VNIVERSIDAD DE SALAMANCA
FACVLTAD DE FARMACIA

Departamento de Ciencias Farmacéuticas

TESIS DOCTORAL

Impacto de un programa de atención farmacéutica en la adherencia al tratamiento antirretroviral

Mª Jesús Hernández Arroyo

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Trabajo presentado por María Jesús Hernández Arroyo para obtener el grado de Doctor en Farmacia.

Fdo: María Jesús Hernández Arroyo

La presente tesis doctoral, se presenta como un compendio de tres artículos previamente publicados o aceptados para su publicación en revistas científicas indexadas en el *Journal Citation Reports*. Además, se incluye otro artículo en el marco de esta línea de investigación, que está en proceso de evaluación por la revista *International Journal of STD and AIDS*, para su publicación.

Las referencias completas de los artículos que constituyen el cuerpo de la tesis son las siguientes:

1. **Hernández Arroyo MJ[1],** Cabrera Figueroa SE[2], Valverde Merino MP[1] and Domínguez-Gil Hurlé A[5]. A pharmacist's role in the individualization of treatment of HIV patients. *Personalized Medicine*. 2016;13(2):169-188. doi: 10.2217/pme.15.54.

2. **Hernández Arroyo MJ[1],** Cabrera Figueroa SE[2], Sepúlveda Correa R[3], Valverde Merino MP[1], Iglesias Gómez A[4], Domínguez-Gil Hurlé A[5] and Tormes Team. Impact of a pharmaceutical care program on clinical evolution and antiretroviral treatment adherence: a 5-year study. *Patient Preference and Adherence*. 2013;7:729–739. doi: 10.2147/PPA.S47519.

3. **Hernández Arroyo MJ[1],** Cabrera Figueroa SE[2], Sepúlveda Correa R[3], Valverde Merino MP[1], Luna Rodrigo G[4], Domínguez-Gil Hurlé A[5] and Tormes Team. Influence of the number of daily pills and doses on adherence to antiretroviral treatment: a 7-year study. *Journal of Clinical Pharmacy and Therapeutics.* 2016;41(1):34-39. doi: 10.1111/jcpt.12343.

4. **Hernández Arroyo MJ[1],** Cabrera Figueroa SE[2], Sepúlveda Correa R[3], Valverde Merino MP[1], Bustos Bernal C[4], Domínguez-Gil Hurlé A[5] and Tormes Team. Influence of the pharmacotherapy follow-up program on change in antiretroviral therapy adherence and clinical outcomes: associated factors. Enviado a *International Journal of STD and AIDS*. Diciembre 2015.

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En calidad de directores de la Tesis titulada "Impacto de un programa de atención farmacéutica en la adherencia al tratamiento antirretroviral", realizada por Dª María Jesús Hernández Arroyo; consideran concluido el trabajo y que reúne las condiciones de originalidad y rigor científico necesarias; por lo que autorizan su presentación, mediante compendio de publicaciones, a fin de que pueda ser defendido ante el Tribunal correspondiente.

Y para que así conste, firman la presente certificación en Salamanca, a 11 de Abril de 2016.

Fdo. D. Salvador Cabrera Fdo. Dª María Paz Valverde Fdo. Dª Rosa Sepúlveda

“La verdadera ciencia enseña,
por encima de todo, a dudar y a ser ignorante”
MIGVEL DE VNAMVNO (1864~1936)

A mis padres

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A Alfonso Díaz, a mis compañeros y amigos,

A todos, GRACIAS.

ÍNDICE

INTRODVCCIÓN

Desde el momento en el que el síndrome de la inmunodeficiencia adquirida fue identificado por primera vez en Estados Unidos en el año 1981, su control se ha convertido en uno de los retos más grandes para la salud pública debido a su impacto en la salud, en lo económico y en lo social; así como por sus características epidemiológicas.

Se han buscado distintas soluciones, entre ellas el desarrollo de una posible vacuna, pero son principalmente los tratamientos farmacológicos los que han evolucionado con el objetivo de mejorar y aumentar la calidad y esperanza de vida de las personas infectadas por el virus de la inmunodeficiencia humana (VIH).

