kilayko MC, Sharp V. All-cause mortality in hospitalized HIV-infected patients at an acute tertiary care hospital with a comprehensive outpatient HIV care program in New York City in the era of highly active anti retroviral therapy (HAART). Infection. 2013;41: 545–51.
9. Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA, et al. Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. J Acquir Immune Defic Syndr. 2014;65:429–37.
10. López C, Masiá M, Padilla S, Aquilino A, Bas C, Gutiérrez F. Deaths due to non-AIDS diseases among HIV infected patients: a 14-year study (1998–2011). Enferm Infecc Microbiol Clin. 2016;34:222–7.
11. Mena A, Moldes L, Meijide H, Cañizares A, Castro-Iglesias A, Delgado M, et al. Seroprevalence of HCV and HIV infections by year of birth in Spain: impact of US CDC and USPSTF recommendations for HCV and HIV testing. PLOS ONE. 2014;9:e113062.
12. Sherman KE, Rouster SD, Chung RT, Rajicic N. Virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002;34:831–7.
13. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. J Hepatol. 2007;47:527–37.
14. Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV infected patients: the French national Mortalite 2005 study. J Hepatol. 2009;50:736–45.
15. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006;166:1632–41.
16. Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo ME, Casado R, et al. Liver cirrhosis in HIV-infected patients: prevalence, aetiology and clinical outcome. J Viral Hepat. 2008;15:165–72.
17. Labarga P, Fernandez-Montero JV, Mendoza C, Barreiro P, Soriano V. Long-term survival and liver – related events after peginterferon/ribavirin therapy in HIV-infected patients with chronic hepatitis C. Antivir Ther. 2015;20:65–72.
18. Aspinall EJ, Hutchinson SJ, Janjua NZ, Grebely J, Yu A, Alavi M, et al. Trends in mortality after diagnosis of hepatitis C virus infection: an international comparison and implications for monitoring the population impact of treatment. J Hepatol. 2015;62:269–77.
19. Elixhauser A, Steiner C, Palmer L. Clinical Classifications Software (CCS), 2008. U.S. Agency for Healthcare Research and Quality; 2008.
20. Wier LM, Barrett ML, Steiner C, Jiang HJ. All-cause readmissions by payer and age, 2008. HCUP Statistical Brief #115 Agency for Healthcare Research and Quality; 2012. http://hcup-us.ahrq.gov/reports/statbriefs/sb115.pdf
21. Crowell TA, Gebo KA, Blankson JN, Korthuis PT, Yehia BR, Rutstein RM, et al. Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. J Infect Dis. 2015;211:1692–702.
22. Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, et al. Impact of risk factors for specific causes death in the first and subsequent years of ART among HIV-infected patients. Clin Infect Dis. 2014;59:287–97.
23. Cowell A, Shenoi SV, Kyriakides TC, Friedland G, Barakat LA. Trends in hospital deaths among human immunodeficiency virus-infected patients during the antirretroviral therapy Era, 1995 to 2011. J Hosp Med. 2015;9:608–14.
24. Nijhawan AE, Clark C, Kaplan R, Moore B, Halm EA, Amarasinghang R. An electronic medical record-based model to predict 30-day risk of readmission and death among HIV-infected inpatients. J Acquir Immune Defic Syndr. 2012;61:349–58.
25. Meyers DJ, Hood ME, Stopka TJ. HIV and hepatitis C mortality in Massachusetts, 2002–2011: spacial cluster and trend analysis of HIV and HCV using multiple cause of death. PLOS ONE. 2014;9:e114822.
26. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. HIV, age, and the severity of hepatitis C virus – related liver disease. Ann Intern Med. 2013;158:658–66.
27. Re VL III, Kallan MK, Tate JP, Localio AR, Lim JK, Goetz MB, et al. Hepatic decompensation in antiretroviral-treated HIV/hepatitis C-coinfected compared to hepatitis C-monoinfected patients: a cohort study. Ann Intern Med. 2014;160:369–79.
28. Crowell TA, Berry SA, Fleishman JA, LaRue RW, Korthuis PT, Nijhawan AE, et al. Impact Hepatitis Coinfection on Healthcare utilization among persons living with HIV. J Acquir Immune Defic Syndr. 2015;68:425–31.

ESTUDIO 2:

Mortalidad relacionada con enfermedad hepática atribuíble al virus de la hepatitis C en pacientes con infección por VIH.

Resumen:

El objetivo del estudio fue comparar la mortalidad relacionada con enfermedad hepática y las hospitalizaciones motivadas por causa hepática en pacientes con infección por VIH que han sido expuestos o no al VHC, para estimar con ello la fracción atribuíble de enfermedad hepática a la coinfección por el VHC.

Para alcanzar un mayor tamaño muestral el periodo de estudio se prolongó 1 año (1993-2014). Tanto los motivos de hospitalización como las causas de muerte fueron recogidas con la ayuda del Servicio de Codificación del centro, siguiendo los criterios llevados a cabo en el primer estudio. La mortalidad relacionada con hígado incluyó la codificación de hepatitis viral, enfermedad hepática alcohólica, enfermedad hepática no alcohólica, hepatocarcinoma y cirrosis descompensada. Los pacientes con infección por VIH fueron clasificados en 3 grupos: sin coinfección por VHC, aquellos con aclaramiento espontáneo del VHC y los pacientes coinfectados crónicamente VIH/VHC. Los pacientes sometidos a tratamiento antiviral para el VHC que alcanzaron RVS fueron excluidos.

Se calculó la mortalidad relacionada con enfermedad hepática en los 3 grupos, tomando como referencia el grupo VIH monoinfectado. Se calculó la razón estandarizada de mortalidad (con su intervalo de confianza al 95%), ajustado por edad al diagnóstico, sexo y vía de transmisión) y la razón estandarizada de hospitalización usando la aproximación de Byar del modelo de Poisson.

_____

Se incluyeron resultados de 2379 pacientes VIH (1390 VIH monoinfectados, 146 aclaradores espontáneos de VHC y 843 con coinfección crónica VIH/VHC). La mortalidad global alcanzó el 33,8% (21,4% relacionada con enfermedad hepática). La mayor parte de los pacientes que sufrieron muerte relacionada con enfermedad hepática estaban bajo tratamiento antirretroviral y tenían un carga viral indetectable. El ratio de mortalidad relacionada con enfermedad hepática en los pacientes coinfectados VIH/VHC fue de 10,01 por 1000 paciente-años frente al 3,84 por 1000 paciente-años en el grupo de VIH monoinfectados (p<0,001). La tasa de mortalidad estandarizada en los pacientes coinfectados fue 4,52 (IC 95% 2,98-5,86). La fracción de mortalidad y hospitalización atribuíble a la infección crónica por VHC fue 0,61 y 0,74, respectivamente. No se encontraron diferencias en eventos relacionados con hígado entre pacientes VIH monoinfectados y los que aclararon espontanánemente el VHC.

_____

Los resultados obtenidos en este estudio han sido publicados en "HIV Medicine" en febrero 2017. Online ISSN: 1568-1293. Factor de Impacto JCR: 3,988 (Primer cuartil).

Liver-related mortality and hospitalizations attributable to chronic hepatitis C virus coinfection in persons living with HIV

A Mena,[1] H Meijide,[1,2] I Rodríguez-Osorio,[1] A Castro[1] and E Poveda[1]

[1]*Clinical Virology group, Institute of Biomedical Research of A Coruña (INIBIC)–University Hospital of A Coruña (CHUAC), Sergas, University of A Coruña (UDC), A Coruña, Spain and* [2]*Internal Medicine Service, Quiron Hospital, A Coruña, Spain*

Objectives

The aim of this study was to compare liver-related mortality and liver-related hospitalizations for persons living with HIV (PLWH) with and without hepatitis C virus (HCV) exposure, and to estimate the fraction of liver disease attributable to chronic HCV coinfection.

Methods

An ambispective cohort study followed PLWH between 1993 and 2014. PLWH were classified into three groups: those who were HIV-monoinfected, those who cleared HCV spontaneously and those with chronic HCV coinfection. Liver-related mortality was estimated for the three groups and compared with the adjusted standardized mortality ratio.

Results

Data for 2379 PLWH were included in the study (1390 monoinfected individuals, 146 spontaneous HCV resolvers and 843 with chronic HCV coinfection). Global mortality was 33.8%, 21.4% of which was liver-related. Patients who died from liver-related causes were mostly on antiretroviral therapy and had an undetectable HIV viral load when they died. The liver-related mortality rate in those with chronic HCV coinfection was 10.01 per 1000 patient-years *vs.* 3.84 per 1000 patient-years in the HIV-monoinfected group ($P < 0.001$). The adjusted standardized mortality ratio in the chronically HCV-coinfected group was 4.52 (95% confidence interval 2.98–5.86). The fractions of liver-related mortality and liver-related hospitalizations attributable to chronic HCV coinfection were 0.61 and 0.74, respectively. There were no differences in liver-related events between HIV-monoinfected individuals and those who spontaneously cleared HCV.

Conclusions

Chronic HCV infection increases the risk of liver-related mortality and liver-related hospitalizations in PLWH, despite good control of HIV infection. Sixty per cent of liver-related mortality in chronically HCV-coinfected PLWH could be attributable to chronic HCV infection. The effect of mass HCV eradication with new therapies should be evaluated.

Keywords: hepatitis C virus coinfection, liver-related hospitalization, liver-related mortality, people living with HIV

Accepted 21 December 2016

Introduction

Liver disease is an important contributor to morbidity and mortality among persons living with HIV (PLWH).

Correspondence: Dr Alvaro Mena, Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), As Xubias s/n, A Coruña 15006, Spain. Tel: +34 981178189; fax: +34 981176033; e-mail: alvaro.mena.de.cea@sergas.es

Liver-related mortality is common in PLWH with chronic hepatitis C virus (HCV) coinfection, accounting for 20–40% of all deaths, and is the main cause of liver-related hospitalizations [1,2].

In chronically HCV-infected persons without HIV infection, approximately 55–65% of liver-related mortality can be attributed to chronic HCV infection, when compared with persons who spontaneously clear HCV. In many cases, HCV infection is associated with a particular lifestyle

1

profile and, in the general population, spontaneous HCV resolvers are a good benchmark group comparator for evaluation of the independent contribution of chronic HCV infection, because they have the same risk factors and lifestyle as those with chronic HCV infection [3]. In PLWH, the differences between HIV-monoinfected individuals and spontaneous HCV resolvers in terms of liver-related mortality and liver-related hospitalizations are unknown.

The role of hepatitis viruses in the progression of liver damage is unquestionable. However, there are many other factors that contribute to the development of liver injury in PLWH, such as HIV replication, immune dysfunction, opportunistic infections, lifestyle exposures (alcohol or other drugs), metabolic disorders and some antiretroviral agents [4–7]. Sometimes these other factors can be overlooked because of the major role of HCV infection in the progression of liver disease in chronically HCV-coinfected PLWH. The aim of this study was to compare liver-related mortality and liver-related hospitalizations in PLWH with and without HCV exposure and to estimate the fraction of liver disease attributable to chronic HCV coinfection in this population.

Methods

This study included data for all PLWH followed in an ambispective cohort in a reference HIV clinic (University Hospital of A Coruña, Spain) between 1993 and 2014. All hospital admissions and the causes of death were obtained from the hospital records encoded according to the International Classification of Diseases (ICD-9). Liver-related disease was considered to include the following codes: viral hepatitis (070, 573.3), alcoholic liver disease (571.0–571.3), nonalcoholic liver disease (570, 571.4–571.9, 572–573), primary liver cancer (155), and decompensated cirrhosis (789.5, 567.23, 456.0). Cholelithiasis and cholecystitis (574–575) were not included as liver-related conditions. Fatal infections occurring in PLWH with cirrhosis were classified as liver-related deaths/hospitalizations when the episode included a code for cirrhotic decompensation.

Clinical and epidemiological variables were collected and a descriptive analysis was performed for all the variables recorded. PLWH were classified into three groups: those without viral hepatitis [negative for hepatitis B virus (HBV) surface antigen and HCV antibodies], those who spontaneously cleared HCV (HCV antibody-positive and undetectable HCV RNA without anti-HCV therapy) and chronically HCV-coinfected patients. PLWH who received anti-HCV therapy and achieved a sustained viral response (SVR) were excluded; those without an SVR were included in the chronically HCV-coinfected group.

Quantitative variables were reported as mean ± standard deviation (SD) and qualitative variables as frequency and percentage. The three groups were compared using chi-square for qualitative variables and one-way analysis of variance (ANOVA) for quantitative variables.

The liver-related mortality rate was estimated in the three groups (monoinfected individuals, HCV spontaneous resolvers and chronically HCV-coinfected individuals). Liver-related mortality rates were compared using the monoinfected group as the reference, and computing the standardized mortality ratios with their 95% confidence intervals (CIs), adjusted for sex, age at HIV diagnosis and transmission route, using Byar's approximation of the Poisson model. Liver-related hospitalization rates were calculated and compared between groups using the adjusted standardized hospitalization ratios.

The fraction of liver-related mortality attributable to chronic HCV infection was calculated relative to that in monoinfected PLWH using the equation (liver-related mortality rate in chronically HCV-coinfected group – liver-related mortality rate in monoinfected group)/liver-related mortality rate in chronically HCV-coinfected group, and relative to that in spontaneous resolvers as (liver-related mortality rate in chronically HCV-coinfected group – liver-related mortality rate in spontaneous resolvers)/liver-related mortality rate in chronically HCV-coinfected group [3]. The fraction of liver-related hospitalizations attributable to chronic HCV infection was calculated in a similar fashion. Results are expressed with the 95% CI.

Statistical analysis was performed using SPSS for Windows (v19.0; IBM Corp., Armonk, NY, USA). The research protocol was approved by the Regional Ethics Committee (register code 2015/164).

Results

A total of 2379 PLWH followed between 1993 and 2014 were included in the study, contributing 26 778 patient-years. The cohort included 75.2% men and had a mean (±SD) of 11.9 ± 4.2 years of follow-up. The main characteristics of the three study groups are shown in Table 1. The prevalence of HBV coinfection in chronically HCV-coinfected PLWH was 10.1%. Sixty-four (7.6%) of the 843 chronically HCV-coinfected PLWH had been treated with anti-HCV agents, all of which were interferon (IFN)-based regiments, without achieving SVR. Seventy chronically HCV-coinfected PLWH who were successfully treated with anti-HCV therapy were excluded. The mean (±SD) duration of HCV infection in the chronically HCV-coinfected group was 13.4 ± 4.2 years.

Table 1 Demographic characteristics, hospitalizations and mortality rates among monoinfected people living with HIV (PLWH), PLWH with spontaneous hepatitis C virus (HCV) clearance and PLWH with chronic HCV coinfection

	Monoinfected PLWH	PLWH who were spontaneous resolvers	Chronically HCV-coinfected PLWH	P-value
Number of patients	1390	146	843	
Male (%)	77.99	69.86	71.65	0.065
Age at HIV diagnosis (years) [mean ± SD]	34.8 ± 9.6	29.8 ± 10.2	28.4 ± 7.4	0.002
HIV transmission route (%)				< 0.001
IDU	23.96	81.51	83.99	
MSM	42.01	8.90	10.32	
CD4 count nadir (cells/μL) [mean ± SD]	204 ± 102	184 ± 126	163 ± 108	< 0.001
CDC-C (%)	51.9	54.8	59.4	0.002
Total follow-up (patient-years)	13 920	1766	11 092	< 0.001
Liver-related mortality events [n (%)]	54 (3.88)	7 (4.79)	111 (13.17)	< 0.001
Non-liver-related mortality events [n (%)]	388 (27.91)	40 (27.40)	203 (24.08)	0.134
Liver-related mortality rate (95% CI)*	3.88 (2.99–5.03)	3.96 (1.92–8.16)	10.01 (8.31–12.04)	< 0.001
Non-liver-related mortality rate (95% CI)*	27.87 (25.27–30.74)	22.65 (16.68–30.69)	18.30 (15.97–20.97)	0.140
Liver-related hospitalizations (n)	105	15	326	–
Non-liver-related hospitalizations (n)	3329	376	2578	–
Liver-related hospitalization rate (95% CI)*	7.54 (6.23–9.12)	8.49 (5.15–13.97)	29.39 (26.41–32.70)	< 0.001
Non-liver-related hospitalization rate (95% CI)*	239.15 (232.14–246.31)	212.91 (194.45–232.62)	232.42 (224.65–240.37)	0.070

CDC-C, Centers for Disease Control and Prevention category C; CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men; SD, standard deviation.
*Per 1000 patient-years.

In the whole cohort of PLWH, all-cause mortality involved 803 individuals (33.8%), including 442 (31.8%) monoinfected individuals, 47 (32.2%) spontaneous HCV resolvers and 314 (37.2%) chronically HCV-coinfected patients. Of these, 78.6% of deaths were secondary to non-liver-related causes; the most common cause of death was AIDS-related (47.7% in the monoinfected group, 48.9% in spontaneous HCV resolvers and 48.1% in the chronically HCV-coinfected group; $P = 0.106$), followed by non-AIDS-related infections (22.8% in the monoinfected group, 19.1% in the spontaneous HCV resolvers and 22.6% in the chronically HCV-coinfected group; $P = 0.060$). The main causes of liver-related mortality in the chronically HCV-coinfected group were liver cancer (34.2%), cirrhotic decompensation (28.8%), nonalcoholic liver disease (18.9%) and alcoholic liver disease (10.8%), whereas in the monoinfected group, they were nonalcoholic liver disease (53.7%), alcoholic liver disease (27.7%), cirrhotic decompensation (11.1%) and liver cancer (5.5%).

The liver mortality rate in each group is shown in Table 1. Compared with the monoinfected group, spontaneous resolvers had similar all-cause mortality (standardized mortality ratio 1.02; 95% CI: 0.71–1.47), but mortality was higher in the chronically HCV-coinfected group (standardized mortality ratio 1.27; 95% CI: 1.06–1.52). The standardized liver-related mortality ratios are presented in Figure 1.

The mean (±SD) time from HIV diagnosis to non-liver-related death was 8.1 ± 6.4 years in the monoinfected group, 7.6 ± 6.0 in the spontaneous HCV resolvers and 7.9 ± 6.6 in the chronically HCV-coinfected group ($P = 0.062$). In contrast, the mean (±SD) time from HIV diagnosis to liver-related death was 7.6 ± 6.8 years in the monoinfected group, 7.9 ± 6.1 in the spontaneous HCV resolvers and 13.3 ± 7.1 in the chronically HCV-coinfected group ($P = 0.003$). Those PLWH who died of liver-related causes were mostly undergoing antiretroviral treatment when they died (87.0% of the monoinfected group, 85.7% of the spontaneous HCV resolvers and 90.0% of the chronically HCV-coinfected group; $P = 0.810$), and most had controlled HIV replication (< 400 HIV-1 RNA copies/mL) (74.0% of the monoinfected group, 71.0% of the spontaneous HCV resolvers and 76.6% of the chronically HCV-coinfected PLWH).

During the study period, 6729 hospitalizations were recorded (6.6% liver-related) in 1844 patients (77.5% of the whole cohort); the median number of admissions was 2 (range 1–4). The main reasons for hospitalization of monoinfected PLWH were AIDS-related diseases (26.2%), other infections (28.5%) and cardiovascular disease (14.3%) whereas in the chronically HCV-coinfected group they were AIDS-related diseases (24.8%), other infections (27.7%) and liver-related diseases (11.2%). Figure 1 shows the standardized liver-related hospitalization ratios.