1. CARACTERÍSTICAS ACTUALES DE LA INFECCIÓN POR EL VIH

El VIH pertenece a la familia de los retrovirus humanos (retroviridae), dentro de la subfamilia lentivirus. Es el causante del síndrome de inmunodeficiencia adquirida, una inmunodepresión grave desencadenada como consecuencia de la infección de las células del sistema inmunitario. Tiene la particularidad de necesitar transformar su información genética para replicarse, de ahí su enorme diversidad.

El porcentaje mundial de personas que viven con el VIH se ha estabilizado desde el año 2000, sin embargo, el número total de personas que viven con el virus ha aumentado como consecuencia de las nuevas infecciones contraídas cada año y del efecto beneficioso que supone el acceso a la terapia antirretroviral.

El Programa Conjunto de las Naciones Unidas sobre el VIH/sida, en su informe sobre la epidemia mundial de sida, estimó que a finales del año 2014 había en el mundo aproximadamente 36,9 millones de personas infectadas por el VIH. En 2014, alrededor de 2 millones de personas se infectaron con el VIH y 1,2 millones de personas murieron a consecuencia de enfermedades relacionadas con el sida (1).

En España se estima que existen unas 150.000 (130.000-160.000) personas con infección por VIH (2), y que un 30% de ellos desconoce que están infectadas. Estas cifras son similares a las barajadas para el conjunto de la Unión Europea (3).

Actualmente el diagnóstico de la infección por VIH se basa en la demostración de los anticuerpos anti-VIH que aparecen en la circulación sistémica entre 2 y 12 semanas después de la infección, en la detección directa del VIH o de algunos de sus

componentes, o en ambos (4). En España, según datos del Sistema de Información de Nuevos Diagnósticos del año 2014, el 46% de los nuevos diagnósticos son tardíos (recuento de linfocitos CD4+ inferior a 350 céls/µl) y el 28%, presentan enfermedad avanzada (menos de 200 céls/µl) (5). Dado que los pacientes con linfocitos CD4+ inferiores a 200 céls/µl o una enfermedad definitoria de sida en el momento del diagnóstico, presentan un riesgo de muerte cinco veces superior (6), el diagnóstico precoz de la infección por VIH resulta de gran importancia para reducir la morbilidad y mortalidad en estos pacientes.

El pronóstico de la infección ha mejorado de modo extraordinario gracias a que desde el año 1996 se dispone de tratamientos farmacológicos específicos, los cuales han evolucionado con el objetivo de mejorar y aumentar la calidad y esperanza de vida de las personas infectadas por el virus. En la actualidad, las muertes relacionadas con enfermedades definitorias de sida han descendido un 42% (1) y la incidencia de infecciones secundarias ha disminuido notablemente. Sin embargo, como resultado de una mayor esperanza de vida, los pacientes han experimentado un aumento de la incidencia de enfermedades graves no asociadas al sida, como la enfermedad cardiovascular, renal y hepática, así como nuevos síndromes clínicos asociados a la cronificación de la enfermedad y a la terapia antirretroviral de largo plazo.

2. CARACTERÍSTICAS DEL TRATAMIENTO DE LA INFECCIÓN POR EL VIH

Los actuales tratamientos antirretrovirales son la base del adecuado control virológico e inmunológico de los pacientes infectados, siendo la supresión continua y duradera de la replicación viral, esencial para la recuperación de linfocitos CD4+. Este aspecto es uno de los factores más importantes que influyen en el pronóstico a largo plazo de los individuos infectados por el VIH.

Las pautas recomendadas para el tratamiento inicial de la infección por el VIH en el momento actual, consisten en una combinación de tres fármacos que incluyen, dos inhibidores de la transcriptasa inversa análogos nucleosídicos (ITIAN) asociados a un inhibidor de la integrasa (INI), un inhibidor de la transcriptasa inversa no análogo nucleosídico (ITINN), o un inhibidor de la proteasa (IP) potenciado (7).

El recuento de linfocitos CD4+ y la carga viral plasmática son, junto con la evaluación clínica, los parámetros que se utilizan para tomar decisiones respecto al inicio y los cambios en el tratamiento antirretroviral. También son útiles para monitorizar la eficacia de la terapia, y deben considerarse siempre conjuntamente (7).

Tradicionalmente, el tratamiento suponía la administración de varios comprimidos en dos o tres tomas diarias, sin embargo, la aparición de los "combos" y la estrategia *"single tablet régimen*" han permitido simplificar la terapia, de tal forma que, en la actualidad, es posible combinar tres antirretrovirales en un único comprimido de administración diaria. Con la simplificación de la terapia se busca que el tratamiento antirretroviral no sólo tenga en cuenta la potencia antiviral del fármaco, la toxicidad y la tolerancia, sino también la comodidad y estilo de vida del paciente; todos ellos, factores que pueden afectar a la adherencia del paciente al tratamiento.

Hay que tener en cuenta que la adherencia es el principal factor modificable por el paciente para contribuir al éxito de su tratamiento, por lo que han sido múltiples las estrategias que se han desarrollado dirigidas a su mejora, además de la simplificación anteriormente comentada.

3. ADHERENCIA AL TRATAMIENTO ANTIRRETROVIRAL

Tal y como la define el Grupo de Estudio del SIDA (8), se entiende por adherencia al tratamiento antirretroviral, la capacidad del paciente para implicarse correctamente en la elección, inicio y cumplimiento del mismo, a fin de conseguir una adecuada supresión de la replicación viral. Este concepto define una actitud y refleja un compromiso del paciente.

Dado que la adherencia incorrecta se considera la primera causa de fracaso terapéutico, y se ha relacionado con mala respuesta virológica, peor reconstitución inmune y mayor riesgo de mortalidad (9,10), es muy importante que antes de iniciar el tratamiento, los pacientes sean conscientes de su enfermedad, entiendan los objetivos de la terapia, estén seguros de querer iniciarla y se sientan capaces de cumplirla.

Los datos obtenidos durante los primeros tratamientos combinados, basados en fármacos inhibidores de la proteasa sin potenciar, constataron que la máxima eficacia requería una adherencia prácticamente perfecta (>95%) (11). Sin embargo, no es

suficiente con alcanzar una buena adherencia, es fundamental mantenerla en el tiempo, por ello, durante el tratamiento, es necesario evaluarla periódicamente.

3.1. Métodos de evaluación de la adherencia

El método ideal de medida de la adherencia debería ser altamente sensible y específico, permitir una medida cuantitativa y continua, fiable, reproducible, además de rápido y económico. Puesto que no se conoce un único método fiable, se recomienda combinar varias técnicas (8).

Existen varios métodos para calcular la adherencia que pueden ser clasificados en directos e indirectos.

Métodos directos

a) Concentraciones plasmáticas de fármacos antirretrovirales

Se considera el método más objetivo, pero no está exento de importantes limitaciones, dado que se han encontrado niveles plasmáticos adecuados en un importante porcentaje de pacientes con una baja adherencia autorreferida (12,13).

Es importante tener en cuenta que no es posible realizar la determinación de niveles plasmáticos en todos los fármacos, que existen muchas variables intra e interindividuales que condicionan el comportamiento cinético de los antirretrovirales y que, establecer un umbral para clasificar a los pacientes como adherentes o no adherentes, resulta cuestionable.

b) Evolución clínica y datos analíticos

Actualmente, la evolución inmuno-virológica del paciente se considera, más que un método de evaluación de la adherencia, una consecuencia de esta.

Métodos indirectos

a) Valoración del profesional sanitario

Suele ser subjetiva, lo que explica que, en diferentes experiencias publicadas, los profesionales sanitarios sobreestimen notablemente la adherencia de los pacientes cuando ésta se compara con otros métodos (14,15).

b) Sistemas de control electrónico

Son dispositivos que registran la hora y día en que se ha abierto el envase. Aunque se considera un método fiable, pueden ser manipulados, y, en un sentido estricto, la apertura del envase no implica necesariamente la toma de la medicación (16,17).

c) Recuento de medicación

Se ha utilizado con éxito en otras patologías crónicas debido a sus ventajas: es poco costoso, permite una medida cuantitativa y es objetivo. Sin embargo, aportar la medicación es molesto y aparatoso para el paciente, y recontarla resulta complejo para los profesionales sanitarios (8).