There were no differences in liver-related hospitalizations and liver-related mortality between monoinfected PLWH and PLWH who spontaneously cleared HCV. After adjusting for age at HIV diagnosis, sex and transmission
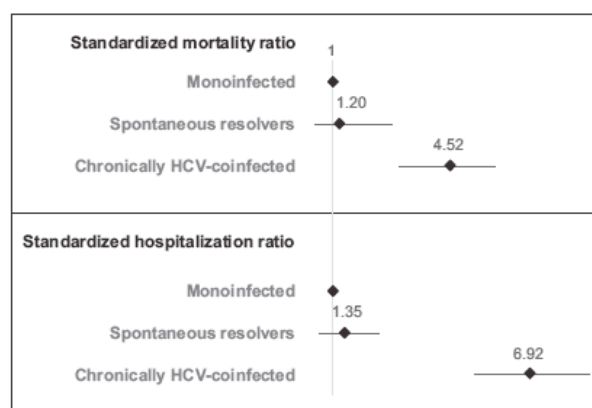
Fig. 1 Standardized liver-related mortality ratios and standardized liver-related hospitalization ratios, with monoinfected people living wih HIV (PLWH) as the reference. The ratios have been adjusted by gender, age at HIV diagnosis and transmission route, and are shown with their 95% confidence intervals. HCV, hepatitis C virus.

route, chronically HCV-coinfected individuals showed a more than fourfold higher rate of liver-related mortality and close to a sevenfold higher rate of liver-related hospitalizations than monoinfected PLWH ($P < 0.001$), as shown in Figure 1.

The fraction of liver-related mortality attributable to chronic HCV infection in PLWH relative to monoinfected PLWH was 0.61 (95% CI: 0.51–0.70) and that relative to spontaneous resolvers was 0.60 (95% CI: 0.51–0.69). The fraction of liver-related hospitalizations in chronically HCV-coinfected PLWH *vs.* monoinfected PLWH was 0.74 (95% CI: 0.69–0.79) and that *vs.* spontaneous resolvers was 0.71 (95% CI: 0.66–0.76); these were not significantly different ($P = 0.102$).

Discussion

In this study, more than one-third of deaths and 11% of hospitalizations in chronically HCV-coinfected PLWH were liver-related, as previously documented [8]. After adjustment, chronically HCV-coinfected PLWH had a higher mortality than monoinfected PLWH, mainly bacause of liver-related causes (standardized mortality ratio 6.92). There were no differences in terms of liver events between monoinfected PLWH and those who spontaneously resolved HCV infection. This similarity may be partly explained by their similar lifestyle exposures, despite the lower proportion of injecting drug users in monoinfected PLWH than in spontaneous

resolvers and the higher prevalence of other liver and metabolic disorders (such as steatosis) in PLWH, compared with the general population [4]. Therefore, in this population, patients without viral hepatitis could be used as a benchmark group comparator to explore the relative contribution of chronic HCV infection.

To our knowledge, this is the first study estimating the fraction of liver disease in PLWH attributable to chronic HCV infection. These data agree with the opinion that the majority of liver deaths in chronically HCV-coinfected patients are attributable to chronic HCV exposure. The attributable-fraction analysis provides further information: it shows that a significant proportion of liver-related mortality can occur independently of HCV infection, which should be considered when the future impact of treatment for HCV infection is estimated [1,2]. There are several studies evaluating the role of SVR to HCV treatment in liver disease progression and liver-related mortality in PLWH, most of which were included in a recent meta-analysis [9]. However, these studies were performed during the IFN era when less than one-third of patients elected to have anti-HCV therapy, so the favourable impact of HCV eradication could be maximized, due to selection bias [10]. Survival of PLWH achieving SVR in these classical studies was usually better than that of HCV-uninfected PLWH because of a selection bias. Consequently, more data on treatment and survival with the newer anti-HCV treatments and a more diverse sample population are needed [1].

In case−control studies comparing chronically HCV-infected patients with and without HIV infection, effective HIV control reduced, but did not eliminate, the higher risk of liver disease progression in coinfected patients in terms of hepatic decompensation, fibrosis progression and hepatocellular carcinoma, and was inversely related to the CD4 count [11,12]. Our study did not include data on the CD4 count at the time of the liver events, but chronically HCV-coinfected PLWH had a lower CD4 nadir than did monoinfected PLWH, despite similar antiretroviral treatment exposure and efficacy in terms of HIV viral load suppression.

This study has some limitations. First, some deaths (such as those attributable to infections in cirrhotic patients, or cancers other than hepatocellular carcinoma in which chronic HCV infection was involved) were coded as non-liver-related disease despite the important contribution of chronic HCV infection. Secondly, some important variables such as alcohol intake and active drug use were not available. Thirdly, PLWH with hepatitis B or D were excluded unless they were chronically HCV-coinfected, and the effect of these hepatitis coinfections on liver-related events was not considered. The impact of anti-HCV treatment and achievement of an SVR were not evaluated. Finally, the immunological status of PLWH was not appropriately recorded.

In conclusion, similar to the general population, close to two-thirds of liver-related mortality in chronically HCV-coinfected PLWH could be attributed to chronic HCV infection, but the liver-related mortality rate in PLWH was double that found in the general population (10.01 vs. 5.35 per 1000 patient-years, respectively) [3]. Chronic HCV infection is a relevant problem in PLWH, significantly increasing the rates of morbidity and mortality. Eradication of chronic HCV coinfection is crucial in PLWH, but is probably not a definitive solution to the problem of liver disease, and preventive, educational and social interventions are particularly important in PLWH.

Acknowledgements

References

1 Kovari H, Ledergerber B, Cavassini M, et al. High hepatic and extrahepatic mortality and low treatment uptake in HCV-coinfected persons in the Swiss HIV cohort study between 2001 and 2013. J Hepatol 2015; 63: 573–580.

2 Grint D, Peters L, Rockstroh JK, et al. Liver-related death among HIV/hepatitis C virus-co-infected individuals: implications for the era of directly acting antivirals. AIDS 2015; 29: 1205–1215.

3 Innes H, Hutchinson SJ, Obel N, et al. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland-Using spontaneous resolvers as the benchmark comparator. Hepatology 2016; 63: 1506–1516.

4 Kooij KW, Wit FW, Van Zoest RA, et al. Liver fibrosis in HIV-infected individuals on long-term antiretroviral therapy: associated with immune activation, immunodeficiency and prior use of didanosine. AIDS 2016; 30: 1771–1780.

5 Sherman KE, Rockstroh J, Thomas D. Human immunodeficiency virus and liver disease: an update. Hepatology 2015; 62: 1871–1882.

6 Kim HN, Nance R, Van Rompaey S, et al. Poorly controlled HIV infection: an independent risk factor for liver fibrosis. J Acquir Immune Defic Syndr 2016; 72: 437–443.

7 Fernández-Montero JV, Vispo E, Barreiro P, et al. Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. Clin Infect Dis 2014; 58: 1549–1553.

8 Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet 2014; 384: 241–248.

9 Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis 2015; 61: 730–740.

10 Berenguer J, Alvarez-Pellicer J, Martín PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2009; 50: 407–413.

11 Lo Re V, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. Ann Intern Med 2014; 160: 369–379.

12 Kramer JR, Kowalkowski MA, Duan Z, Chiao EY. The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection. J Acquir Immune Defic Syndr 2015; 68: 456–462.

ESTUDIO 3:

Aumento de la incidencia de cáncer en pacientes coinfectados

VIH/VHC vs VIH monoinfectados, 1993-2014.

Resumen:

En el seno de las comorbilidades no SIDA asociadas a la infección por VIH, el cáncer es un problema emergente. Parece que el VHC podría tener un paper adicional en el desarrollo de carcinogénesis. El objetivo del estudio fue evaluar todas las neoplasias presentes en pacientes con infección por VIH y comparar las diferencias que puedan existir con la población coinfectada VIH/VHC.

Se identificaron retrospectivamente todos los casos de cáncer en población VIH en el periodo 1993-2014, que a su vez se diferenciaron en neoplasias definitorias de SIDA (NDS) y no definitorias de SIDA (NNDS). La incidencia de cáncer cruda fue expresada como número de casos por 100000 persona-años de seguimiento, que vino determinado desde la fecha de diagnóstico de VIH hasta el final del periodo analizado. Se calculó la incidencia de cáncer y se comparó con la observada en la población general (utilizando la herramienta GLOBOCAN, 2012), calculando el ratio de incidencia estandarizada (RIE) con la aproximación de Byar del modelo de Poisson. Para estimar la probabilidad de cáncer tras el diagnóstico de VIH se realizó un análisis de riesgos competitivos. En este caso, la muerte antes del desarrollo de un cáncer fue considerada como un evento que compite. La incidencia acumulada de cáncer (NDS y NNDS) en VIH monoinfectados y VIH/VHC coinfectados fue también comparada mediante un análsis multivariante usando el modelo de regresión de Cox.

Un total de 185 pacientes (117 VIH monoinfectados y 68 coinfectados VIH/VHC) desarrollaron cáncer en una cohorte de 26580 paciente-años, con una tasa de incidencia cruda de 696 neoplasias por 100000 persona-años, mayor que en la

_____

población general (RIE=3,8). La tasa de incidencia cruda de NNDS en pacientes coinfectados VIH/VHC fue 415,0 (RIE=3,4), significativamente mayor que en VIH monoinfectados (377,3; RIE=1,8). Tras el ajuste, los pacientes coinfectados VIH/VHC tenía una mayor incidencia acumulada de NNDS que los pacientes VIH monoinfectados (HR=1,80), incluso después de excluír del análisis el hepatocarcinoma (HR=1,26).

_____

Increased incidence of cancer observed in HIV/hepatitis C virus-coinfected patients versus HIV-monoinfected

Héctor Meijide[a,b], Sonia Pértega[c], Iria Rodríguez-Osorio[a], Ángeles Castro-Iglesias[a], Josefa Baliñas[a], Guillermo Rodríguez-Martínez[d], Álvaro Mena[a,*] and Eva Poveda[a,*]

Background: Cancer is a growing problem in persons living with HIV infection (PLWH) and hepatitis C virus (HCV) coinfection could play an additional role in carcinogenesis. Herein, all cancers in an HIV-mono and HIV/HCV-coinfected cohort were evaluated and compared to identify any differences between these two populations.

Methods: A retrospective cohort study was conducted including all cancers in PLWH between 1993 and 2014. Cancers were classified in two groups: AIDS-defining cancer (ADC) and non-AIDS-defining cancer (NADC). Cancer incidence rates were calculated and compared with that observed in the Spanish general population (GLOBOCAN, 2012), computing the standardized incidence ratios (SIRs). A competing risk approach was used to estimate the probability of cancer after HIV diagnosis. Cumulative incidence in HIV-monoinfected and HIV/HCV-coinfected patients was also compared using multivariable analysis.

Results: A total of 185 patients (117 HIV-monoinfected and 68 HIV/HCV) developed cancer in the 26 580 patient-years cohort, with an incidence rate of 696 cancers per 100 000 person-years, higher than in the general population (SIR = 3.8). The incidence rate of NADC in HIV/HCV-coinfected patients was 415.0 (SIR = 3.4), significantly higher than in monoinfected (377.3; SIR = 1.8). After adjustments, HIV/HCV-coinfected patients had a higher cumulative incidence of NADC than HIV-monoinfected (adjusted hazard ratio = 1.80), even when excluding hepatocellular carcinomas (adjusted hazard ratio = 1.26).

Conclusion: PLWH have a higher incidence of NADC than the general population and HCV-coinfection is associated with a higher incidence of NADC. These data justify the need for prevention strategies in these two populations and the importance of eradicating HCV.

---

[a]Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña–Complexo Hospitalario Universitario de A Coruña, Sergas, Universidade da Coruña, Coruña, [b]Servicio de Medicina Interna, Hospital Quirón, [c]Unidad de Epidemiología Clínica y Bioestadística, Instituto de Investigación Biomédica de A Coruña–Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña, and [d]Unidad de Admisión y Documentación Clínica, Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, A Coruña, Spain.

Correspondence to Dr Álvaro Mena, PhD, Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña, Complexo Hospitalario Universitario de A Coruña, As Xubias s/n, A Coruña 15006, Spain.

Tel: +34 981178189; fax: +34 981176033; e-mail: alvaro.mena.de.cea@sergas.es

[*] Álvaro Mena and Eva Poveda contributed equally in this work.

Received: 1 November 2016; revised: 14 February 2017; accepted: 14 February 2017.

DOI:10.1097/QAD.0000000000001448

Introduction

Antiretroviral therapy (ART) has improved the survival of people living with HIV (PLWH), leading to a growing interest in the epidemiology of chronic illnesses, such as cardiovascular diseases or malignancies [1−7]. Cancer incidence in PLWH is expected to increase because of advances in treatment, demographic changes, immune dysfunction/reconstitution, aging, and continuous exposure to carcinogens [8−11]. Despite a decline of AIDS-defining cancers (ADCs), the risk of the most frequent non-AIDS-defining cancers (NADCs) remains higher than in the general population [12−14].

Globally, hepatitis C virus (HCV) coinfection is common among PLWH; in high-income countries, about 30% of PLWH are coinfected with HCV [15]. Liver disease progression is faster in HIV/HCV-coinfected patients than in HCV-monoinfected [16], and HCV is an increasingly frequent cause of death among PLWH. At the diagnosis of hepatocellular carcinoma (HCC), PLWH are younger and more frequently symptomatic with advanced tumors than HIV-negative patients [17]. With the improvement and the globalization of ART, the incidence of HCC has increased steadily in PLWH, driven primarily by HCV infection.

Regardless of the HIV infection, around 15% of cancer cases worldwide are attributable to infectious agents [18]. In addition to HCC, HCV infection has also been associated with an increased risk of developing many other nonliver cancers, with a higher incidence, mortality and a younger age at diagnosis and death than the general population [19,20]. Non-HIV-infected patients with chronic HCV infection have two- to three-fold increased risk of non-Hodgkin lymphoma (NHL) compared with the HCV-negative population [21,22].

There are few studies analyzing the impact of chronic HCV infection in PLWH, in terms of malignancy development and mortality [23,24]. The aim of this study is to analyze the incidence of cancer in PLWH infected and noninfected with HCV and determine the additional cancer risk in comparison to the general population.

Methods

Data collection

All PLWH older than 18 years and above at Complexo Hospitalario Universitario de A Coruña (CHUAC) between 1993 and 2014 were included in the cohort. Chronic HCV coinfection was defined by the presence of a measurable viral load by PCR, without acute hepatitis. Epidemiological, demographic, clinical, immunovirological data were recorded. Chronic hepatitis B virus (HBV) infection was defined by the presence of positive hepatitis B surface antigen for more than 6 months. Patients in care were defined as at least two visits to the outpatient clinic and a measure of $CD4^+$ cell count. Loss of care was defined by the nonappearance for reasons other than death.

All cancers in PLWH were obtained through the hospital-coding department. The method of selection was based on the review of the medical records of patients recognized by the encoding unit with a previous diagnosis of HIV infection and cancer. Malignancies registered during the follow-up in the clinical record were also included. Cancers were classified into two groups: ADC and NADC. Second malignancy was defined as the appearance, simultaneously or not, of a different tumor with malignant histology and the possibility of metastasis due to the first cancer was excluded. The end of the observation period was determined by date of cancer diagnosis, death or last follow-up visit for patients lost to follow-up, whichever occurred first. Patients with cancer were followed until their last regular clinical visit, death or lost to follow-up, to analyze the development of second malignancies.

Patients who are diagnosed of HCV infection during the follow-up contributed in person-years to the HIV-monoinfected group from HIV diagnosis to HCV diagnosis and to the HIV/HCV-coinfected group after. In coinfected patients who received anti-HCV treatment, the follow-up was censored when achieved sustained viral response (if applicable).

Ethical considerations

The research protocol was reviewed and approved by the regional ethics committee (register code 2015/164). All clinical data were anonymized and de-identified prior to analysis and the identification numbers of the patients were blinded.

Statistical analyses

A descriptive analysis was performed for all the variables recorded. Quantitative variables are reported as mean $\pm$ SD or median (interquartile range). Qualitative variables are expressed as frequencies and percentages.

A comparison of HIV-monoinfected and HIV/HCV-coinfected patients was performed and the percentages were compared using the χ^2 test. Quantitative parameters were compared by means of Student's t test.

Cancer incidence rates were estimated for both ADC and NADC. Crude incidence rates were expressed as the number of cases per 100 000 person-years of follow-up, and the follow-up was determined from the date of HIV diagnosis to the end of the observation period. Cancer incidence rates in this cohort were then compared with that observed in the Spanish general population, computing the standardized incidence ratios (SIRs) for coinfection groups and their 95% confidence intervals, with the Byar's approximation of Poisson model. Age-SIRs were also determined for each group using the age strata of the

reference population. For this purpose, cancer incidence data published for Spain in the GLOBOCAN 2012 statistics were used [25]. A comparison of mortality outcomes between the coinfection groups was evaluated using the χ^2 test. Logistic regression analyses were also performed to predict the death rate after 1 year.

A competing risk approach was used to estimate the probability of cancer at different time points in the follow-up after HIV diagnosis. Death before cancer was considered a competing risk event. The death-adjusted cumulative incidence for the marginal probability of cancer was obtained and the cumulative incidences in the competing risk data were compared using the modified log-rank test [26].

To compare the subdistribution hazard ratios (SHRs) for cancer occurrence between HIV-monoinfected and HIV/HCV-coinfected patients, multivariable analyses were conducted using modified Cox regression hazard models [27]. This analysis has been carried out for both ADC and NADC (all cancers and excluding HCC).

Data management and analyses were performed using SPSS, version 19.0 for Windows (IBM Corp., Armonk,

New York, USA). The cumulative incidence in competing risk analyses was calculated using the cmprsk package of R (Gray B. cmprsk: subdistribution analysis of competing risks. Available from http://cran.r-project.org/web/packages/cmprsk/index.html. Accessed 2 February 2016). $P < 0.05$ (two-sided) was considered statistically significant.

Results

A total of 2318 patients were included in the cohort, of which, 1461 (63.0%) were HIV-monoinfected patients and 857 (37.0%) were HIV/HCV-coinfected. The prevalence of chronic HBV infection was 2.6% in the first group and 6.4% in the second. One hundred and forty-nine (17.4%) coinfected patients received anti-HCV therapy (all with interferon based regimens); of these, 71 (47.6%) achieved sustained viral response. The main characteristics of the cohort population are shown in Table 1.

Cancer incidence rate and comparison with general population
In the study, the number of person-years at risk was 27 086, with an average of 11.7 ± 7.4 years per patient.

Table 1. Baseline characteristics and comparison between HIV-monoinfected patients and HIV/ hepatitis C virus-coinfected patients.

	Total ($n = 2318$)	HIV ($n = 1461$)	HIV/HVC ($n = 857$)	P
Age at HIV diagnosis (years), mean ± SD	32.3 ± 10.1	34.1 ± 10.8	29.1 ± 7.4	<0.001
Age at end of follow-up (years), mean ± SD	44.0 ± 9.7	44.1 ± 9.9	43.9 ± 7.9	0.580
Sex, n (%)				0.260
Male	1756 (75.8%)	1118 (76.5%)	638 (74.4%)	
Female	562 (24.2%)	343 (23.5%)	219 (25.6%)	
Transmission route, n (%)				<0.001
IDU	1266 (54.6%)	702 (48.0%)	564 (65.8%)	
Heterosexual	605 (26.1%)	437 (29.9%)	168 (19.6%)	
MSM	410 (17.7%)	290 (19.8%)	120 (14.0%)	
Other	37 (1.6%)	32 (2.2%)	5 (0.6%)	
Year of HIV diagnosis, n (%)				<0.001
Prev 1994	883 (38.1%)	431 (29.5%)	452 (52.7%)	
1995-2004	901 (38.9%)	589 (40.3%)	312 (36.4%)	
2005-2014	534 (23.0%)	441 (30.2%)	93 (10.9%)	
Follow-up (patient-years), sum	27,086	14,448	12,638	–
Dead during the follow-up, n (%)	778 (33.6%)	461 (31.6%)	317 (37.0%)	0.007
Crude mortality rate (deaths per 100 patient-years of follow)	2.9	3.2	2.5	
Lost to follow-up, n (%)	397 (17.1%)	247 (16.9%)	150 (17.5%)	0.010
Patients with cancer				
Patients, n (%)	185 (8.0%)	117 (8.0%)	68 (7.9%)	
Age at cancer diagnosis (years), mean ± SD	44.4 ± 10.1	44.8 ± 12.6	43.7 ± 7.8	0.516
Male sex, n (%)	150 (81.1%)	102 (87.2%)	48 (70.6%)	0.005
CD4+ cells nadir (cells/μl), median (range)	132 (58–266)	128 (52–286)	146 (63–210)	0.198
CDC C category[a], n (%)	139 (75.1)	89 (76.1%)	50 (73.5%)	0.726
CD4+ cells (cells/μl)[a], median (range)	236 (136–384)	234 (110–446)	243 (160–367)	0.672
Patients on ART[a], n (%)	110 (59.5%)	64 (54.7%)	46 (67.6%)	0.070
Time on ART (years)[a], median (range)	4.0 (1.0–10.0)	1.0 (0–6.0)	8.0 (4.0–11.5)	<0.001
HIV viral load <400 copies/ml[a], n (%)	95 (51.4%)	64 (54.7%)	31 (45.6%)	0.090
ADC, n (%)	79 (42.7)	63 (53.8%)	16 (23.5%)	<0.001
NADC, n (%)	106 (57.3)	54 (46.2%)	52 (76.5%)	<0.001
One-year mortality, n (%)	88 (47.6)	52 (44.4%)	36 (52.9%)	0.288
Cancer-related mortality, n (%)	87 (47.0)	56 (47.9%)	31 (45.6%)	0.879

ADC, AIDS-defining cancer; ART, antiretroviral therapy; NADC, non-AIDS-defining cancer.
[a]Data at cancer diagnosis.

Table 2. Observed cancers among the HIV-infected patients as compared to the general population (GLOBOCAN 2012).

	Number of patients	Number of cancers	Person-years	Crude incidence rate[a]	SIR (95% CI)
Total cancers					
Total cohort	2318	185	26580	696.0	3.8 (3.3–4.4)
HIV	1461	117	14112	829.1	3.8 (3.1–4.6)
HIV/HCV	857	68	12468	545.4	3.9 (3.0–4.9)
1993–2003	1704	53	11332	467.7	–
2004–2014	1906	132	15248	865.7	–
ADC					
Total cohort	2318	79	26824	294.5	27.2 (21.7–33.8)
HIV	1461	63	14248	442.2	37.4 (28.8–48.0)
HIV/HCV	857	16	12576	127.2	13.2 (7.5–21.3)
1993–2003	1704	43	11440	375.9	–
2004–2014	1906	36	15310	235.1	–
NADC					
Total cohort	2318	106	26844	394.9	2.3 (1.9–2.8)
HIV	1461	54	14313	377.3	1.8 (1.3–2.3)
HIV/HCV	857	52	12531	415.0	3.4 (2.5–4.4)
1993–2003	1704	38	11412	333.0	–
2004–2014	1906	68	15216	446.9	–

Differences between HIV-monoinfected and HIV/HCV-coinfected patients. ADC, AIDS-defining cancer; CI, confidence interval; HCV, hepatitis C virus; NADC, non-AIDS-defining cancer; SIR, standardized incidence rate.
[a]Per 100.000 person-years.

A total of 185 patients (117 HIV-monoinfected and 68 HIV/HCV-coinfected) had at least one malignancy during follow-up, with an overall incidence rate of 696.0 cases per 100 000 person–years of follow-up (829.1 in HIV-monoinfected patients and 545.4 in HIV/HCV-coinfected patients). Crude incidence rates for ADC and NADC in HIV-monoinfected patients and HIV-HCV-coinfected patients are presented in Table 2.

After computing age-standardized rates, a statistically significant increased incidence rate was observed for all types of cancer when compared with the incidence in general population (SIR = 3.8; 95% CI: 3.3−4.4). HIV/HCV-coinfected patients, in comparison to HIV-mono-infected, showed a higher SIR for NADC and a lower SIR for ADC (Table 2). For all age groups, a higher cancer incidence was observed in comparison to the general population, reaching statistically significance for groups between 18 and 64 years (Fig. 1). Monoinfected HIV patients showed higher incidence rates for groups between 18 and 44 years, whereas HIV/HVC-coinfected patients showed higher incidence for ages between 45 and 64 years. The 5.13% of HIV-monoinfected and 0.58% of HIV/HCV-coinfected patients of the cohort was older than 64 years (at the end of follow-up or cancer diagnosis); eight cancers were found in this age group (all in monoinfected) (Fig. 1).

The study period has been divided into two (1993−2003 and 2004−2014) and the crude incidence of ADC and NADC is shown in Table 2. The crude incidence of ADC in HIV-monoinfected patients was much higher during the first period (682.6 cases per 100 000 person–years) than in the second (282.3 cases per 100 000 person–years). Conversely, the incidence in coinfected patients was lower during the first period than in the second (61.2 versus 196.1 cases per 100 000 person–years).

At HIV diagnosis, patients with NADC were older (36.6 ± 11.7 years) than those with ADC (35.3 ± 13.1 years) and those without cancer (31.9 ± 9.7), $P < 0.001$. At cancer diagnosis, patients with NADC were also older (47.8 ± 10.4 years) than those with ADC (40.0 ± 11.9 years), $P < 0.001$.

Cancer location
The description of the location of all cancers is included in Table S1, http://links.lww.com/QAD/B57. The NHL was the most common cancer (26.5%), the majority of them (90.2%) were B-cell high-grade lymphomas. Comparatively with the general population the SIR of
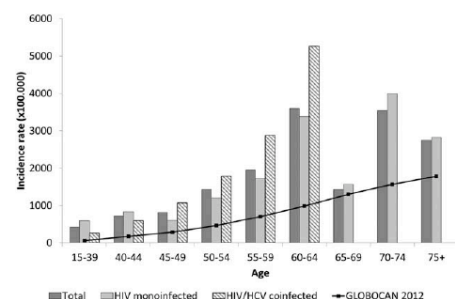

Fig. 1. Age-specific incidence rates of cancer in HIV-mono-infected and HIV/hepatitis C virus (HCV)-coinfected patients, comparatively with that in the general population (GLOBOCAN 2012).

NHL in HIV-monoinfected patients was SIR = 19.1 (95% CI: 12.1−40.7) and in HIV/HCV-coinfected patients was SIR = 12.2 (6.1−20.7). The 82.9% of NHL in HIV-monoinfected were diagnosed between 1993 and 2003, whereas in the coinfected group most of the NHL was diagnosed between 2004 and 2014 (78.6%). The NHL was diagnosed 0.5 years (0−2.6) after HIV diagnosis in monoinfected patients and 7.8 years (2.1−10.4) in coinfected patients, $P < 0.001$. The time of ART exposure was also much shorter in monoinfected than in coinfected patients [1.0 years (0−2.4) versus 6.2 (2.4−8.2), $P < 0.001$]. The incidence of Hodgkin lymphoma (HL) was higher than for the general population in monoinfected patients (SIR = 16.1; 95% CI: 5.0−51.3) and in coinfected patients (SIR = 21.7; 6.7−67.9).

Lung cancer (LC) is the most incident NADC. The main histological type of LC was adenocarcinoma (60.0% of the cases) and most LC was diagnosed in advanced stages (78.0% in stage III or IV). The incidence was higher than in the general population for both groups: HIV-monoinfected patients (SIR = 4.2; 2.8−6.5) and HIV/HCV-coinfected patients (SIR = 4.1; 2.7−6.3). All HCC (18 cases) appeared in HIV/HCV-coinfected patients, with the majority of being cirrhotic (94.4%). The SIR in coinfected was SIR = 24.0 (10.6−54.3).

Cumulative incidence of cancer in the follow-up

Figure 2 shows the cumulative incidence of ADCs and NADCs at different time points in the follow-up after HIV diagnosis. Globally, the cumulative incidence of cancer reached 3.5% (95% CI: 2.7−4.2%) at 5 years after HIV diagnosis and 6.4% (5.4−7.4%) at 10 years. The probability for a PLWH of being alive and cancer-free at the same time points was 88.8% and 79.3%, respectively.

The 10 and 20 years cumulative incidence of ADC was 3.8% and 4.3% in monoinfected patients and 1.1% and 1.7% in coinfected patients. On the contrary, the cumulative incidence of NADC was 2.3% (10 years) and 3.6% (20 years) in monoinfected, in coinfected patients was 1.9% and 4.8%, respectively.

During the follow-up, ADCs were less frequent in HIV/HCV-coinfected patients than in HIV-monoinfected patients. On the contrary, no differences were observed in the incidence rate of NADC between coinfected and monoinfected patients. However, after adjusting for age at HIV diagnosis, sex and transmission route, a higher cumulative incidence of NADC was observed for HIV/HCV-coinfected patients when compared with HIV-monoinfected patients (adjusted SHR = 1.80; 95% CI: 1.15−2.81). After excluding the HCC, the cumulative incidence of NADC remains higher in coinfected patients (adjusted SHR = 1.26; 1.02−1.94) (Table 3).

Cancer prognosis

Seven (3.8%) patients developed a second neoplasia; five of them had ADCs as their first cancer [four Kaposi's sarcoma (KS) and one NHL] and two NADCs (HL and prostate). Regarding the second tumor, six of seven were NADCs and the median time from the first to the second malignancy was 6.0 years (3.2−12.5).

In the mortality analysis, 124 patients (64.6% of patients with ADC and 68.9% with NADC) died after cancer diagnosis, with a median survival of 6 months (0−14). One-year mortality was 39.2% in ADCs (95% CI: 28.8−50.1) and 53.8% in NADCs (44.3−63.0), with an odds ratio = 1.8 (1.0−3.3) and $P = 0.055$. The comparison of
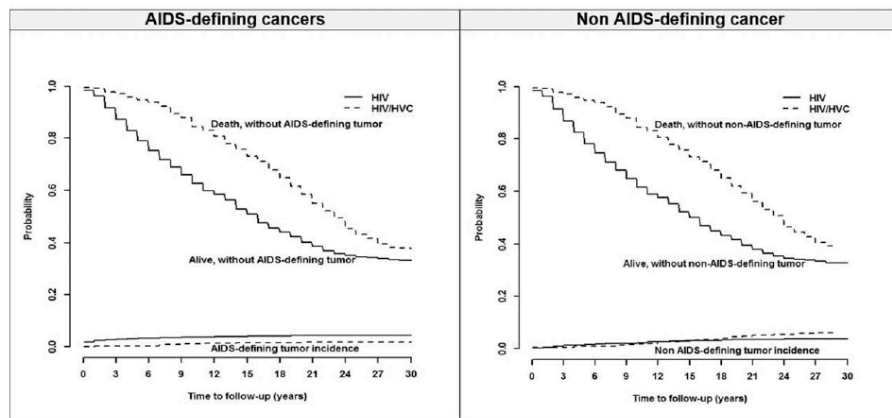

Fig. 2. Competing risk analysis of AIDS-defining and non AIDS-defining cancer incidence in the follow-up after diagnosis of HIV patients.

Table 3. Cumulative incidence of cancer in HIV-monoinfected and HIV/hepatitis C virus-coinfected patients.

	SHR (95% CI)	Adjusted SHR (95% CI)[b]
Total cancers		
Age at HIV diagnosis	1.05 (1.04, 1.06)	1.05 (1.03, 1.06)
Sex		
Female	1	1
Male	0.96 (0.69, 1.33)	0.95 (0.67, 1.34)
Transmission route		
IDU	1	1
MSM	1.06 (0.72, 1.56)	1.09 (0.72, 1.64)
Heterosexual	1.13 (0.82, 1.56)	1.11 (0.78, 1.56)
HIV	1	1
HIV/HCV	0.74 (0.55, 0.98)	1.01 (0.73, 1.38)
ADC		
Age at HIV diagnosis	1.04 (1.01, 1.06)	1.03 (1.00, 1.05)
Sex		
Female	1	1
Male	1.16 (0.68, 1.98)	1.09 (0.62, 1.91)
Transmission route		
IDU	1	1
MSM	1.4 (0.82, 2.38)	1.36 (0.77, 2.41)
Heterosexual	1.19 (0.74, 1.94)	1.19 (0.71, 2.01)
HIV	1	1
HIV/HCV	0.36 (0.21, 0.62)	0.44 (0.25, 0.74)
NADC		
Age at HIV diagnosis	1.06 (1.04, 1.07)	1.06 (1.05, 1.08)
Gender:		
Female	1	1
Male	0.84 (0.55, 1.28)	0.87 (0.55, 1.35)
Transmission route		
IDU	1	1
MSM	0.81 (0.45, 1.43)	0.87 (0.47, 1.60)
Heterosexual	1.07 (0.70, 1.65)	1.09 (0.68, 1.72)
HIV	1	1
HIV/HCV	1.15 (0.79, 1.66)	1.80 (1.15, 2.81)
NADC excluding HCC[a]		
HIV	1	1
HIV/HCV	0.98 (0.58, 1.46)	1.26 (1.02, 1.94)

CI, confidence interval; HCC, hepatocellular carcinoma; hepatitis C virus, hepatitis C virus; SHR, subhazard ratio.
[a]Hepatocellular carcinomas.
[b]Adjusted by age at HIV diagnosis, sex and transmission route.

mortality between HIV-mono and HIV/HCV-coinfected patients is shown in Table 1.

Discussion

In 2318 PLWH followed for 26 580 person-years, 8.0% of patients developed at least one cancer. This is in accordance with other previously published data, such as a large French study of 99,817 PLWH followed for 18 years in which 7.7% presented with at least one tumor [13], or the recently published data from the Veterans Aging Cohort Study (VACS) from North America, in which the 7.8% of the PLWH developed at least one cancer [28]. In our cohort, PLWH has double risk of developing a NADC than the general population, after adjustment for sex and age.

The analysis revealed a higher incidence of ADC in HIV-monoinfected than in coinfected patients. KS accounted for approximately 50% of ADC in HIV-monoinfected patients (41.3%), but only 12.5% of the ADC in coinfected patients. KS affects mainly to MSM, and the proportion of MSM in the coinfected group was lower in our cohort. KS is frequently an early manifestation of HIV infection, sometimes the first one; in this study, some coinfected patients were diagnosed with HCV infection months or years after HIV infection, and they were considered monoinfected up to the HCV-coinfection diagnosis. Active drugs users had less access to the health system during the 1990s; this could also contribute to the lower incidence of ADC in coinfected versus monoinfected patients during the first period (1993−2003).

The timing of cancer incidence after HIV diagnosis differed between ADC and NADC, being much shorter in ADC as shown previously [12]. However, in this study, we found that HIV/HCV-coinfected patients developed both ADC and NADC significantly later than HIV-monoinfected patients. Coinfected patients were mostly IDUs, with a higher mortality due to other reasons (violence, substance abuse, etc.), which could compete with the risk of early cancer development.

The competing risk analysis showed that, after adjusting for age at HIV diagnosis, sex transmission route and considering death without cancer a competitive risk; coinfected patients had a higher cumulative incidence of NADC than HIV-monoinfected. The weight of HCC in the incidence of NADC in the coinfected group is unquestionable but, when the HCC is excluded from the analysis, the cumulative incidence of NADC remains significantly higher in coinfected than in monoinfected patients (adjusted SHR = 1.26). HCV infection appears to have a role in cancer incidence and mortality and a higher incidence of lung, digestive tract and kidney cancers in HCV-infected patients has been reported previously. The molecular mechanism is unknown, but extrahepatic manifestation of hepatitis C with a chronic inflammatory condition, such as glomerulonephritis, cryoglobulinemia or lichen planus, can play a role [29−31]. HCV eradication reduces liver-related and nonliver-related mortality in patients with chronic HCV infection [32]. Nevertheless, the specific role of HCV eradication in cancer development is unknown.

The HCC represents the 34.6% of the NADC in HIV/HCV-coinfected patients. In our study, the HCC incidence in coinfected patients was 1.42/1000 person-years, close to that reported in other recent study with a mainly European population (1.59/1000 person-years) [33] but below the 4.44/1000 person-years published in a huge US Veterans cohort [17]. The older age, ethnic variability and earlier HIV-infection acquisition in the US cohort may explain this difference. Gjærde et al. [34] reported an alarming increase in HCC incidence between 2001 and 2014 (up to 2.3/1000 person-years); in our

cohort, all HCCs were diagnosed after 2003 and the incidence will presumably continue to grow over the following years. The development of new drugs against HCV and the eradication of HCV co-infection in PLWH may improve the prognosis of coinfected patients. Nonetheless, the impact on HCC incidence is not well established. Recent data suggest the increased risk of HCC early recurrence in patients treated with direct-acting antivirals for HCV infection, but more studies are needed to confirm these preliminary data [35,36].

A recent study by the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) has demonstrated a reduction of NHL incidence in monoinfected PLWH, but this favorable impact is minimized in hepatitis-coinfected patients [24]. In our study, the incidence of ADC in HIV-monoinfected patients decreases with the time, probably related with ART exposure and immune restoration, but the incidence in coinfected (most of cases NHL) is increasing, despite the ART exposure, in accordance with the COHERE Study, where HIV/HCV-coinfected patients receiving ART had higher risk of NHL than HIV-monoinfected patients (HR $= 1.73$). Several studies in HIV-uninfected persons have investigated the association between chronic HCV and lymphoma development, with odds ratios between 2.0 and 2.5 [37]. All these data suggest that HCV-coinfection has a role in the development of NHL, which becomes more evident when controlling the immunosuppression caused by the HIV-infection. Diverse mechanisms have been proposed, such as a direct oncogenic role of HCV, an immune dysregulation or a more prevalent coinfection by other viruses involved in lymphoma development (mainly herpes viruses). Without the eradication of viral hepatitis, it is expected that the incidence of NHL in coinfected will increase.

The immune status is closely related to the development of ADC. With the introduction of ART, many studies have observed a progressive decline in the incidence of ADC [28,38,39]. The inverse relation between $CD4^+$ cell count and NADC incidence is controversial. Some studies have documented the impact of a higher CD4 and ART exposure on lower NADC incidence (mainly in virus related-NADC), whereas others have not [28,40,41]. We found differences in $CD4^+$ cell count and ART exposure between HIV-monoinfected and HIV/HCV-coinfected patients at cancer diagnosis, but these differences were related to the higher incidence of ADC in the monoinfected group. No differences between mono- and coinfected patients were found when patients with NADC were compared. A recent analysis from the START study, published by Borges *et al.* [42], demonstrated that immediate ART initiation in patients with more than 500 $CD4^+$ cells/μl significantly reduces risk of cancer, mainly at the expense of infection-related cancer.

This study has several limitations. First, the retrospective design cannot ensure that all patients with cancer were included, mainly those with ambulatory treatment (skin tumors or high-grade cervix lesions). However, the regular monitoring in the HIV unit and the low mobility of the patients minimized this bias. Data regarding tobacco and alcohol consumption were not available, and we were unable to control for them in the multivariate analysis, and presumably their prevalence was higher in the coinfected group, which would be an important confounder. The cancers in this study were classified as ADC and NADC; currently, some studies use the infection-related and unrelated cancers classification for grouping cancers as infections and immunosuppression could play a role, but this classification also has some inaccuracies. In addition, the treatment data and anatomic stage from the registries, particularly in the first years of the study period, may have been incomplete. GLOBO-CAN provides estimates of cancer incidence, mortality, and prevalence for countries and world regions. Incidence data are derived from population-based cancer registries that vary in coverage and may capture the population of an entire country, but more often cover smaller areas, such as mayor cities, plus it is a point in time record and, in this study, it is used comparatively with a cohort followed for 22 years; despite these limitations, GLOBOCAN 2012 is a key source of information on the profile of cancer and represents the best estimates available. Finally, comparison with GLOBOCAN in persons older than 64 years must be interpreted with caution as this age group is under-represented in our cohort (3.45% globally). Nevertheless, it is expected than the incidence increases with the progressive aging of PLWH.