d) Registros de dispensación

Este método parte de la asunción de que un paciente no puede tomar la medicación que no le es dispensada y que toma de forma adecuada aquella que se le dispensa. Se ha visto una buena correlación con los resultados inmuno-virológicos (18) y aceptable especificidad y sensibilidad (12,19). Este método exige que la dispensación se realice de forma centralizada.

e) Cuestionarios

El procedimiento consiste en solicitar al paciente que conteste unas preguntas previamente definidas para, en función de sus respuestas, poder valorar el grado de adherencia. Es un sistema que requiere pocos recursos, asequible y adaptable a las características de cada centro. Entre los cuestionarios validados en población española, cabe destacar el cuestionario *Simplified Medication Adherence Questionnaire* (SMAQ) (20).

f) Combinaciones de métodos

Se considera mínimamente aceptable la asociación de un cuestionario validado y el registro de dispensación, obtenidos con una frecuencia trimestral. En el contexto de un estudio clínico, que pueda incluir intervenciones para la mejora de la adherencia, se debe utilizar al menos uno de los métodos más objetivos (21).

Estudios recientes realizados en España muestran que, entre un 40-50% de pacientes con tratamiento antirretroviral activo, presentan una adherencia inadecuada al mismo (22,23). Puesto que el tratamiento con fármacos antirretrovirales constituye un régimen

de tratamiento complejo y la falta de adherencia supone una causa de ineficiencia de la terapia y del uso de los recursos públicos, es fundamental conocer los factores que pueden influir en ella, así como desarrollar estrategias que ayuden a mejorarla.

3.2. Factores que afectan a la adherencia

Existen diversas causas y factores que pueden conducir al fracaso terapéutico y que dependen tanto del virus, de los fármacos, como del propio paciente. Entre los que dependen del paciente, el más importante es el grado de cumplimiento que tiene con su tratamiento antirretroviral y puede verse afectado, a su vez, por diferentes circunstancias (8) (figura 1).

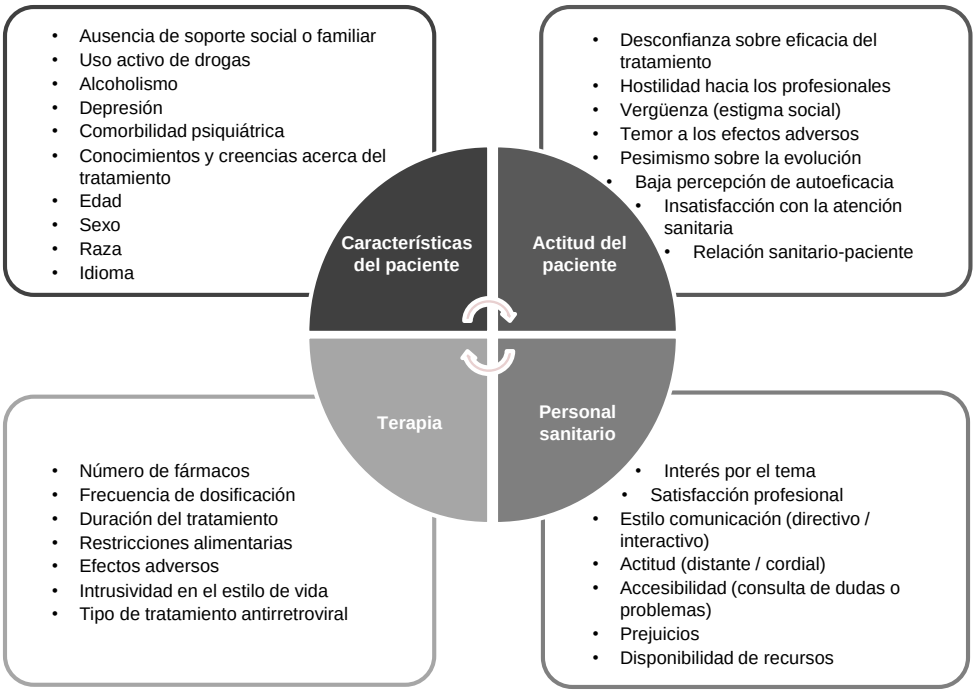

Figura 1. Factores relacionados con la adherencia incorrecta al tratamiento antirretroviral

3.3. Estrategias para mejorar la adherencia

Existen numerosas estrategias dirigidas a incrementar la adherencia al tratamiento farmacológico, sin embargo, parece no existir una estrategia de intervención superior a otras (24,25). Distintas revisiones sistemáticas concluyen que las intervenciones que combinan los componentes cognitivos, conductuales y afectivos son más eficaces que los centrados en uno sólo de estos aspectos (8).