In conclusion, malignancies are an important comorbidity in PLWH, with a higher incidence than in the general population. After adjusting for epidemiological factors and mortality without cancer, HIV/HCV-coinfected patients presented more NADC than HIV-monoinfected patients, even excluding the HCC. Treatment of HCV infection and HIV replication control are fundamental strategies, but the valuable role of cancer-screening programs and early treatment must be assessed.

Acknowledgements

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Hogg RS, Heath KV, Yip B, Craib KJ, O'Shaughnessy MV, Schechter MT, et al. **Improved survival among HIV-infected individuals following initiation of antiretroviral therapy.** *JAMA* 1998; **279**:450–454.
2. Mocroft A, Phillips AN, Friis-Moller N, Colebunders R, Johnson AM, Hirschel B, et al. **Response to antiretroviral therapy among patients exposed to three classes of antiretrovirals: results from the EuroSIDA study.** *Antivir Ther* 2002; **7**:21–30.
3. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. **Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study.** *J Acquir Immune Defic Syndr* 2006; **43**:27–34.
4. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** *N Engl J Med* 1998; **338**:853–860.
5. d'Arminio Monforte A, Sabin CA, Phillips A, Sterne J, May M, Justice A, et al. **The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy.** *Arch Intern Med* 2005; **165**:416–423.
6. Ruxrungtham K, Brown T, Phanuphak P. **HIV/AIDS in Asia.** *Lancet* 2004; **364**:69–82.
7. Chen M, Jen I, Chen YH, Lin MW, Bhatia K, Sharp GB, et al. **Cancer Incidence in a Nationwide HIV/AIDS Patient Cohort in Taiwan in 1998-2009.** *J Acquir Immune Defic Syndr* 2014; **65**:463–472.
8. Engels EA, Pfeiffer RM, Goedert JJ, Vrigo P, McNeel TS, Scoppa SM, et al. **Trends in cancer risk among people with AIDS in the United States 1980-2002.** *AIDS* 2006; **20**:1645–1654.
9. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. **Cancer burden in the HIV infected population in the United States.** *J Natl Cancer Inst* 2011; **103**:753–762.
10. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. **Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antirretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS.** *Int J Epidemiol* 2005; **34**:121–130.
11. Simard EP, Engels EA. **Cancer as a cause of death among people with AIDS in the United States.** *Clin Infect Dis* 2010; **51**:957–962.
12. Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, et al. **Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy.** *Clin Infect Dis* 2013; **55**:756–764.
13. Hleyhel M, Belot A, Bouvier Am, Tattevin P, Pacenowski J, Genet P, et al. **Trends in survival after cancer diagnosis among HIV-infected individuals between 1992 and 2009. Results from the FHDH-ANRS CO4 cohort.** *Int J Cancer* 2015; **137**:2443–2453.
14. Meijide H, Mena A, Pernas B, Castro A, Lopez S, Vazquez P, et al. **Malignancies in HIV-infected patients. Descriptive study of 129 cases between 1993-2010.** *Rev Chil Infectol* 2013; **30**:156–161.
15. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. **Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010.** *Ann Intern Med* 2014; **160**:293–300.
16. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. **HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study.** *Ann Intern Med* 2013; **158**:658–666.
17. Kramer JR, Kowalkowski MA, Duan Z, Chiao EY. **The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection.** *J Acquir Immune Defic Syndr* 2015; **68**:456–462.
18. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. **Global burden of cancers attributable to infections in 2012: a synthetic analysis.** *Lancet Glob Health* 2016; **4**:e609–e616.
19. Duberg AS, Nordström M, Törner A, Reichard O, Strauss R, Janzon R, et al. **Non-Hodgkin's lymphoma and other nonhepatic malignancies in Swedish patients with hepatitis C virus infection.** *Hepatology* 2005; **41**:652–659.
20. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. **Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010.** *J Hepatol* 2015; **63**:822–828.
21. Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. **Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium.** *Clin Gastroenterol Hepatol* 2008; **6**:451–458.
22. Terrier B, Costagliola D, Prevot S, Chavez H, Missy P, Rince P, et al. **Characteristics of B-cell lymphomas in HIV/-coinfected patients during the combined antiretroviral therapy era: an ANRS CO16 LYMPHOVIR cohort study.** *J Acquir Immune Defic Syndr* 2013; **63**:249–253.
23. Hurtado-Cordovi J, Davis-Yadley AH, Lipka S, Vardaros M, Shen H. **Association between chronic hepatitis C and hepatitis C/HIV co-infection and the development of colorectal adenomas.** *J Gastrointest Oncol* 2016; **7**:609–614.
24. Wang Q, De Luca A, Smith C, Zangerle R, Sambatakou H, Bonnet F, et al. **Chronic hepatitis B and C virus infection and risk for non-Hodgkin lymphoma in HIV-infected patients: a cohort study.** *Ann Intern Med* 2017; **166**:9–17.
25. Ferlay J, Soerjomataram I, Ervik M, et al. **GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase no. 11.** Lyon: International Agency for Research on Cancer; 2013. http://GLOBOCAN.iarc.fr. Accessed 30 August 2016.
26. Gray R. **A class of K-sample tests for comparing the cumulative incidence of a competing risk.** *Ann Stat* 1988; **16**:1141–1154.
27. Fine JPGR. **A proportional hazard model for the subdistribution of a competing risk.** *J Am Stat Assoc* 1999; **94**:496–509.
28. Park LS, Tate JP, Sigel K, Rimland D, Crothers K, Gibert C, et al. **Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era 1997-2012.** *AIDS* 2016; **30**:1795–1806.
29. Kamar N, Izopet J, Alric L, Guilbeaud-Frugier C, Rostaing L, Hepatitis. **C virus-related kidney disease: an overview.** *Clin Nephrol* 2008; **69**:149–160.
30. Gumber SC, Chopra S. **Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations.** *Ann Intern Med* 1995; **123**:615–620.
31. Nagao Y, Sata M, Noguchi S, Seno'o T, Kinoshita M, Kameyama M, et al. **Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues.** *J Oral Pathol Med* 2000; **29**:259–266.
32. Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. **Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer.** *Cancer* 2016; **122**:1312–1337.
33. Gjærde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. **Trends in Incidences and risk factors for hepatocellular carcinoma and other liver events in HIV and hepatitis C virus-coinfected individuals from 2001 to 2014: a multicohort study.** *Clin Infect Dis* 2016; **63**:821–829.
34. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. **Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution.** *J Hepatol* 2016; **65**:719–726.

35. ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). **Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts.** *J Hepatol* 2016; **65**:734–740.

36. Dal Maso L, Franceschi S. **Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies.** *Cancer Epidemiol Biomarkers Prev* 2006; **15**:2078–2085.

37. Tada T, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, *et al.* **Viral eradication reduces all-cause mortality in patients with chronic hepatitis C virus infection: a propensity score analysis.** *Liver Int* 2016; **36**:817–826.

38. Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, *et al.* **Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort.** *Clin Infect Dis* 2013; **57**:1638–1647.

39. Silverberg MJ, Lau B, Achenbach CJ, Jing Y, Althoff KN, D'Souza G, *et al.* **Cumulative incidence of cancer among persons with HIV in North America: a cohort study.** *Ann Intern Med* 2015; **163**:507–518.

40. Borges AH, Dubrow R, Silverberg MJ. **Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk.** *Curr Opin HIV AIDS* 2014; **9**:34–40.

41. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, *et al.* **HIV infection and the risk of cancers with and without a known infectious cause.** *AIDS* 2009; **23**:2337–2345.

42. Borges ÁH, Neuhaus J, Babiker AG, Henry K, Jain MK, Palfreeman A, *et al.* **Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection.** *Clin Infect Dis* 2016; **63**:1668–1676.

DISCUSIÓN

_____

7.1 Discusión Estudio 1: Tendencias en hospitalizaciones, reingresos y mortalidad hospitalaria en pacientes con infección por VIH entre 1993-2013. Impacto de la coinfección VIH/VHC.

Este estudio evalúa las tendencias en hospitalización en pacientes con infección por VIH en el área sanitaria de A Coruña. En general, la ratio de hospitalización disminuyó de 31/100 pacientes en 1993 a 20/100 pacientes en 2013, aunque permanece todavía más alta que la poblacion general, datos en concordancia con estudios previos publicados en otros países [Berry SA et al, 2013, Crowell TA et al, 2015]. El análisis de tendencias joinpoint estableció un punto de cambio en el año 1996, año que coincide con la introducción del TARGA y su rápido impacto en el descenso de las enfermedades definitorias de SIDA. En dicha fecha, la tendencia en hospitalización se modificó desde un crecimiento porcentual anual del 11,8% a un descenso porcentual del 3,4%.

Se observaron cambios significativos en las causas de hospitalización cuando se comparan los dos periodos (1993-2002 vs 2003-2013). Así, se apreció un descenso de aquellas motivadas por procesos infecciosos (principalmente definitorias de SIDA) y eventos psiquiátricos (trastornos mentales, abuso de tóxicos, etc), en contra de un incremento significativo y progresivo de ingresos motivados por enfermedades neoplásicas (preferentemente no definitorias de SIDA), enfermedades respiratorias crónicas, enfermedades cardiovasculares y relacionadas con enfermedad hepática. De hecho, en global, las hospitalizaciones por enfermedades definitorias de SIDA disminuyeron en nuestra cohorte desde un 28% a un 16,2%, aunque su mortalidad persistió muy elevada (15% primer periodo vs 12,3% en el segundo); este último dato

refleja que las enfermedades definitorias de SIDA son todavía a día de hoy un problema de salud pública, que requiere la universalización del TARGA y la implantación de medidas diagnósticas y preventivas adecuadas [Berry SA et al, 2012]. La alta tasa de diagnósticos tardíos motiva, en buena parte, el estancamiento en el descenso en la incidencia de eventos SIDA en los últimos años.

Los ingresos en la Unidad de Cuidados Intensivos se triplicaron en el segundo periodo, probablemente en relación con un incremento en la esperanza de vida de este colectivo, una mejora en el cuidado del mismo, así como un mayor acceso a las distintas modalidades de tratamiento de una manera similar a la población general. A pesar de esta destacada mejoría, tanto la estancia media como la tasa de reingreso a los 30 días, en torno al 20%, obtuvieron unos resultados similiares en ambos periodos a los ya publicados previamente [Berry SA et al, 2013, Lopez C et al, 2016, Wier LM et al, 2012]. Es bien conocido que la tasa de reingresos tiene un impacto sobre la mortalidad. De hecho, la mortalidad intrahospitalaria en nuestra cohorte se mantiene elevada, también acorde con trabajos previos [Crowell TA et al, 2015; Ingle SM et al, 2014]. En el análisis más detallado de las causas de muerte, observamos de nuevo, una significativa contribución de eventos NO SIDA en el segundo periodo en detrimento de un descenso notable de eventos SIDA.

La coinfección crónica VIH/VHC parece tener un papel añadido en las hospitalizaciones. En nuestra cohorte casi el 40% de los pacientes estaban coinfectados de manera crónica. Este subgrupo de pacientes tuvo más hospitalizaciones, más tasa de reingreso y mayor número de estancias totales en comparación con el grupo de VIH-monoinfecados, acorde con lo descrito previamente

_____

en otros trabajos [Castellares C et al, 2008]. De forma llamativa, la incidencia hospitalaria en el año 2013 fue el doble respecto al grupo de VIH-monoinfectado. El impacto positivo del TARGA, a partir de 1996, en el descenso en la tasa de hospitalizaciones, es tres veces menor en los pacientes VIH/VHC coinfectados que en los monoinfectados, al verse amortiguado por las hospitalizaciones motivadas por descompensaciones hepáticas, que aumentan con el tiempo de seguimiento en los coinfectados. La tasa de ingresos por descompensaciones hepáticas en coinfectados fue el doble en el segundo periodo respecto del primero. En base a lo expuesto, parece que la coinfección VIH/VHC podría enmascarar el beneficio del TARGA y las mejoras en el cuidado del paciente VIH en términos de mayor hospitalización y mortalidad intrahospitalaria, aunque también es posible que otros factores tengan un impacto en estas observaciones (alcohol, UDVP, tabaco, etc). Estudios previos han demostrado que la mortalidad relacionada con la infección por VIH ha descendido mientras que la mortalidad relacionada con la infeccion por VHC se mantiene estable. Por todo ello, es esperable que en los próximos años se observe un aumento la morbi-mortalidad en este colectivo en caso de que la infección por VHC no sea erradicada [Meyers DJ et al, 2014]. El impacto que pueden tener en esta situación los nuevos antivirales de acción directa está por evaluar.

El presente estudio tiene algunas limitaciones que merecen ser mencionadas. Se trata de un estudio retrospectivo con datos de un solo centro lo que podría afectar a la generalización de resultados. Se utilizó la herramienta CIE-9 para codificar las causas de hospitalización, lo que podría generar errores, aunque estos han sido minimizados al ser realizado por un único observador. Aunque en nuestro área no hay

_____

otras clínicas con atención a pacientes VIH, hay pacientes con alguna hospitalización sin tener un seguimiento activo en la Unidad, lo que podría sobreestimar la tasa de hospitalización, debido a que se trata de un centro de referencia y los pacientes pueden ser enviados para realizar determinados estudios o tratamientos. Además, hay variables que non han podido ser recogidas y podrían tener también un impacto en los resultados (tabaco, alcohol, situación inmunológica, tiempo exposicion a TARGA, etc). Por último, el estudio no incluyó pacientes tratados con los nuevos antivirales de acción directa para el tratamiento de la infección por VHC ni tampoco un grupo control de pacientes sin infección por VIH. Las pérdidas de seguimiento, aunque pocas, tampoco fueron codificadas.

En resumen, presentamos resultados de cohorte extensa de pacientes con infección por VIH durante más de 20 años con un descenso significativo en la tasa de hospitalizaciones, especialmente, a expensas de una disminución progresiva de enfermedades definitorias de SIDA. Consecuentemente, en los últimos 10 años se ha observado un ascenso significativo de comorbilidades crónicas NO SIDA y enfermedades neoplasicas no definitorias de SIDA. Sin embargo, la estancia media, la tasa de reingreso y la mortalidad intrahospitalaria continúa siendo elevada. Por último señalar que la coinfección VIH/VHC tiene un impacto negativo en la morbi-mortalidad y en el consumo de recursos en la población VIH. Estos resultados son determinantes para implementar estrategias en el manejo de estos pacientes, prestando especial atención a las comorbilidades que justifican la mayor parte de las hospitalizaciones y muertes a día de hoy.

_____

7.2 Discusión Estudio 2: Mortalidad relacionada con enfermedad hepática atribuíble al virus de la hepatitis C en pacientes con infección por VIH.

En este estudio más de la tercera parte de las muertes y el 11% de las hospitalizaciones en pacientes coinfectados VIH/VHC estuvieron en relación con enfermedad hepática, cifras similares a estudios previos [Smith CJ et al, 2014]. Además, en estos pacientes se observa una mayor mortalidad que en los pacientes VIH monoinfectados (ratio de mortalidad estandarizada 6,92), sin encontrar diferencias entre el grupo de VIH monoinfectados y aquellos que aclararon espontaneamente el VHC. Esta similitud podría explicarse en parte porque ambas poblaciones comparten factores de riesgo exposicionales. De esta forma, los pacientes sin hepatitis vírica podrían utilizarse como grupo comparador (benchmark) con el objetivo de explorar la contribución relativa de la coinfección por VHC.

El análisis de la fracción atribuíble demostró que la mayor parte de los eventos relacionados con enfermedad hepática en pacientes coinfectados son atribuíbles a la exposición al VHC. Pero, por otro lado, hay una proporción importante de muertes por enfermedad hepática en pacientes VIH/VHC coinfectados (39%) que podría ocurrir de manera independiente de la infección crónica por VHC, dato que se debe tener en cuenta cuando se intenta estimar el efecto beneficioso del acceso masivo al tratamiento del VHC con alta eficacia con antivirales de acción directa [Grint D et al, 2015]. Hasta el momento, solo disponemos de trabajos realizados en la era del interferón [Kovary H et al, 2015; Simmons B et al, 2015], en los que únicamente un tercio de los pacientes coinfectados eran elegibles para el tratamiento antiviral, con

_____

todos los sesgos que eso conlleva al intentar extrapolar estos datos a un escenario de acceso universal al tratamiento frente al VHC.

El estudio no está exento de limitaciones. De nuevo, algunos factores de riesgo implicados en mortalidad no están recogidos, como las coinfecciones por VHB y VHD que fueron excluidas. Tampoco se evaluó la respuesta viral sostenida pues los pacientes tratados y curados VHC fueron excluidos. Además, es posible que puedan existir errores en la codificación de las muertes, así como tampoco se evaluaron ni se codificaron las pérdidas de seguimiento. A pesar de todo ello, nuestro estudio demostró que cerca de dos terceras partes de la mortalidad por causa hepática en los pacientes coinfectados VIH/VHC podría ser atribuída al VHC, dato similar a la población general, si bien es necesario destacar que esta mortalidad es el doble en los pacientes coinfectados VIH/VHC con respecto a la esperada en población general (10.01 vs. 5.35 por 1000 paciente-años, respectivamente) [Innes H et al, 2016].

En conclusión, la infección crónica por VHC es un problema relevante en pacientes con infección por VIH que aumenta de manera significativa la tasa de morbilidad y mortalidad. La erradicación del VHC es crucial en este grupo de pacientes, aunque probablemente no sea la solución definitiva al problema de la enfermedad hepática, de ahí que sea especialmente importante en estos pacientes implementar intervenciones con carácter preventivo, educacional y social.

_____

7.3 Discusión Estudio 3: Incidencia aumentada de cáncer en pacientes coinfectados

VIH/VHC vs VIH monoinfectados, 1993-2014.

En un estudio con un seguimiento de 26580 paciente-años encontramos que un 8% de los pacientes con infección por VIH desarrollaron al menos una neoplasia, datos que se asemejan a los datos de otras cohortes internacionales como la cohorte francesa [Hleyhel M et al, 2015] u otra americana [Brickman C et al,2015]. El análisis reveló que los pacientes VIH tienen un riesgo duplicado de desarrollar una NNDS respecto a la población general ajustado por sexo y edad. Asímismo, se observó una mayor incidencia de NDS en pacientes VIH monoinfectados respecto a coinfectados VIH/VHC, a expensas fundamentalmente de sarcoma de Kaposi. Probablemente estos resultados puedan estar relacionados con una mayor proporción de HSH en el grupo de VIH monoinfectados y una mayor proporción de UDVP en el de coinfectados, hecho que podría haber contribuído a un menor acceso de este último colectivo al sistema sanitario, especialmente durante el primer periodo del estudio (1993-2002).