Intervenciones simplificadoras del tratamiento

La simplificación del tratamiento antirretroviral se define como el cambio de un régimen con el que se ha conseguido una adecuada respuesta, por otro que mantenga la misma eficacia y permita reducir su complejidad.

Numerosos estudios establecen una relación directa entre la complejidad del tratamiento prescrito (en términos de dosificación, vía de administración, número de fármacos, etc.) y la falta de adherencia (26,27), pudiéndose englobar en esta complejidad, las interferencias con las actividades de la vida diaria del paciente (28). Parece lógico pensar, por tanto, que toda estrategia encaminada a simplificar el tratamiento debería tener como resultado la mejora en la adherencia terapéutica.

Intervenciones informativas / educativas

La trasmisión de información tendría su papel sobre la adherencia a través del proceso de aprendizaje orientado para que el individuo adopte voluntariamente la conducta más beneficiosa, ofreciéndole los medios adecuados (29), apoyándose en que los pacientes desean recibir información y principalmente desean recibirla de los profesionales que les atienden habitualmente (30). En este sentido, este tipo de intervenciones tienen como objetivo la mejora del cumplimiento a través del aumento de conocimientos sobre su enfermedad, las posibles complicaciones, el tratamiento prescrito, etc.

Entregar información escrita (31), realizar sesiones educativas grupales (32) y proporcionar información individualizada (33,34) son algunas de las estrategias que han demostrado buenos resultados sobre la adherencia.

Intervenciones de refuerzo conductual

Se ha demostrado que, cuando el paciente cree que el tratamiento indicado incidirá positivamente en la evolución de su proceso y cuando se considera responsable del mismo, tiende a seguir dicho tratamiento con mayor adherencia que en los casos contrarios (35); por este motivo, cabe pensar que las intervenciones que van encaminadas a mejorar la capacidad del paciente en el manejo de su proceso a través de técnicas de responsabilización, autocontrol y refuerzo conductual, pueden conducir a la mejora de la adherencia terapéutica (36).

Counselling

El Programa Global del SIDA de la Organización Mundial de la Salud, define el *counselling* como un proceso dinámico de diálogo a través del cual una persona ayuda a otra en una atmósfera de entendimiento mutuo. Este proceso se sustenta en las habilidades de comunicación y las estrategias de autocontrol para facilitar la toma de decisiones y la resolución de problemas.

El *counselling* en pacientes infectados por el VIH puede dirigirse a la resolución de problemas específicos, la toma de decisiones, el proceso para hacer frente a las crisis o el trabajo a través de los sentimientos o los conflictos internos (37). El papel del profesional consiste en facilitar la tarea, respetando sus valores, sus recursos personales y su capacidad de autodeterminación (38).

4. PAPEL DEL FARMACÉUTICO EN LOS PROGRAMAS DE SEGUIMIENTO

La aparición del tratamiento antirretroviral de gran actividad a principios del siglo XXI, supuso un cambio radical en el escenario terapéutico del sida, siendo mucho más eficaz y complejo que los primeros tratamientos desarrollados. Esta circunstancia propició una participación más activa del farmacéutico, más allá de la simple dispensación. Se inició la atención farmacéutica al paciente VIH, incluyendo como retos asistenciales, la integración en el equipo interprofesional, la relación directa con el paciente, así como la gestión de los fármacos de un modo coste-efectivo.

En el año 1990, Hepler y Strand definieron la atención farmacéutica como la provisión responsable de la farmacoterapia, con el propósito de alcanzar unos resultados

concretos que mejoren la calidad de vida del paciente (39). Hoy en día, para alcanzar este objetivo en los pacientes infectados por el VIH, el farmacéutico debe tener un profundo conocimiento de la farmacoterapia, de la fisiopatología de la enfermedad, de la metodología de atención farmacéutica y de la metodología de entrevista clínica. Además, dada la complejidad del paciente en tratamiento con fármacos antirretrovirales, es necesario que se establezcan sistemáticas de trabajo que permitan una atención individualizada, específica para esta patología y necesariamente integrada dentro de un equipo multidisciplinar.