El análisis de riesgos competitivos mostró que, tras ajustar por edad al diagnóstico de VIH y ruta de transmisión y considerando la muerte sin cáncer como un riesgo competitivo, los pacientes coinfectados tuvieron una incidencia acumulada de NNDS mayor que los pacientes VIH monoinfectados. Es incuestionable la contribución del hepatocarcinoma en estos datos, no obstante, excluyéndolo del analisis, la incidencia acumulada de NNDS continúa siendo mayor en coinfectados vs monoinfectados (SHR ajustado=1,26). La infección por VHC parece tener un papel en la incidencia de cáncer. De hecho, se ha mostrado previamente una mayor incidencia de linfomas, neoplasias del tracto gastrointestinal, genitourinario, entre otras, en

_____

pacientes con infección crónica por VHC. El mecanismo etiopatogénico es desconocido, pero parece que las manifestaciones extrahepáticas del VHC podrían generar una condición de inflamación crónica persistente y jugar un papel en la carcinogénesis [Kamar N et al, 2008; Nagao Y et al, 2000; Ryerson AB et al, 2016]. Sin embargo, el papel de la erradicación del VHC, sobre el desarrollo de cáncer, más allá del hepatocarcinoma, está todavía por determinar.

En el presente estudio la incidencia de NDS en pacientes VIH monoinfectados disminuye con el tiempo, en relación con el mejor control inmunovirológico y la reconstitución inmune; sin embargo, la incidencia en pacientes VIH/VHC aumenta, y lo hace a expensas de los linfomas no hodgkin (LNH). Se observaron resultados similares en un estudio de la cohorte COHERE [Innes H et al, 2016], que demostró una reducción significativa de LNH en pacientes VIH monoinfectados con el inicio y uso continuado del TAR, pero este impacto positivo se vio minimizado en pacientes coinfectados, de tal forma que el riesgo de desarrollar LNH era 1,73 veces mayor en coinfectados vs monoinfectados con adecuado TAR. Mientras que estudios previos ya habían relacionado VHC y LNH en pacientes VIH, se han propuesto numerosas hipótesis han para esta relación: el papel oncogenico del VHC, una disrregulación inmune o la presencia de otros virus oncogénicos, entre otros. Con el tratamiento frente al VHC cabría esperar una reducción en la incidencia de LNH.

El hepatocarcinoma representa el 34% de todas las NNDS en nuestra serie en pacientes coinfectados, con una incidencia de 1,42/1000 paciente-años, cercana a otros datos publicados en población europea [GJerde LI et al, 2016]. Además, todos los hepacarcinomas han sido diagnosticados en el segundo periodo, concretamente

después de 2003, por lo que es esperable que la incidencia continúe aumentando en los próximos años. Se desconoce el papel que pueden jugar los nuevos antivirales de acción directa en la evolución de la enfermedad y el desarrollo de hepatocarcima, una vez erradicada la infección por VHC [ANRS Collaborative Study Group on Hepatocellular Carcinoma, 2016; Reig M et al, 2016].

Este estudio presenta limitaciones que deben ser mencionadas. En primer lugar, el diseño retrospectivo no puede asegurar que todos los enfermos de cáncer hayan sido incluidos (tumores de piel, lesiones cervicales de alto riesgo quedaron excluídas). Sin embargo, el seguimiento clínico continuado en la unidad y la escasa movilidad de estos pacientes minimizarían este sesgo. En segundo lugar, datos sobre factores de riesgo como tabaco y alcohol no fueron recogidos y probablemente sean más prevalentes en el grupo de coinfectados, lo que supone un importante sesgo. Por último, GLOBOCAN es una herramienta para estimar incidencia, prevalencia y mortalidad por cáncer por países, una valiosa fuente de información del perfil de cáncer según el país. Sin embargo, tenemos que tener en cuenta que GLOBOCAN está basada en registros poblacionales con una cobertura variable en cada país y que además aporta un punto exacto en el tiempo. Por el contrario, en nuestro estudio la usamos como comparativa para una cohorte seguida en un perido de más de 20 años.

En conclusión, las neoplasias son una comorbilidad importante en pacientes con infección por VIH, con una incidencia incluso mayor que en población general. Tras ajustar por factores epidemiológicos, los pacientes coinfectados VIH/VHC presentan más NNDS que VIH monoinfectados, incluso tras excluir el hepatocarcinoma. El tratamiento del VHC y el control de la replicación del VIH son estrategias

fundamentales. El papel en la disminución de la morbi-mortalidad inherente a estas

estrategias todavía necesita ser evaluado.

CONCLUSIONES

_____

1. Se ha observado un descenso significativo en la tasa de hospitalizaciones (3,4% anual a partir de 1996) en los pacientes con infección por VIH en el área sanitaria de A Coruña entre 1993 y 2013. Este descenso, se debe fundamentalmente a la progresiva disminución de las enfermedades definitorias de SIDA. Sin embargo, en este mismo período se ha observado un aumento importante de las comorbilidades crónicas no SIDA, especialmente las enfermedades neoplásicas no definitorias de SIDA.

2. La coinfección VIH/VHC tiene un impacto negativo en la morbimortalidad y el consumo de recursos de los pacientes con infección por VIH. Se observó que los los pacientes coinfectados VIH/VHC tuvieron un 50% más hospitalizaciones por paciente, un 10% mayor tasa de reingreso, lo que conlleva a mayor número de estancias totales y mayor mortalidad global que los pacientes VIH monoinfectados.

3. La enfermedad hepática representó mas de la tercera parte de las muertes y el 11% de las hospitalizaciones en pacientes coinfectados VIH/VHC. La mayor parte de los eventos relacionados con el hígado en pacientes coinfectados (61% de las muertes y 74% de las hospitalizaciones) son atribuibles a la exposición crónica al VHC.

_____

4. La tasa de mortalidad por causa hepática fue mayor en pacientes coinfectados VIH/VHC que en monoinfectados (razón de mortalidad estandarizada = 4,52). No se observaron diferencias significativas entre el grupo de VIH monoinfectados y aquellos que aclararon espontaneamente el VHC (razón de mortalidad estandarizada = 1,20).

5. En general, se observó que los pacientes VIH tienen un riesgo duplicado de desarrollar una neoplasia no definitoria de SIDA respecto a la población general (razón de incidencia estandarizada = 2,3).

6. Los pacientes coinfectados VIH/VHC presentan más neoplasias no definitorias de SIDA que los pacientes VIH monoinfectados (subhazard ratio ajustado = 1,80), incluso tras excluir el hepatocarcinoma (subhazard ratio ajustado = 1,26).

BIBLIOGRAFÍA

_____

1.   Abecasis AB, Wensing AM, Paraskevis D, Vercauteren J, Theys K, Van der Vijver DA, et al. HIV-1 subtype distribution and its demographic determinants in newly diagnosed patients in Europe suggest highly compartmentalized epidemics. Retrovirology 2013;10:7.

2.   Amendola A, Bloisi M, Marsella P, Sabatini R, Bibbò A, Angeletti C, Capobianchi MR. Standardization and performance evaluation of "modified" and "ultrasensitive" versions of the Abbott RealTime HIV-1 assay, adapted to quantify minimal residual viremia. J Clin Virol 2011;52:17-22.

3.   Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative análisis of 13 HIV cohort studies. Clin Infect Dis. 2010;50:1387–96.

4.   ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. J Hepatol 2016; 65:734–740.

5.   Área de Vigilancia de VIH y Comportamientos de Riesgo. Vigilancia Epidemiológica del VIH y sida en España: Sistema de Información sobre Nuevos Diagnósticos de VIH y Registro Nacional de Casos de Sida. Plan Nacional sobre el Sida - S.G. de Promoción de la Salud y Epidemiología / Centro Nacional de Epidemiología - ISCIII. Madrid; Nov 2016.

6.   Barré-Sinoussi F, Chermann J, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L et al. Isolation of a T-lymphotropic retrovirus from a patient risk for acquired immune deficiency syndrome (AIDS). Science 1983;220:868-871.

7.   Berenguer J, Alvarez-Pellicer J, Mart_ın PM, et al. Sustained virological response to interferon plus ribavirin reduces liverrelated complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2009; 50: 407–413.

8.   Berry SA, Fleishman JA, Yehia BR, Korthuis PT, Agwu AL, Moore RD, et al. Thirty-day hospital readmission rate among adults living with HIV. AIDS. 2013;27:2059–68.

9.   Berry SA, Fleishman JA, Moore RD, Gebo KA, HIV Research Network. Trends in reasons for hospitalization in a multisite united states cohort of persons living with HIV, 2001–2008. J Acquir Immune Defic Syndr. 2012;59: 368–75.

10.   Borges ÁH, Silverberg MJ, Wentworth D, et al. Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. AIDS 2013; 27:1433–41.

11.   Borges AH, Dubrow R, Silverberg MJ. Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antirretroviral therapy will alter this risk. Curr Opin HIV AIDS 2014; 9:34– 40.

12.   Borges A´ H, Neuhaus J, Babiker AG, Henry K, Jain MK, Palfreeman A, et al. Immediate antiretroviral therapy reduces risk of nfection-related cancer during early HIV infection. Clin Infect Dis 2016; 63:1668–1676.

13.   Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. J Hepatol. 2007;47:527–37.

14.   Brickman C, Palefsky JM. Cancer in the Host: Epidemiology and Pathogenesis in the Antirretroviral Era. Curr HIV/AIDS Rep. 2015 Dec;12(4):388-96.

15.   Buchacz K, Baker RK, Moorman AC, Richardson JT, Wood KC, Holmberg SD, Brooks JT. HIV Outpatient Study (HOPS) Investigators. Rates of hospitalizations and associated diagnoses in a largemultisite cohort of HIV patients in the United States, 1994-2005. AIDS 2008 Jul 11;22(11):1345-54.

16.   Camoni L, Raimondo M, Regine V, Salfa MC, Suligoi B; regional representatives of the HIV Surveillance System. Late presenters among persons with a new HIV diagnosis in Italy, 2010-2011. BMC Public Health 2013;13:281.

17.   Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo ME, Casado R, et al. Liver cirrhosis in HIV-infected patients: prevalence, aetiology and clinical outcome. J Viral Hepat. 2008;15:165–72.

18.   Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992; 41:1–19.

19.   Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.

20.   Collini P, Morris A. Maintaining lung health with longstanding HIV. Curr Opin Infect Dis. 2016;29:31–8.

21.   Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA, et al. Impact of hepatitis coinfection on hospitalization rates and causes in a multicenter cohort of persons living with HIV. J Acquir Immune Defic Syndr. 2014;65:429–37.

22. Crowell TA, Gebo KA, Blankson JN, Korthuis PT, Yehia BR, Rutstein RM, et al. Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. J Infect Dis. 2015;211:1692–702.

23. Crum-Cianflone NF, Grandits G, Echols S, Ganesan A, Landrum M, Weintrob A et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? J Acquir Immune Defic Syndr. 2010 Jul;54(3):248-57.

24. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. Lancet Respir Med. 2014;2:583–92.

25. Dominguez-Molina B, Leon A, Rodriguez C, Benito JM, Lopez-Galindez C, Garcia F et al. Analysis of Non-AIDS-Defining Events in HIV Controllers. Clin Infect Dis 2016;62(10):1304-9.

26. Elixhauser A, Steiner C, Palmer L. Clinical Classifications Software (CCS), 2008. U.S. Agency for Healthcare Research and Quality; 2008.

27. Fernandez-Montero JV, Vispo E, Barreiro P, et al. Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. Clin Infect Dis 2014; 58: 1549–1553.

28. Gallo RC, Sliski A, Wong-Staal F. Origin of human T-cell leukaemia-limphoma virus. Lancet 1983;2:962-963.

29. Giordano TP, Kramer JR, Souchek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in HIV infected veterans with and without the hepatitis C virus:a cohort study,1992-2001. Arch Intern Med. 2004;164(21):2349-54.

30. Gjærde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. Trends in Incidences and risk factors for hepatocellular carcinoma and other liver events in HIV and hepatitis C virus-coinfected individuals from 2001 to 2014: a multicohort study. Clin Infect Dis 2016; 63:821–829.

31. Grint D, Peters L, Rockstroh JK, et al. Liver-related death among HIV/hepatitis C virus-co-infected individuals: implications for the era of directly acting antivirals. AIDS 2015; 29: 1205–1215.

32. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez G, McMahon D et al. N Engl J Med. 1997 Sep 11;337(11):734-9.

33. Hadigan C, Liebau J, Andersen R, Holalkere NS, Sahani DV. Magnetic resonance spectroscopy of hepatic lipid content and associated risk factors In HIV infection. J Acquir Immune Defc Syndr. 2007 Nov 1;46(3):312-7.

_____

34.   HIV/AIDS Surveillance in Europe, 2013. Available at www.ecdc.europa.eu.

35.   Hleyhel M, Belot A, Bouvier Am, Tattevin P, Pacenowski J, Genet P, et al. Trends in survival after cancer diagnosis among HIV-infected individuals between 1992 and 2009. Results from the FHDH-ANRS CO4 cohort. Int J Cancer 2015; 137:2443– 2453.

36.   Hurtado-Cordovi J, Davis-Yadley AH, Lipka S, Vardaros M, Shen H. Association between chronic hepatitis C and hepatitis C/HIV co-infection and the development of colorectal adenomas. J Gastrointest Oncol 2016; 7:609–614.

37.   Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, et al. Impact of risk factors for specific causes death in the first and subsequent years of ART among HIV-infected patients. Clin Infect Dis. 2014;59:287–97.

38.   Innes HA, McDonald SA, Dillon JF, Allen S, Hayes PC, Goldberg D et al. Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause specific outcomes. Hepatology. 2015 Aug;62(2):355-64.

39.   Innes H, Hutchinson SJ, Obel N. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland-Using spontaneous resolvers as the benchmark comparator. Hepatology 2016; 63: 1506–1516.

40.   INSIGHT START Study Group;Lundgren JD, Babiker AG, et al. Initiation of antiretroviraltherapy in early asymptomatic HIV infection. N Engl J Med 2015; 373:795–807.

41.   Kamar N, Izopet J, Alric L, Guilbeaud-Frugier C, Rostaing L, Hepatitis. C virus-related kidney disease: an overview. Clin Nephrol 2008; 69:149–160.

42.   Kim JH, Psevdos G, Gonzalez E, Singh S, Kilayko MC, Sharp V. All-cause mortality in hospitalized HIV-infected patients at an acute tertiary care hospital with a comprehensive outpatient HIV care program in New York City in the era of highly active anti retroviral therapy (HAART). Infection. 2013;41: 545–51.

43.   Kooij KW, Wit FW, Van Zoest RA, et al. Liver fibrosis in HIV-infected individuals on long-term antiretroviral therapy: associated with immune activation, immunodeficiency and prior use of didanosine. AIDS 2016; 30: 1771–1780.

44.   Kovari H, Ledergerber B, Cavassini M, et al. High hepatic and extrahepatic mortality and low treatment uptake in HCVcoinfected persons in the Swiss HIV cohort study between 2001 and 2013. J Hepatol 2015; 63: 573–580.

45.   Lee YA, Friedman SL. Reversal, maintence or progression: what happens to the liver after a virologic cure of hepatits C? Antiviral Res. 2014 Jul;107:20-30.

_____

46.   López C, Masiá M, Padilla S, Aquilino A, Bas C, Gutiérrez F. Deaths due to non-AIDS diseases among HIV infected patients: a 14-year study (1998–2011). Enferm Infecc Microbiol Clin. 2016;34:222–7.

47.   Luft LM, Gill MJ, Church DL. HIV-1 viral diversity and its implications for viral load testing: review of current platforms. Int J Infect Dis 2011; 15:e661-670.

48.   Meijide H, Mena A, Pernas B, Castro A, Lopez S, Vazquez P, et al. Malignancies in HIV-infected patients. Descriptive study of 129 cases between 1993-2010. Rev Chil Infectol 2013; 30:156–161.

49.   Mena A, Moldes L, Meijide H, Cañizares A, Castro-Iglesias A, Delgado M, et al. Seroprevalence of HCV and HIV infections by year of birth in Spain: impact of US CDC and USPSTF recommendations for HCV and HIV testing. PLOS ONE. 2014;9:e113062.

50.   Meyers DJ, Hood ME, Stopka TJ. HIV and hepatitis C mortality in Massachusetts, 2002–2011: spacial cluster and trend analysis of HIV and HCV using multiple cause of death. PLOS ONE. 2014;9:e114822.

51.   Moreno S, Mocroft A, D´amino A. Medical and societal consequences of late presentation. Antivir Ther 2010;15 (Suppl 1):9-15.

52.   Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352:1725-1730.

53.   Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003;362:22–9

54.   Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, et al. Causes of death among HIV-infected patients in France in 2010 (nacional survey): trends since 2000. AIDS. 2014;28:1181–91.

55.   Nagao Y, Sata M, Noguchi S, Seno'o T, Kinoshita M, Kameyama M, et al. Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. J Oral Pathol Med 2000; 29:259– 266.

56.   Nguyen ML, Farrel FJ, Gunthel CJ. Non-AIDS-Defining Malignancies in Patiens with HIV in the HAART era. Curr Infect Dis Rep 2010;14:556-63.

57.   Obel N, Omland LH, Kronborg G, Larsen CS, Pedersen C, et al. Impact of Non-HIV and HIV Risk Factors on Survival in HIV-Infected Patients on HAART: A Population-Based Nationwide Cohort Study. PLoS ONE 2011. 6(7): e22698.

58.   Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human

immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853-860.

59.   Pernas B, Mena A, Cañizares A, Grandal M, Castro-Iglesias A, Pertega S et al. Trends on epidemiological, virological and clinical features among newly diagnosed HIV-1 persons in Northwest Spain over the last 10 years. J Med Virol 2015 Aug;87(8):1319-26.

60.   Peters MG, Bacchetti P, Boylan R, French AL, Tien PC, Plankey MW et al. Enhanced liver fibrosis marker as a noninvasive predictor of mortality in HIV/hepatitis C virus-coinfected women from a multicenter study of women with or at risk for HIV. AIDS 2016 Mar 13;30(5):723-9.

61.   Pineda JA, Garcia-Garcia JA, Aguilar-Guisado M, et al. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology 2007; 46:622–30.

62.   Popovic M, Sarin PS, Robert-Gurroff M, Kalyanaraman VS, Mann D, Minowada J, et al. Isolation and transmission of human retrovirus (human T-cell leukemia virus). Science 1983;219:856-859.

63.   Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016; 65:719–726.

64.   Ronit A, Haissman J, Kirkegaard DM, Kristensen TS, Lebech AM, Benfield T et al. Copenhagen comorbidity in HIV infection (COCOMO) study: a study protocol for a longitudinal, non-interventional assessment of non-AIDS comorbidity in HIV infection in Denmark. BMC Infect Dis 2016. 16:713.

65.   Rowland-Jones SL, Whittle HC. Out of Africa: what can we learn from HIV-2 about protective immunity to HIV-1? Nat Immunol 2007;8:329-331.

66.   Rustagi T, Zarookian EI, Qasba O, Diez LF. Chronic Hepatitis C as a risk factor for colorectal adenoma. Int J Colrectal Dis 2014;29:75-80.

67.   Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016; 122:1312–1337.

68.   Sabin CA, Schwenk A, Johnson MA, Gazzard B, Fisher M, Walsh J, et al. UK Collaborative HIV Cohort (UK CHIC) Steering Committee. Late diagnosis in the HAART era: proposed common definitions and associations with mortality. AIDS 2010;24:723-727.

_____

69.   Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV infected patients: the French national Mortalite 2005 study. J Hepatol. 2009;50:736–45.

70.   Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antirretroviral therapy: New York City. Ann Intern Med. 2006;145:397–406

71.   Schouten J, Wit FW, Stolte IG, Kootstra NA, der Valk V, Geerlings SE, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis. 2014;59:1787–97

72.   Sherman KE, Rouster SD, Chung RT, Rajicic N. Virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002;34:831–7.

73.   Silverberg MJ, Chao C, LeydenWA, Xu L, Tang B, HorbergMA, et al. HIV infection and the risk of cancers with and without a known infectious cause. AIDS 2009; 23:2337– 2345.

74.   Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis 2015; 61: 730–740.

75.   Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, Law M, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS. 2010;24:1537–48.

76.   Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet. 2014;384:241–8.