Las diferentes actuaciones de los farmacéuticos en el cuidado de los pacientes infectados por el VIH, han demostrado reducir el número de comprimidos y la frecuencia de administración de antirretrovirales, mejorar la adherencia al tratamiento (40,41), incrementar el recuento de linfocitos CD4+ y las tasas de supresión viral (42,43) y reducir los errores de medicación (44).

El farmacéutico cuenta con una posición privilegiada para ejercer sus funciones de corresponsabilidad en la mejoría clínica de los pacientes, especialmente en el campo de la adherencia y el control de las interacciones; dada la facilidad de acceso a los datos de dispensación de medicamentos, sus conocimientos farmacológicos y la tradicional relación de cercanía con los pacientes que favorece la comunicación activa y el *counselling*.

Un reciente estudio (45) ha analizado la situación actual de la atención farmacéutica al paciente VIH en España y la ha comparado con el análisis de situación del año 2004. Entre sus resultados destacan que, actualmente se proporciona más información, tanto oral como escrita, sobre la terapia; el farmacéutico interviene más en los cambios de tratamiento y ha mejorado la monitorización de la adherencia, siendo el registro de dispensación el método más utilizado. Sin embargo, la adherencia al tratamiento antirretroviral sigue sin determinarse de forma periódica, el grado de integración del farmacéutico dentro del equipo asistencial es limitado y existe escasa aplicación de la farmacocinética y la farmacogenética en la práctica asistencial rutinaria.

Esta investigación surge a partir de una larga experiencia en la atención especializada a los pacientes con VIH atendidos en el Hospital Clínico de Salamanca, de un equipo interprofesional integrado por médicos, farmacéuticos y enfermeras que se creó tras instaurar, en el año 2005, un programa de seguimiento farmacoterapéutico integral que incluía, dentro de sus estrategias, un programa de atención farmacéutica.

HIPÓTESIS DE TRABAJO Y OBJETIVOS

La adherencia al tratamiento antirretroviral desempeña un papel primordial en el grado y duración de la respuesta antiviral. Es el resultado de un proceso complejo que se desarrolla a través de la aceptación del diagnóstico, la percepción de la necesidad de realizar el tratamiento de forma correcta, la motivación para hacerlo, la disposición y entrenamiento de habilidades para realizarlo, la capacidad de superar las dificultades que aparezcan y el mantenimiento de los logros alcanzados con el paso del tiempo (8). Varios estudios han demostrado que la adherencia al tratamiento antirretroviral es un buen predictor de fracaso virológico, progresión a sida y muerte (10,46,47).

No obstante, la adherencia no es el único factor determinante del fracaso o éxito del tratamiento antirretroviral; otros factores que pueden influir son, por ejemplo, las diferencias genéticas en el metabolismo de los fármacos o la aparición de resistencias e infecciones oportunistas. Sin embargo, es uno de los pocos factores potencialmente modificables que es determinante para conseguir buenos resultados clínicos en pacientes con VIH. Por este motivo, resulta necesaria la instauración de programas de atención global al paciente, que incluyan, tanto la evaluación de la adherencia, como la elaboración de estrategias de actuación dirigidas a optimizar los resultados en salud.

En lo que respecta a la evaluación de la adherencia, si bien se ha avanzado de forma notable en la caracterización de la especificidad y sensibilidad de los distintos métodos, en su validación y en el análisis de sus limitaciones y relaciones entre sí, continúa vigente la recomendación de combinar varios de ellos para obtener información de la situación real con la mayor exactitud posible (7). Algunos de los métodos de evaluación de la adherencia son, emplear un cuestionario estructurado y validado durante la entrevista al paciente, registrar la recogida de la medicación por el Servicio de Farmacia y determinar las concentraciones plasmáticas de los fármacos antirretrovirales susceptibles de monitorizar. Por lo anteriormente expuesto, sería recomendable conocer de qué manera se relacionan los diferentes métodos de medida de adherencia entre sí, para conocer si existe asociación entre sus resultados o, por el contrario, son dispares.