77.   Soriano V, Berenguer J. Extrahepatic comorbidities associated with hepatitis C virus in HIV-infected patients. Curr Opin HIV AIDS 2015; 10:309–15.

78.   Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006;166:1632–41.

79.   WHO/UNAIDS 2015. Available at http://www.unaids.org/sites/default/files/media_asset/AIDS_by_the_numbers_2015_es.pdf.

_____

80.   Wier LM, Barrett ML, Steiner C, Jiang HJ. All-cause readmissions by payer and age, 2008. HCUP Statistical Brief #115 Agency for Healthcare Research and Quality; 2012. http://hcup-us.ahrq.gov/reports/statbriefs/sb115.pdf

81.   Worm SW, Bower M, Reiss P, et al. Non-AIDS defining cancers in the D:A:D Study—time trends and predictors of survival: a cohort study. BMC Infect Dis 2013; 13:471.

ABREVIATURAS

APC	Cambio porcentual anual
CDC	Centers for Prevention and Disease Control
CHUAC	Complejo Hospitalario Universitario de A Coruña
HSH	Hsombres que tienen sexo con hombre
LNH	Linfoma no Hodgkin
LH	Linfoma Hodgkin
NDS	Neoplasias definitorias de SIDA
NNDS	Neoplasias no definitorias de SIDA
OMS	Organización Mundial de la Salud
P-A	Personas –año
RVS	Respuesta viral sostenida
SIDA	Sindrome de inmunodeficiencia adquirida
TARGA	Tratamiento antirretroviral de alta eficacia
UDVP	Usuario a drogas por vía parenteral
VIH	Virus de inmunodeficiencia humana
VHB	Virus de la hepatitis B
VHC	Virus de la hepatitis C

ANEXOS

ANEXO 1. OTRAS PUBLICACIONES SURGIDAS DE ESTA TESIS

1- LUNG CANCER IN PATIENTS WITH HIV INFECTION. <u>Meijide H</u>, Mena A, Marcos PJ, Rodríguez- Osorio I, Suárez-Fuentetaja R, Castro A, Poveda E, Pedreira JD. AIDS 2015;29:2363-4. IF: 5,554 (Primer decil).

2- LUNG CANCERS IN HIV-INFECTED PATIENTS. Mena A, <u>Meijide H</u>, Marcos PJ. AIDS Rev, 2016 JUL-SEP;18(3):138-144. IF: 3,787 (Segundo cuartil).

3- CANCER INCIDENCE IN PERSONS LIVING WITH HIV**. <u>H Meijide</u>, A Mena, I Rodriguez, A. Castro, E Poveda. Clin Infect Dis. 2017 Feb 1;64(3):388-389. IF: 8,886 (Primer decil)

Correspondence

Lung cancer in patients living with HIV infection

We read with interest the article by Hessol et al. [1] regarding the characteristics of lung cancers in a large HIV population cohort. Incidence rates of several common malignancies, including lung cancer, are rising in HIV-infected patients. Although cigarette smoking is probably the main known risk factor [2,3], ageing, existing pulmonary disease, HIV-related immunosuppression and inflammation due to HIV could lead to immune system dysfunction and promote the development of lung cancer in this population as described recently [4].

We would like to share our experience regarding this issue. We conducted an observational retrospective study in a single centre in the Northwest of Spain. Between 1993 and 2013, we detected 28 lung cancers, with a 24 330 person-years follow-up. Similar to the data reported by Hessol et al. [1], we observed a trend to a higher diagnosis of lung cancer in the last decade than the first (1993–2003: eight cases vs. 2003–2013: 20 cases) The profile patient is a young man (mean age 49 ± 9 years old), heavy smoker (more than 85% of our cohort were active smokers), with an intravenous drug use background, Centers for Disease Control and Prevention-C AIDS category, mainly with undetectable viral load and a reasonable immunological status. The mean time from the HIV infection to the diagnosis of lung cancer was 9.8 ± 6.6 years. As reported by Hessol et al. [1], we found that adenocarcinoma was the most common histological type (50% of the cases). This differs from studies of non-HIV Spanish population, wherein squamous cell carcinoma is the most prevalent in men [5]. Similar to non-HIV observed data, most of the lung cancer was diagnosed in advanced stages, as 22 patients (78%) were in stages III or IV, with a mean survival time of 9.6 ± 4.3 months [95% confidence interval (95% CI) 1.1–18.2]; the Kaplan−Meier analysis is shown in Fig. 1. Our results are quite similar to those described by Okuma et al. [6], who conducted a study in Japanese population, with important environmental and ethnic differences, suggesting that, therefore, genetic and the role of HIV infection may be contributing to lung cancer development.

In summary, as the survival of HIV-infected patients is improving, it is expected that the incidence and mortality from lung cancer will increase. From a preventive point of view, smoking cessation seems mandatory and, although controversial [7,8], further research regarding the impact of low-dose computed tomography screening in this high-risk population will be welcomed [7,8].
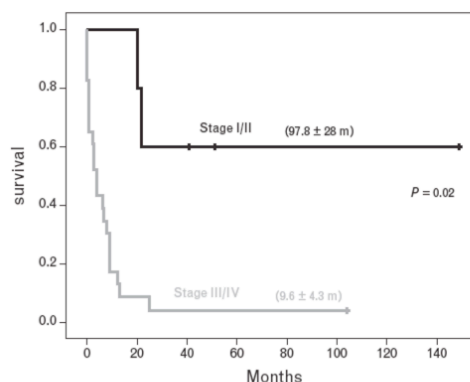

Fig. 1. Kaplan−Meier survival analysis (mean survival $\pm$ SD in months) comparing lung cancer stages at the moment of diagnosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

Hector Meijide[a], Alvaro Mena[a], Pedro J. Marcos[b], Iria Rodriguez-Osorio[a], Rebeca Suárez-Fuentetaja[a], Angeles Castro[a], Eva Poveda[a] and Jose D. Pedreira[a], [a]Grupo de Virología Clínica, and [b]Servicio de Neumología, Instituto de Investigación Biomédica de A Coruña (INIBIC)-Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), A Coruña, Spain.

Correspondence to Hector Meijide, INIBIC- Complejo Hospitalario Universitario De A Coruña, 15006 A Coruña, Spain.
E-mail: hectormeijide@hotmail.com

Received: 2 June 2015; revised: 11 June 2015; accepted: 29 July 2015.

References

1. Hessol NA, Martinez-Maz O, Levine AM, Morris A, Margolick JB, Cohen MH, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. AIDS 2015; 29:1183–1193.

2363

_____

2. Winstone TA, Man FP, Hull M, Montaner JS, Sin DD. **Epidemic of lung cancer in patients with HIV infection.** *Chest* 2013; **143**:305–314.

3. Sigel K, Wisnivesky J, Gordon K, Redfield RR, Dennis PA, Bryant J. **HIV as an independent risk factor for incident lung cancer.** *AIDS* 2012; **26**:1010–1025.

4. Kawabata S, Heredia A, Gills J, Redfield RR, Dennis PA, Bryant J. **Impact of HIV on lung tumorigenesis in an animal model.** *AIDS* 2015; **29**:633–635.

5. Sanchez de Cos J, Serra M, Hernandez J, Hernandez H. **The Spanish Society of Pulmonology and Thoracic Surgery Lung Cancer Cooperative Group-II Registry. A Descriptive Study.** *Arch Bronconeumol* 2013; **49**:462–467.

6. Okuma Y, Tanuma J, Kamiryo H, Kojima Y, Youtsumoto M, Ajisawa A, *et al.* **A multiinstitutional study of clinicopathological features and molecular epidemiology of epidermal growth factor receptor mutations in lung cancer patients living human immunodeficiency virus infection.** *J Canc Res Clin Oncol* 2015; (Epub ahead of print).

7. Sigel K, Wisnivesky J, Shahrir S, Brown ST, Justice A, Kim J, *et al.* **Findings in asymptomatic HIV-infected patients undergoing chest computed tomography testing: implications for lung cancer.** *AIDS* 2014; **28**:1007–1014.

8. Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, Aberle DR, *et al.* **Cost-effectiveness of CT screening in the National Lung Screening Trial.** *N Engl J Med* 2014; **371**:1793–1802.

Curing HIV/AIDS beyond hematopoietic stem cell transplant

The case of Timothy Ray Brown, who received hematopoietic stem cell transplant (HSCT) from a CCR5-Δ32 donor to treat AIDS-related lymphoma, remains the only example of a patient cured from HIV infection [1]. HSCT from CCR5 wild-type donors failed to cure HIV in two other AIDS-related lymphoma patients, but delayed viral rebound after combined antiretroviral therapy (cART) interruption [2,3]. At least one of two conditions must be fulfilled to achieve HIV cure: elimination of all latent HIV reservoirs or protection of CD4$^+$ T cells from de-novo infection.

Purging viral reservoirs requires that all cells bearing functional HIV provirus are accessible for activation and susceptible to viral cytopathicity and/or immune-mediated clearance. For the latter, it is essential that HIV-specific cytotoxic T-lymphocyte (CTL) responses be restored [4].

Preventing infection of new targets may be more challenging. Transplants of rare heterologous human leukocyte antigen (HLA)-matched CCR5-Δ32 or autologous genetically modified CCR5-KO hematopoietic stem cell [5] may require immunoablation to ensure total resistance to infection.

There is general consensus on the hypothesis that some degree of graft-vs-host (GVH) reactivity may have reduced the viral reservoir in the HSCT patients who showed delayed viremia rebound [5]. Thus, similar to the extensively studied graft-vs-leukemia phenomenon [6], a graft-vs-viral reservoir effect (GVVR) could target host cells that survived immunoablation, thus shrinking the HIV reservoir. Could GVVR be independently exploited of immunoablation? Would it be advantageous, and how could it be delivered and tested?

Several independent reports spanning 40 years suggest a strategy for addressing these issues. Exposing non-ablated, cART-treated HIV patients to HLA-allogeneic leukocytes could simultaneously induce GVVR; reactivate latent HIV reservoirs; enhance or restore host HIV-specific immunity; and activate restriction factors that prevent CD4$^+$ T-cell infection (Fig. 1).

Approximately 1 : 1000 T lymphocytes recognize allogeneic major histocompatibility complex (MHC) molecules, 1000-fold more frequent than peptide-specific T lymphocytes [7]. MHC-allospecific T-helper cell responses are retained in most asymtpomatic HIV-infected patients [8], but these responses would be eliminated by immunoablation. Immunization with allogeneic leukocytes in immunocompetent women experiencing recurrent spontaneous abortion caused no major side-effects [9], and resulted in enhanced resistance of CD4$^+$ T cells to in-vitro HIV infection [10].

The combined reactions of donor T cells against patient MHC (GVH) and of patient leukocytes against donor's MHC (host-vs-graft) could lead to HIV reactivation and enhanced presentation of retroviral peptides in deep anatomical sites (Fig. 1). Thus, activation of host latent murine leukemia retrovirus was reported in a murine GVH model, including latent provirus in bystander T cells that do not recognize allogeneic MHC [11]. Similar experiments in rats showed increased MHC expression in host epidermal cells, gut epithelium [12], and MHC-negative nervous tissue [13].

Treatment with allogeneic donor cells could also promote host HIV-specific CTL-mediated immunity (host-vs-viral reservoir) (Fig. 1). Thus, stimulation with allogeneic leukocytes restored T-cell-mediated help to autologous influenza virus-specific [14] and HIV-specific CTLs (M.C. and G.M.S., unpublished observations).

Finally, stimulation with allogeneic MHC can activate a broad range of restriction factors (APOBEC3G, RANTES, MIP-1α/β, and CD8-derived suppressor factor) [10,15] that could synergize with cART to protect CD4$^+$ cells from HIV during reservoir reactivation.

Infusion of allogeneic cells into nonablated HIV-positive patients is less likely to cause GVH disease

112

Lung Cancer in HIV-Infected Patients

Álvaro Mena[1], Héctor Meijide[1,2] and Pedro J. Marcos[3]

[1]*Clinical Virology Group, Instituto de Investigación Biomédica de A Coruña, Complexo Hospitalario Universitario de A Coruña, Sergas, Universidade da Coruña; [2]Department of Internal Medicine, Hospital Quiron; [3]Department of Pneumology, Instituto de Investigación Biomédica de A Coruña, Complexo Hospitalario Universitario de A Coruña, Sergas, Universidade da Coruña (UDC). A Coruña, Spain*

Abstract

The widespread use of HAART for persons living with HIV since 1996 has resulted in a dramatic decline in AIDS-related mortality. However, other comorbidities are increasing, such as metabolic disturbances or cancers, including solid organ malignancies. Among the latest, lung cancer, especially the adenocarcinoma subtype, is on the rise. HIV infection, even controlling for smoking, is an independent risk factor for developing lung cancer. HIV could promote lung cancers through immunosuppression, chronic inflammation, and a direct oncogenic effect.

Smoking, lung infections, and chronic pulmonary diseases are risk factors for lung cancer. All may contribute to the cumulative incidence of lung cancer in persons living with HIV. It is double that in the general population. The role of HAART in lung cancer development in persons living with HIV is not well established. Although data supporting it could be too preliminary, persons living with HIV should be considered within high-risk groups that could benefit from screening strategies with low-dose computed tomography, especially those with airway obstruction and emphysema. Current evidence suggests that quitting smoking strategies in persons living with HIV achieve abstinence rates comparable to those in healthy HIV-negative smokers. (AIDS Rev. 2016;18:138-44)

Corresponding author: Alvaro Mena, alvaro.mena.de.cea@sergas.es

Key words

HIV. PLWH. Lung cancer. Cancer screening. Smoking.

Introduction

Antiretroviral therapy (ART) has prolonged the lifespan of persons living with HIV (PLWH)[1]. However, this longer life expectancy has led to a relative increase in diseases with longer latency period such as solid organ malignancies. Cancer is increasingly common in this population[2], with a higher burden than in the general population, largely as result of impaired immune function, chronic inflammation, and higher prevalence of risk factors[3,4].

The spectrum of malignancies in PLWH has changed with the use of ART, especially following the introduction of HAART. The incidence of AIDS-defining cancers (ADC), such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer has declined markedly. In contrast, there has been a relative increase in non-AIDS-defining cancers (NADC) that surpasses rates seen in the general population[5].

Calendar trends in cancer incidence in PLWH have been recently evaluated[6]. After examination of cumulative

Correspondence to:
Alvaro Mena
Grupo de Virología Clínica, Instituto de Investigación Biomédica
de A Coruña (INIBIC), Complexo Hospitalario Universitario de
A Coruña (CHUAC)
As Xubias, s/n
15006 A Coruña, Spain
E-mail: alvaro.mena.de.cea@sergas.es

_____

Álvaro Mena, et al.: **Lung Cancer in HIV-Infected Patients**

Table 1. Main studies of lung cancer in persons living with HIV

Study	Years	Patients (n)	Median age (years)	Male (%)	Smoking (%)	IDUs (%)	AdenoCa (%)	CD4 > 200 cells/µl (%)	Stage III/IV (%)	Median OS (months)
Brock, et al. 2006[13]	1996-2004	92	46	67	99	58	48	–	87	6.3
Engles, et al. 2006[60]	1989-2003	33	46	67	85	57	48	51	–	–
Chatuverdi, et al. 2007[11]	1980-2002	393	47	85	80	33	34	28	–	–
Hakimian, et al. 2007[15]	1996-2003	34	44	68	100	59	–	62	90	5.2
Lavole, et al. 2009[16]	1996-2007	49	46	67	99	17	67	–	84	8.1
D'Jaen, et al. 2010[17]	1996-2008	75	50	83	99	30	46	–	77	9.0
Pakkala, et al. 2012[18]	1995-2008	80	52	80	100	25	38	–	78	6.1
Clifford, et al. 2012[10]	1984-2010	68	50	79	76	37	–	45	–	–
Okuma, et al. 2015[19]	1988-2013	43	60	97	91	0	59	85	63	25.0
Meijide, et al. 2015[20]	1993-2013	28	49	82	85	50	50	67	78	12.3

IDU: intravenous drug user; AdenoCa adenocarcinoma; OS: overall survival.

cancer incidences by 75 years of age, it was found that the cumulative incidence of anal, colorectal, and liver cancer has increased significantly in PLWH. The highest cumulative incidence is seen for Kaposi's sarcoma, non-Hodgkin's lymphoma, and lung cancer. Furthermore, malignancies in PLWH are often characterized by earlier age at onset, atypical pathology (higher tumor grade), more aggressive clinical behavior, and more advanced stage at presentation[7,8]. These features have implications for treatment and contribute to poorer outcomes than in HIV-negative persons.

Magnitude of the problem

The incidence of lung cancer is increased approximately 2-4-fold in PLWH compared with age and gender matched HIV-negative populations. The incidence of lung cancer is also more than 50% higher in PLWH than expected[9]. Of note, there is a higher prevalence of cigarette smoking in this population, up to 2-3 times more than in the general population[10,11]. Tobacco smoking is probably the best-known risk factor for lung cancer. Nicotine and other components of tobacco smoke induce complex pathophysiological changes in HIV infection that seem to be different than in the general population. Thus, tobacco-related harm in the setting of HIV infection is underestimated[12]. Nevertheless, the risk of lung cancer in HIV persons remains elevated even after adjusting for smoking status. Thus, there is a need for more research to understand the mechanisms driving lung cancer risk in this population.

The main features of PLWH that develop lung cancer have been reported elsewhere[13-20]. They include important environmental and ethnic differences, suggesting that both genetics and HIV infection may contribute to lung cancer development in this population. Table 1 summarizes the main features of studies that have examined lung cancer in PLWH.

The PLWH who develop lung cancer are typically young men with a mean age of 45-50 years (compared to 62 years old in the general population) and heavy smokers. More often they are staged as CDC class C (AIDS) although they currently exhibit undetectable viral load and CD4 counts > 200 cells/ml. Resembling the general population in recent years, adenocarcinoma is the most common histological type in PLWH. Diagnosis in advanced tumor stages is more frequent in PLWH, and death is common within the first year after diagnosis.

Cancer-specific mortality is significantly higher in PLWH compared with HIV-uninfected persons for many cancers, even after adjustment for tumor treatment.

139

_____

Coghill, et al.[21] reported a mortality adjusted hazard ratio of 1.28 (95% CI: 1.17-1.39) for lung cancer. Several classic factors are associated with poor median survival of lung cancer in PLWH, including disease stage, performance status, and histological subtype. In addition, ART use and low absolute CD4 counts contribute as well. Thus, the higher mortality rate for lung cancer seen in PLWH is further influenced by immunosuppression[22,23].

Lung tumorigenesis in HIV infection

Factors other than smoking play a role in the increased risk of lung cancer in PLWH. These include HIV-related factors and a potentially increased susceptibility to carcinogens.

Role of lung infections

Pulmonary infections, throughout producing lung inflammation and tissue damage, may be involved in the development of lung cancer. Several studies have examined the association between tuberculosis and lung cancer, with odds ratios in the range of 2-4[3,24]. The chronicity and prolonged treatment required for Mycobacterium tuberculosis infection induces substantial pulmonary inflammation, tumor necrosis factor (TNF) production, and pulmonary fibrosis[25].

Although pulmonary inflammation in bacterial pneumonia is shorter than in lung tuberculosis, a number of case-control studies have reported an association between bacterial or Pneumocystis jirovecii pneumonia and increased risk for lung cancer[3,26]. These epidemiological associations have several limitations as not all these studies strictly controlled for tobacco consumption. Smoking-induced lung disease may predispose to pulmonary infections, and tobacco is ultimately the major risk factor for lung cancer. On the other hand, the higher frequency or clinical and radiological controls in patients with lung infections may overestimate the incidence of cancer compared to uncontrolled populations and give rise to spurious associations. Nonetheless, some studies have reported associations with lung cancer for latencies over 10 years following pulmonary infections[27].

Role of HIV reservoirs

Despite the clearance of HIV in the peripheral bloodstream with suppressive HAART, low-level HIV replication persists in all infected persons. Interestingly, bronchoalveolar cells of PLWH may host at least 7.6-fold more HIV proviral DNA than cells in the peripheral blood[28]. Indeed, the lung and the intestinal tract harbor the highest levels of viremia after the lymph nodes[29]. This is largely due to its rich content in macrophages. HIV in the lung activates alveolar macrophages, leading to a marked cellular activation and accumulation of inflammatory mediators in the alveolar space[30].

Alveolar macrophages are fairly resilient to HIV in the lungs. Compared to HIV-uninfected persons, HIV-infected individuals depict a lower secretion of TNF-α and interferon-gamma (IFN-γ) in the lung[30].

Role of immunosuppression and chronic inflammation

HIV infection promotes a massive early depletion of CD4+ T-cells. In contrast to other locations such as the gastrointestinal tract, the lung appears relatively resistant to the early depletion of CD4+ T-cells. This has been attributed to several mechanisms, including a lesser mass of HIV-susceptible secondary lymphoid tissue, elevated presence of mucosal HIV-specific polyfunctional CD4+ T-cells in the lungs, and the apparent efficacy of pulmonary HIV-specific cytotoxic T-cell responses, as reflected by intense alveolitis[31,32].

Nonetheless, human body defenses progressively deteriorate, leading to CD4+ T-cell depletion and immune activation. Chronic immune activation during HIV infection results in increased production of immunosuppressive cytokines, i.e., transforming growth factor-beta 1 (TGF-β1), contributing to HIV-related immunosuppression throughout induction of FoxP3 and promotion of collagen deposition and fibrosis in secondary lymphoid tissues. TGF-β1 has also been implicated in the pathogenesis of several malignancies, including lung cancer[33,34]. Even in the context of HAART-mediated viral suppression, circulating levels of TGF-β1 remain elevated, which is consistent with the presence of ongoing chronic immune activation[35].

Chronic lung diseases such as asthma or chronic obstructive pulmonary disease (COPD) are associated with lung inflammation and may favor lung cancer independently of smoking. These lung conditions are more common in PLWH than in uninfected persons. Smoking has an immunosuppressive and proinflammatory effect similar to HIV infection. In addition, tobacco contains several carcinogenic agents. To date, the contribution of HIV infection and smoking on lung cancer development is still unclear[12].

40

115

_____

Álvaro Mena, et al.: **Lung Cancer in HIV-Infected Patients**
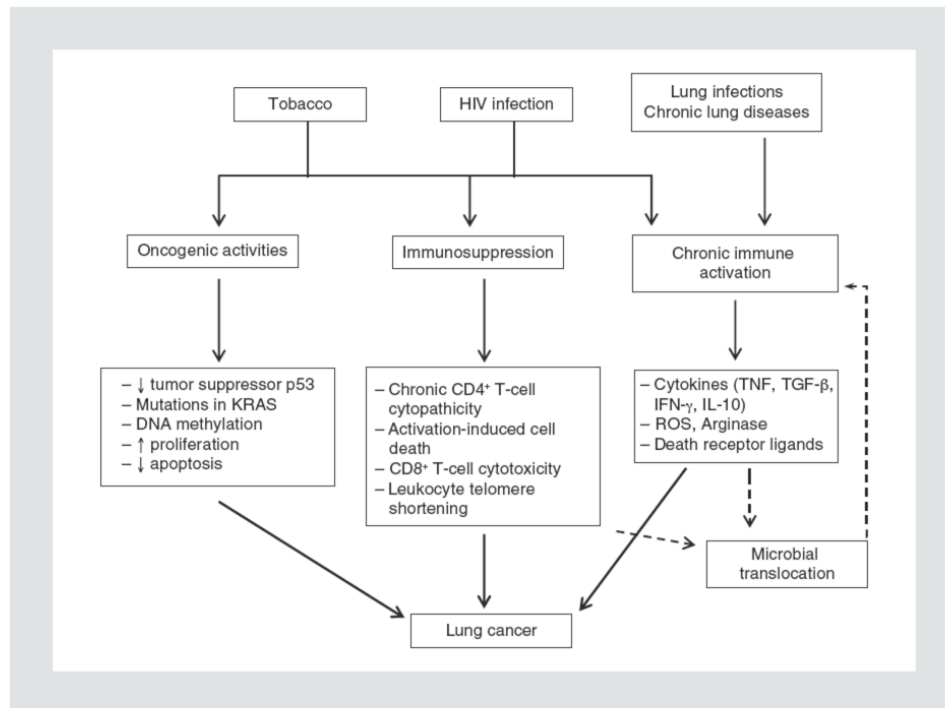
Figure 1. *Proposed mechanism by which HIV infection, tobacco, lung infections, and chronic lung diseases cause immunosuppression, chronic immune activations, and different oncogenic activities. All of them lead to the development of lung cancer in persons living with HIV. TNF: tumor necrosis factor; TGF-β: transforming growth factor beta; IFN-γ: interferon gamma; IL-10: interleukin 10; ROS: reactive oxygen species.*

In the oncology field, epidermal growth factor receptor (EGFR) mutations predispose to lung cancer development and worse prognosis. These mutations are more prevalent in Asia, but recent data have shown that the rate of these mutations in PLWH is similar to the general population, at least in Japan[19]. The role of HIV infection, tobacco, chronic lung diseases, and pulmonary infections on lung cancer development is summarized in figure 1.

Impact of antiretroviral therapy exposure

HAART has dramatically improved the morbidity/mortality of PLWH, but it does not completely restore their health. The rate of ADCs has significantly dropped in the HAART era and short and medium-term survival has extended in PLWH with cancers[35,36]. This is why first-line treatment of some ADCs, such as Kaposi's sarcoma, should include HAART, which often leads to

complete resolution of the neoplasm. In contrast, NADCs have been steadily increasing in recent years.

The role of ART exposure in NADC development is not well known. On the one hand, the restoration of immunity could have a protective role, but on the other hand some studies have linked ART with some cancers, such as nonnucleoside reverse transcriptase inhibitors (NNRTI) with Hodgkin's lymphoma, or protease inhibitors (PI) with anal cancer. However, these epidemiological links come from observational retrospective studies with known limitations[37,38].

Antiretroviral therapy decreases the HIV viral load in the bronchoalveolar lavage to undetectable levels in more than 80% patients, also decreasing IFN-γ, IL-6, and CD8+ T lymphocytes while increasing CD4+ T-cells[39]. Glutathione and cysteine levels in the bronchoalveolar lavage are surrogate markers of oxidative stress in the lung. The PLWH without HAART show significantly decreased levels of both molecules than patients on HAART

141

116

_____

and HIV-uninfected persons, suggesting that increased oxidative stress in the lungs is an important feature of uncontrolled HIV infection[40].

The inhibition of cytochrome p450, namely CYP3A4, induced by ritonavir-boosted PI might have deleterious effects on tobacco carcinogenesis. CYP450 plays a role in the activation and metabolism of polyaromatic hydrocarbons and nitrosamines[41]. The effect of CYP450 inhibitors on the risk of lung cancer is unproven and, accordingly, recent data suggest that PI exposure is not linked to an increased risk of lung cancer in PLWH[42].

Data on HAART choice in PLWH with lung cancer are scarce. Toxicity, tolerability, and potential drug interactions between chemotherapy and HAART should be considered. Integrase inhibitors, such as raltegravir or dolutegravir, exhibit low toxicity and drug interactions and have been widely used in these patients[43]. Retrospective cohort studies have found that integrase inhibitor-based regimens are safer and more effective in maintaining viral suppression than ritonavir-boosted PI or NNRTI-based combinations in PLWH receiving chemotherapy, although those data must be assessed with caution[44].

Screening and preventive strategies

Lung cancer screening in persons living with HIV

The National Lung Screening Trial (NLST) published in 2011 was the first well-designed study able to demonstrate that lung cancer screening with low-dose computed tomography (LDCT) could allow reduction of lung cancer mortality by roughly 20% as well as all-cause mortality around 7%[45]. Lung cancer screening using LDCT is currently recommended by several guidelines[46-49] and mainly relies on the NLST inclusion criteria (age, 55-74; ≥ 30 pack-years; tobacco cessation within the previous 15 years for former smokers). However, concerns exist about the lack of sensitivity of LDCT in detecting lung cancer and therefore some authors have suggested implementing individualized risk assessment considering further considerations[50] such as the presence of airway obstruction and emphysema[51,52]. Since HIV infection could be an independent factor for lung cancer after controlling for smoking, and that the prevalence of COPD and emphysema in PLWH is higher than in the general population, PLWH could benefit from specific lung cancer screening programs.

When data from lung cancer screening trials are analyzed, information regarding HIV status is not displayed as being HIV-infected is not contraindicated for entering into the study[53]. However, age for eligibility in the trial was between 55 and 74, a range over most younger PLWH. Moreover, some questions regarding sensitivity could arise in PLWH, such as a higher frequency of nonspecific lymphadenopathy and a greater risk for bacterial infections, which could potentially interfere with likelihood of false positive computed tomography (CT) scans[54]. To date, only one trial has evaluated these questions[53]. Hulbert, et al. followed 224 PLWH and current/former smokers to assess CT detection rates of lung cancer. The study concluded that despite high rates of active smoking among HIV-infected participants, only one lung cancer was detected in 678 patient-years of examinations. The inclusion of younger patients (threshold at 25 years old) could explain these results.

Another prospective multicenter study (NCT01207986), which is still ongoing, aims to evaluate the prevalence of lung cancer detected by LDCT in HIV-infected patients. It will analyze 450 individuals with HIV infection, a nadir level of CD4+ T-cells < 350/µl, ≥ 40 years old, and smoking history ≥ 20 packs a year (either active or with < 3 years of weaning). Once completed, the study will provide very valuable information on the role of LDCT screening in PLWH.

Smoking cessation in persons living with HIV

As in non-HIV-infected persons, smoking is the most important modifiable risk factor for disease and mortality in PLWH. Accordingly, smoking cessation will be the cornerstone of any preventive strategy for lung cancer (and many more diseases) in PLWH.

Smoking cessation interventions in PLWH have shown discordant results[55,56]. Most smoking cessation trials used motivational interviewing with or without nicotine replacement therapy. A recent meta-analysis[57] showed that individualized smoking cessation interventions that tailor interventions to psychosocial comorbidities and polysubstance abuse are effective in PLWH. A combination of several approaches, including counseling/education, pharmacotherapy, and self-monitoring, may lead to the greatest benefits.

Although more clinical trials testing pharmacological therapies for quitting smoking in PLWH are needed, to date those using varenicline have concluded that the percentage of adverse events (even in patients on

_____

Álvaro Mena, et al.: **Lung Cancer in HIV-Infected Patients**

HAART) and abstinence rates are roughly comparable to those seen in randomized trials conducted in healthy HIV-negative smokers[58,59]. Compared to nicotine, varenicline seems to have better outcomes, with biochemically confirmed abstinence rates at three months of 26 vs. 12% in the nicotine intervention arm[59].

Conclusions

- The cumulative incidence of lung cancer in PLWH increases with age, and is overall twofold that of the general population.
- As in HIV-negative persons, smoking, lung infections, and chronic pulmonary diseases are risk factors for developing lung cancer in PLWH.
- HIV-infection, even controlling for smoking, is an independent risk factor for developing lung cancer. HIV could be carcinogenetic through immunosuppression, chronic inflammation, and direct oncogenic effects.
- The role of HAART in preventing lung cancer development in PLWH is not well established.
- Although data are scarce, PLWH would benefit from inclusion within high-risk groups to develop lung cancer and take advantage of screening strategies with low-dose CT scan, especially PLWH with airway obstruction and emphysema.
- Quitting smoking strategies in PLWH achieve abstinence rates comparable to those obtained in healthy HIV-negative smokers.

Declaration of interest

All authors declare no conflicts of interest.

References

1. Wada N, Jacobson LP, Cohen M, French A, Phair J, Muñoz A. Cause-specific life expectancies after 35 years of age for HIV-infected and HIV-negative individuals followed simultaneously in long-term cohort studies, 1984-2008. Am J Epidemiol. 2013;177:116-25.
2. Shiels M, Pfeiffer R, Gail M, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011;103:753-62.
3. Brenner A, Wang Z, Kleinerman R, et al. Previous pulmonary diseases and risk of lung cancer in Gansu Province, China. Int J Epidemiol. 2001;30:118-24.
4. Helleberg M, Gerstoft J, Afzal S, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. AIDS. 2014;28:1499-508.
5. Patel P, Hanson D, Sullivan P, et al. Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148:728-36.
6. Silverberg M, Lau B, Achenbach C, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America. Ann Intern Med. 2015;163:507-18.
7. Deeken J, Tjen-A-Looi A, Rudek M, et al. The rising challenge of non-AIDS-defining cancers in HIV-infected patients. Clin Infect Dis. 2012; 55:1228-35.
8. Meijide H, Mena A, Pernas B, et al. Malignancies in HIV-infected patients: descriptive study of 129 cases between 1993 and 2010. Rev Chilena Infectol. 2013;30:156-61.
9. Robbins H, Pfeifer R, Shiells M, et al. Excess cancers among HIV-infected people in the United States. J Natl Cancer Inst. 2015; 6;107:4.
10. Clifford G, Lise M, Franceschi S, et al. Lung cancer in the Swiss Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer. 2012;106:447-52.
11. Chaturvedi A, Pfeiffer R, Chang L, et al. Elevated risk of lung cancer among people with AIDS. AIDS. 2007;21:207-13.
12. Calvo M, Laguno M, Martinez M, Martinez E. Effects of tobacco smoking on HIV-infected individuals. AIDS Rev. 2015;17:47-55.
13. Brock M, Hooker C, Engels E, et al. Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care. J Acquir Immune Defic Syndr. 2006;43:47-55.
14. Engels E, Pfeiffer R, Goedert J, et al. Study HACM. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS. 2006;20:1645-54.
15. Hakimian R, Fang H, Thomas L, Edelman M. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. J Thorac Oncol. 2007;2:268-72.
16. Lavole A, Chouaid C, Baudrin L, et al. Effect of highly active antiretroviral therapy on survival of HIV-infected patients with non-small-cell lung cancer. Lung Cancer. 2009;65:345-50.
17. D'Jaen G, Pantanowitz L, Bower M, et al. HIV-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration. Clin Lung Cancer. 2010;11:396-404.
18. Pakkala S, Chen Z, Rimland D, et al. HIV-associated lung cancer in the era of highly active antiretroviral therapy. Cancer. 2012;118:164-72.
19. Okuma Y, Tanuma J, Kamiryo H, et al. A multiinstitutional study of clinico-pathological features and molecular epidemiology of epidermal growth factor receptor mutations in lung cancer patients living HIV infection. J Canc Res Clin Oncol. 2015;141:1669-78.
20. Meijide H, Mena A, Marcos P, et al. Lung cancer in patients living with HIV infection. AIDS. 2015;29:2363-4.
21. Coghill A, Shiells M, Suneja G, Engles E. Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol. 2014;33:2376-83.
22. Winstone T, Paul Man S, Hull M, Montaner J, Sin D. Epidemic of lung cancer in patients with HIV infection. Chest. 2013;143:305-14.
23. Hessol N, Martinez-Maz O, Levine A, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. AIDS. 2015;29:1183-93.
24. Alavanja M, Brownson R, Boice J, Hock E. Pre-existing lung disease and lung cancer among non-smoking women. Am J Epidemiol. 1992;136:623-32.
25. Dheda K, Booth H, Huggett J, Johnson M, Zumla A, Rook G. Lung remodeling in pulmonary tuberculosis. J Infect Dis. 2005;192:1201-9.
26. Schabath M, Delclos G, Martynowicz M, et al. Opposing effects of emphysema, hay fever, and select genetic variants on lung cancer risk. Am J Epidemiol. 2005;161:412-22.
27. Wu A, Fontham E, Reynolds P et al. Previous lung disease and risk of lung cancer among lifetime non-smoking women in the United States. Am J Epidemiol. 1995;141:1023-32.
28. Clarke J, Gates A, Coker R, et al. HIV-1 proviral DNA copy number in peripheral blood leucocytes and bronchoalveolar lavage cells of AIDS patients. Clin Exp Immunol. 1994;96:182-6.
29. Horiike M, Iwami S, Kodama M, et al. Lymph nodes harbor viral reservoirs that cause rebound of plasma viremia in SIV-infected macaques upon cessation of combined antiretroviral therapy. Virology. 2012;423:107-18.
30. Gordon S, Janoff E, Sloper D, et al. HIV-1 infection is associated with altered innate pulmonary immunity. J Infect Dis. 2005;192:1412-6.
31. Jambo K, Banda D, Kankwatira A, et al. Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. Mucosal Immunol. 2014;7:1116-26.
32. Segal L, Methé B, Nolan A, et al. HIV-1 and bacterial pneumonia in the era of antiretroviral therapy. Proc Am Thorac Soc. 2011;8:282-7.
33. Tange S, Oktyabri D, Terashima M, et al. JARID2 is involved in transforming growth factor-beta-induced epithelial-mesenchymal transition of lung and colon cancer cell lines. PloS One. 2014;9:e115684.
34. Chen H, Wang JW, Liu L, et al. Expression and significance of transforming growth factor-beta receptor type II and DPC4/Smad4 in non-small cell lung cancer. Exp Ther Med. 2015;9:227-31.
35. Malherbe G, Steel HC, Cassol S, et al. Circulating biomarkers of immune activation distinguish viral suppression from non-suppression in HAART-treated patients with advanced HIV-1 subtype C infection. Mediators Inflamm. 2014; 2014:198413.
36. Grabar S, Abraham B, Mahamat A, Del Giudice P, Rosenthal E, Costagliola D. Differential impact of combination antiretroviral therapy in preventing Kaposi´s sarcoma with and without visceral involvement. J Clin Oncol. 2006;24:3408-14.
37. Hoffmann C, Wolf E, Fatkenheuer G, et al. Response to highly active antiretroviral therapy strongly predicts outcome in patients with AIDS-related lymphoma. AIDS. 2003;17:1521-9.

AIDS Reviews. 2016;18

38. Chao C, Leyden W, Xu L, et al. Exposure to antiretroviral therapy and risk of cancer in HIV-infected persons. AIDS. 2012;26:2223-31.
39. Twigg H, Cnox K. Impact of antiretroviral therapy on lung immunology and inflammation. Clin Chest Med. 2013;34:155-64.
40. Cribbs S, Guidot D, Martin G, et al. Antiretroviral therapy is associated with decreased alveolar glutathione levels even in healthy HIV-infected individuals. PLoS One. 2014;9:e88630.
41. Anttila S, Raunio H, Hakkola J. Cytochrome P450-mediated pulmonary metabolism of carcinogens: regulation and crosstalk in lung carcinogenesis. Am J Respir Cell Mol Biol. 2011;44:583-90.
42. Bruyand M, Le Marec F, Lavole A, et al. Protease inhibitors exposure is not related to lung cancer risk in HIV smoker patients: a nested case-control study. AIDS. 2015;29:1105-9.
43. Bañón S, Machuca I, Araujo S, et al. Efficacy, safety, and lack of interactions with the use of raltegravir in HIV-infected patients undergoing antineoplastic chemotherapy. J Int AIDS Soc. 2014;17:e19590.
44. Torres H, Rallapalli V, Saxena A, et al. Efficacy and safety of antiretroviral in HIV-infected patients with cancer. Clin Microbiol Infect. 2014;20: 672-9.
45. Aberle D, Adams A, Berg C, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011; 365:395-409.
46. American Lung Association. Providing guidance on lung cancer screening to patients and physicians. 2012 Available at: http://www.lung.org/lung-disease/ lung-cancer/lung-cancer-screening- guidelines/lung-cancer-screening.pdf. [Accessed 2015 Oct 17].
47. Detterbeck F, Mazzone P, Naidich D, Bach P. Screening for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143: e78-92S.
48. Jaklitsch M, Jacobson F, Austin J, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012;144:33-8.
49. Wender R, Fontham E, Barrera E, et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin. 2013;63:107-17.
50. Bach P, Gould M. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. Ann Intern Med. 2012;157:571-3.
51. de Torres J, Bastarrika G, Wisnivesky J, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest. 2007;132:1932-8.
52. Wilson D, Weissfeld J, Balkan A, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. Am J Respir Crit Care Med. 2008;178:738-44.
53. Hulbert A, Hooker C, Keruly J, et al. Prospective CT screening for lung cancer in a high-risk population: HIV-positive smokers. J Thorac Oncol. 2014;9:752-9.
54. Pathak V, Rendon I, Hasalla I, Tsegaye A. Evaluation of solitary pulmonary nodule in HIV- infected patients. Respir Care. 2012;57:1115-20.
55. Gritz E, Danysh H, Fletcher F, et al. Long-term outcomes of a cell phone-delivered intervention for smokers living with HIV/AIDS. Clin Infect Dis. 2013;57:608-15.
56. Humfleet G, Hall S, Delucchi K, et al. A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings. Nicotine Tob Res. 2013;15:1436-45.
57. Moscou-Jackson G, Commodore-Mensah Y, Farley J, DiGiacomo M. Smoking cessation interventions in people living with HIV infection: A systematic review. J Assoc Nurses AIDS Care. 2014;25:32-45.
58. Ferketich A, Diaz P, Browning K, et al. Safety of varenicline among smokers enrolled in the lung HIV study. Nicotine Tob Res. 2013;15: 247-54.
59. Cui Q, Robinson L, Elston D, et al. Safety and tolerability of varenicline tartrate (Champix®/Chantix®) for smoking cessation in HIV-infected subjects: a pilot open-label study. AIDS Patient Care STDS. 2012; 26:12-9.
60. Engels EA, Brock MV, Chen J, et al. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol. 2006;24:1383-8.

144

_____

Lucy B. Palmer,[1] Daniel A. Sweeney,[2] Mark L. Metersky,[3] and Andre C. Kalil[4]

[1]Department of Medicine, Division of Pulmonary Critical Care and Sleep Medicine, State University of New York at Stony Brook; [2]Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego; [3]Division of Pulmonary and Critical Care Medicine, University of Connecticut School of Medicine, Farmington; [4]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha

References

1. Abu-Salah T, Dhand R. Inhaled antibiotic therapy for ventilator-associated tracheobronchitis and ventilator-associated pneumonia: an update. Adv Ther 2011; 28:728–47.
2. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant *Pseudomonas aeruginosa*. Ann Pharmacother 2006; 40:1677–80.
3. Lu Q, Yang J, Liu Z, Gutierrez C, Aymard G, Rouby JJ; Nebulized Antibiotics Study Group. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. Am J Respir Crit Care Med 2011; 184:106–15.
4. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. N Engl J Med 2007; 357:2310–1.
5. Palmer LB. Aerosolized antibiotics in the intensive care unit. Clin Chest Med 2011; 32:559–74.
6. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. Ann Am Thorac Soc 2014; 11:425–34.
7. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63:e61–e111.
8. Montgomery AB, Corkery KJ, Brunette ER, Leoung GS, Waskin H, Debs RJ. Occupational exposure to aerosolized pentamidine. Chest 1990; 98:386–8.
9. Tsai RJ, Boiano JM, Steege AL, Sweeney MH. Precautionary practices of respiratory therapists and other health-care practitioners who administer aerosolized medications. Respir Care 2015; 60:1409–17.
10. Feeley TW, Du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol polymyxin and pneumonia in seriously ill patients. N Engl J Med 1975; 293:471–5.
11. Corkery KJ, Bacci R, Kadrichu. Low airborne concentrations following simulated amikacin inhale delivery during on-ventilator and handheld use. Berlin, Germany: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 2013.
12. Bassetti M, Luyt CE, Nicolau DP, Pugin J. Characteristics of an ideal nebulized antibiotic for the treatment of pneumonia in the intubated patient. Ann Intensive Care 2016; 6:35.
13. Berlana D, Llop JM, Fort E, Badia MB, Jódar R. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. Am J Health Syst Pharm 2005; 62:39–47.
14. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. Clin Infect Dis 2010; 51:1238–44.
15. Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med 2014; 189:1225–33.
16. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med 2008; 36:2008–13.
17. Luyt CE, Bréchot N, Combes A, Trouillet JL, Chastre J. Delivering antibiotics to the lungs of patients with ventilator-associated pneumonia: an update. Expert Rev Anti Infect Ther 2013; 11:511–21.
18. Dhand R. Aerosol delivery during mechanical ventilation: from basic techniques to new devices. J Aerosol Med Pulm Drug Deliv 2008; 21:45–60.

Cancer Incidence in Persons Living With HIV

To THE EDITOR—We read with interest the report by Borges et al [1] assessing the cancer incidence in person living with human immunodeficiency virus (HIV) who start antiretroviral treatment (ART) immediately or who defer until CD4 counts drop to <350 cells/µL. The Strategic Timing of Antiretroviral Treatment (START) study is a multicenter, randomized trial including 4685 naive people living with HIV from 35 countries worldwide [2].

Perhaps the design of the START trial is not the most appropriate to analyze cancer incidence (especially infection-unrelated cancers), due to the short HIV exposure, short follow-up, and participants with young age and few comorbidities. Nevertheless, the study has shown a lower incidence of infection-related cancers, and a trend of fewer infection-unrelated cancers, in patients with immediate ART start vs those starting at a CD4 count <350 cells/µL.

We collected all cancers in our institution between 1993 and 2014, with a total of 185 cancers in 2318 people living with HIV, contributing to 27086 person-years. We conducted a comparative analysis between HIV-monoinfected patients and those chronically coinfected with hepatitis C virus (HCV). Cancers were classified as AIDS-defining cancer (ADC) or non-AIDS-defining cancer (NADC). The overall incidence rate was 6.96 cases per 1000 person-years (5.45 in HIV-monoinfected patients and 8.29 in HIV/HCV-coinfected patients). After adjusting for age at HIV diagnosis, sex, and transmission route, a higher cumulative incidence of NADC was observed for HIV/HCV-coinfected patients compared with HIV-monoinfected patients (adjusted hazard ratio [HR], 1.70; ; 95% confidence interval [95% CI], 1.15–2.81), and significantly lower cumulative incidence of ADC (adjusted HR, 0.44; ; 95% CI, 0.25–0.74).
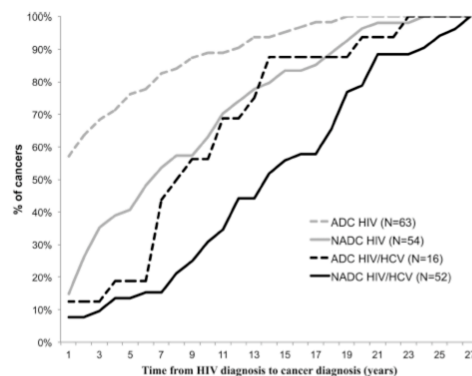
Figure 1. Time from HIV diagnosis to cancer in HIV-monoinfected and HIV/hepatitis C virus–coinfected patients. Abbreviations: ADC, AIDS-defining cancer; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NADC, non-AIDS-defining cancer.

In our data, the median time from HIV diagnosis to cancer was 11.0 years (IQR, 4.0-18.0) for NADC and 1.5 years (0.0–8.2) for ADC. Coinfected patients developed NADC 6.0 years (3.0–8.3) later than monoinfected patients and ADC 7.1 years (3.5–10.4) later (Figure 1). The median time from HIV diagnosis to randomization in START was 1 year and, after that, the time to infection-related cancer was 0.7 (0.3–3.4) years and to infection-unrelated cancer was 2.3 (0.6–4.9) years; the maximum follow-up was 5 years. After 5 years, in our cohort, close to 40% of NADCs were diagnosed in HIV-monoinfected patients, but only just over 10% in HCV-coinfected patients. With a longer follow-up in the START trial, an increase of cancer events is expected, mainly infection unrelated; it could help to explore better the differences between both strategies, as the authors acknowledge properly in the limitations.

Our data suggest a role of HCV coinfection in cancer development, beyond hepatocellular carcinoma, as data in HIV-uninfected patients have suggested [3]. In START, the independent predictors of infection-unrelated cancer were older age and baseline CD8 count. Less than 5% of patients in START were HCV coinfected, but the prevalence was >3 times higher in patients with infection-unrelated cancer than those without cancer. Based on our data, with a longer follow-up and a prevalence of HCV coinfection close to real life, it is expected that HCV coinfection could be a predictor of infection-unrelated cancer.

The data published by Borges et al are novel and important; despite the limitations exposed, when these data are analyzed in real-life cohorts, it is likely that the gap between early and deferred ART can be even higher. More studies to understand some aspects, such as the role of CD8, are needed.

Note

Potential conflicts of interest. All authors certify. No potential conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Héctor Meijide,[1,2] Álvaro Mena,[1] Iria Rodríguez-Osorio,[1] Ángeles Castro-Iglesias[1] and Eva Poveda[1]

[1]Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña–Complexo Hospitalario Universitario de A Coruña, Sergas, Universidade da Coruña; and [2]Servicio de Medicina Interna, Hospital Quirón, A Coruña, Spain

References

1. Borges ÁH, Neuhaus J, Babiker AG, et al. Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection [manuscript published online ahead of print 8 September 2016]. Clin Infect Dis 2016. doi:10.1093/cid/ciw621.
2. Lundgren JD, Babiker AG, Gordin F, et al; INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373:795–807.
3. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006–2010. J Hepatol 2015; 63:822–8.

Reply to Meijide et al

To THE EDITOR—We thank Meijide and colleagues [1] for their interest in our article [2]. They rightly point out that the short follow-up in the Strategic Timing of Antiretroviral Treatment (START) study [3] and an inherent low cancer risk at study entry hampered our ability to identify factors independently associated with infection-unrelated malignancies. Efforts are under way to extend follow-up beyond 2017 among START participants. This will allow us to determine with more accuracy the predictors for infection-unrelated cancer and better understand the effects of immediate vs deferred combination antiretroviral therapy initiation on cancer risk. In the meantime, data from large prospective cohort studies with long follow-up remain an invaluable source to determine risk factors for cancer among Human Immunodeficiency Virus (HIV)-infected persons.

Meijide and colleagues report the findings from an investigation involving HIV-infected persons carried out at their hospital in Spain [1]. They retrospectively classified malignancies into AIDS-defining and non-AIDS-defining cancer. An association was found between hepatitis C virus (HCV) coinfection and risk for non-AIDS-defining cancer in analyses adjusted for age, sex, and HIV transmission route. On the basis of this, they hypothesize that HCV coinfection may facilitate the development of malignancies other than hepatocellular carcinoma (HCC).

A direct comparison between Meijide et al's results and our report is difficult owing to differences in recruitment period, study design, and categorization of malignancies. As mentioned in our report [2], we opted for classifying incident malignancies in START into infection-related and infection-unrelated cancer. Although not perfect, this classification takes into account emerging data from epidemiological surveillance [4] and establishes a framework to study the interactions between HIV, coinfection by pro-oncogenic viruses, and cancer development.

Hepatocellular carcinoma is a non-AIDS-defining cancer that may be classified as an infection-related or infection-unrelated malignancy depending on whether the patient is coinfected or not with HCV or hepatitis B virus (HBV). In START, the only HCC event was classified as an infection-unrelated cancer because it occurred in a participant without HCV or HBV coinfection. We wonder whether the increased risk of non-AIDS-defining cancer among HCV-coinfected participants in Meijide et al's report was driven by an association with HCC. Shepherd and colleagues have recently published a report informative to this debate [5]. They investigated factors associated with infection-related and infection-unrelated cancers in EuroSIDA, a large HIV cohort with participants from across Europe, Israel, and Argentina. In analyses adjusted for demographics, HIV-specific variables, comorbidities, and smoking, there was no association between HCV coinfection

_____

_____

ANEXO 2A. COMUNICACIONES PRESENTADAS EN CONGRESOS INTERNACIONALES

1- IMPACT OF HCV INFECTION IN A HIV COHORT FOLLOWED OVER 18 YEARS: PAST AND PRESENT**.** A Mena, I Rodríguez-Osorio, H Meijide, A Castro-Iglesias, S López, P Vázquez, B Pernas, M Grandal, JD Pedreira, E Poveda. International Liver Congress, EASL. Viena, April 22- 26, 2015.

2- TRENDS IN HOSPITALIZATIONS, READMISSIONS AND IN-HOSPITAL MORTALITY IN HIV-INFECTED PATIENTS BETWEEN 1993-2013. IMPACT OF HEPATITIS C COINFECTION. H Meijide, Á. Mena, I. Rodríguez-Osorio, S. Pértega, Á. Castro, G. Rodríguez, J. Pedreira, E. Poveda. Presentado como Comunicación Oral en Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)San Diego, September17-21, 2015.

3- INCREASED INCIDENCE OF CANCER AND CANCER-RELATED MORTALITY AMONG HIV/HCV COINFECTED PATIENTS, 1993-2014**.** A. Mena, H. Meijide, I. Rodríguez-Osorio, Á. Castro-Iglesias, S. Pértega, G. Rodríguez, B. Pernas, J. Baliñas, E. Poveda, J.D. Pedreira. Comunicado en 15th European AIDS Conference, Barcelona, October 21-24, 2015.

ANEXO 2B. COMUNICACIONES PRESENTADAS EN CONGRESOS NACIONALES

1- CAMBIOS EN LA HOSPITALIZACION DE PACIENTES CON INFECCION POR VIH. ESTUDIO DESCRIPTIVO DEL PERIODO 1993-2013. H Meijide, A Mena, I Rodriguez, S Lopez, P Vazquez, B Pernas, E Poveda, JD Pedreira. XXXI Reunion Anual de la SOGAMI. 13-14 Junio 2014. Ourense.

2- PESO DE LA COINFECCION VIH-VHC . IMPACTO EN LA MORBIMORTALIDAD DE LOS PACIENTES VIH/VHC. H Meijide, A Mena, I Rodriguez, A Castro, B Pernas, S Lopez, P Vazquez, JD Pedreira, E Poveda. XXXII Reunion Anual de la SOGAMI. 5-6 Junio 2015. Pontevedra.

3- IMPACTO DE LA INFECCIÓN POR VHC EN UNA COHORTE DE PACIENTES VIH + DURANTE 18 AÑOS DE SGUIMIENTO: PASADO, PRESENTE Y FUTURO. A Mena, I Rodriguez, H Meijide, A Castro, S Lopez, P Vazquez, B Pernas, JD Pedreira, E Poveda. 40 Congreso Anual de la Asociación Española para el Estudio del Higado (AEEH). 24-27 Febrero 2015. Madrid.

4- DESCENSO DE LA SUPERVIVENCIA DE LOS PACIENTES VIH COINFECTADOS POR VHC TRAS 18 AÑOS DE SEGUMIENTO Y SIN CONTROL DE VHC. A Mena, I Rodriguez, H Meijide, A Castro, S Lopez, P Vazquez, B Pernas, JD Pedreira, E Poveda. 40 Congreso Anual de la Asociación Española para el Estudio del Higado (AEEH). 24-27 Febrero 2015. Madrid.

_____

5- CARACTERISTICAS EPIDEMIOLOGICAS DEL CANCER DE PULMON EN PACIENTES CON INFECCION POR VIH**.** H Meijide, A Mena A, R Suarez R, I Rodriguez , A Castro-Iglesias, B Pernas, JD Pedreira, E Poveda. XIX Congreso Nacional de SEIMC. 28-30 Mayo 2015. Sevilla.

6- SUPERVIVENCIA DE LOS PACIENTES VIH COINFECTADOS POR VHC TRAS 18 AÑOS DE SEGUIMIENTO. A Mena, I Rodriguez, H Meijide, A Castro, S Lopez, P Vazquez, B Pernas, JD Pedreira, E Poveda. III Xornadas de BiointegraSaude (BIS). 16 Junio de 2015. Vigo.

7- DINAMICA DE LAS HOSPITALIZACIONES MOTIVADAS POR BRONCOPATIA CRONICA EN PACIENTES CON INFECCION POR VIH EN LOS ULTIMOS 20 AÑOS (1993-2013). H Meijide, Á. Mena, I. Rodríguez-Osorio, R Suárez, Á. Castro, B Pernas, J. Pedreira, E. Poveda. VII Congreso del Grupo Nacional de GESIDA. 1-4 Diciembre 2015. Madrid.

8- SINDROME CORONARIO AGUDO EN PACIENTES CON INFECCION POR VIH,1993-2013. I Rodriguez, E Clavero, A Mena, H Meijide, A Castro, B Pernas, JD Pedreira, E Poveda. VII Congreso del Grupo Nacional de GESIDA. 1-4 Diciembre 2015. Madrid.

9- COINFECCION POR VHC E INCIDENCIA DE CANCER EN PACIENTES VIH. A Mena, H Meijide, S Pertega, I Rodriguez, A Castro, B Pernas, G Rodriguez, E Poveda. XXXIII Reunion Anual de la SOGAMI. 3-4 Junio 2016. A Coruña.

_____

10- INCIDENCIA DE CANCER EN PACIENTES VIH +. IMPACTO DE LA COINFECCION POR EL VIRUS DE LA HEPATITS C. H Meijide, Á. Mena, S Pertega, I. Rodríguez-Osorio, Á. Castro, B Pernas, G Lopez, E. Poveda. II Congreso Nacional del Grupo de Estudio de las Hepatitis Viricas de la SEIMC_Gehep. 29 Septiembre-1 Octubre 2016. Valencia

_____

ANEXO 3. PREMIOS DE INVESTIGACIÓN.

- 2ª **PREMIO A LA MEJOR COMUNICACIÓN ORAL** EN EL XXXII REUNION ANUAL
  DE LA SOCIEDAD GALLEGA DE MEDICINA INTERNA (SOGAMI) CELEBRADA EL 5-6
  JUNIO 2015. SANXENXO – PONTEVEDRA.

*"PESO DE LA COINFECCION VIH-VHC . IMPACTO EN LA MORBIMORTALIDAD DE LOS
PACIENTES VIH/VHC."* <u>H Meijide</u>, A Mena, I Rodriguez, A Castro, B Pernas, S Lopez,
P Vazquez, JD Pedreira, E Poveda.

- 1ª **PREMIO A LA MEJOR COMUNICACIÓN ORAL** EN LAS III XORNADAS DE
  BIOINTEGRASAUDE, CELEBRADAS EL 16 JUNIO 2015. VIGO.

*"SUPERVIVENCIA DE LOS PACIENTES VIH COINFECTADOS POR VHC TRAS 18
AÑOS DE SEGUIMIENTO"*. A Mena, I Rodriguez, <u>H Meijide</u>, A Castro, S Lopez, P
Vazquez, B Pernas, JD Pedreira, E Poveda.

- 2ª **PREMIO A LA MEJOR COMUNICACIÓN ORAL** EN EL XXXIII REUNION ANUAL
  DE LA SOCIEDAD GALLEGA DE MEDICINA INTERNA (SOGAMI) CELEBRADA EL 3-4
  JUNIO 2016. A CORUÑA.

"COINFECCION POR VHC E INCIDENCIA DE CANCER EN PACIENTES VIH". A Mena, <u>H
Meijide</u>, S Pertega, I Rodriguez, A Castro, B Pernas, G Rodriguez, E Poveda.