En cuanto a las estrategias de mejora de la adherencia al tratamiento antirretroviral, dado su carácter multifactorial, implican necesariamente el conocimiento de los factores influyentes y la manera en que ejercen dicha influencia.

Se han identificado varios factores asociados con tasas subóptimas de adherencia al tratamiento antirretroviral, que se han clasificado en tres grandes grupos en función de

su relación con el individuo, con el tratamiento o con el equipo asistencial y sistema sanitario.

Dentro de los factores relacionados con el individuo, se ha observado una mayor adherencia en los pacientes naïve (48), más jóvenes (49,50), con mayor nivel educativo (51) y, aunque existen pocos trabajos que comparen la adherencia entre mujeres y hombres, algunos estudios han mostrado una mejor adherencia en ellos (52,53). Un factor que está relacionado con el tratamiento y que puede influir en la adherencia al mismo, es la duración prolongada de la terapia. Actualmente su impacto es controvertido; mientras que algunos autores asocian una mayor duración con mejor adherencia, otros consideran que tiene un efecto negativo al igual que ocurre en otras enfermedades crónicas (54).

Tener pautado un tratamiento menos complejo, también se ha relacionado con mayor posibilidad de alcanzar buena adherencia (55,56). En este sentido, se ha descrito una asociación directa entre el incumplimiento del tratamiento antirretroviral y la sobrecarga en el número de comprimidos (26,27), así como mayores niveles de adherencia en los pacientes que reciben la medicación una vez al día frente a los que la reciben dos o tres veces al día (48,57). Por este motivo, en la pasada década ha habido un importante progreso en la simplificación del número de comprimidos y de su frecuencia de administración, que ha permitido realizar tratamientos sencillos y de alta potencia. La coformulación de varios principios activos en una sola forma de dosificación y la disponibilidad de fármacos que se pueden administrar una vez al día, han conseguido que los regímenes hayan evolucionado desde aquellos que incluían más de 25 comprimidos repartidos en tres tomas diarias, a los más actuales, que sólo incluyen un comprimido administrado una vez al día.

A pesar de las dificultades para alcanzar una adherencia adecuada al tratamiento, hasta el momento, no se conoce ningún método de intervención que haya demostrado superioridad frente a otros, pero existe consenso en que la intervención más frecuente, sencilla y que ha demostrado mejores resultados, es la basada en proporcionar información, motivación y educación al paciente (58). Haciendo comprender al paciente el objetivo del tratamiento y la importancia de la adherencia al mismo, es posible alcanzar su máximo compromiso con la terapia (59).

La participación del farmacéutico en los programas de atención farmacéutica, mediante la transmisión al paciente de los conocimientos suficientes para conseguir

una correcta utilización de los medicamentos, permite optimizar la terapia antirretroviral y, obtener así, el máximo beneficio (60). Además, a través del seguimiento farmacoterapéutico, el farmacéutico se responsabiliza de las necesidades del paciente relacionadas con los medicamentos mediante la detección, prevención y resolución de problemas relacionados con la medicación, de forma continuada, sistemática y documentada, en colaboración con el propio paciente y con el resto de profesionales sanitarios. Por otro lado, sus conocimientos en farmacogenética y farmacocinética permiten realizar un diseño personalizado del tratamiento antirretroviral.

Los **objetivos** de esta investigación son:

1. Revisar el papel del farmacéutico en la individualización de los tratamientos en los pacientes infectados por el VIH.

2. Detectar si existe asociación entre las diferentes medidas de valoración de la adherencia: determinación de las concentraciones plasmáticas de los fármacos antirretrovirales susceptibles de monitorizar [therapeutic drug monitoring (TDM)], un cuestionario estructurado validado en población española (SMAQ) y registros de dispensación de antirretrovirales.

3. Evaluar el impacto que tiene la instauración de un programa de atención farmacéutica sobre la evolución de la adherencia al tratamiento antirretroviral en la cohorte de pacientes externos con VIH del Hospital Universitario de Salamanca.

4. Determinar la repercusión de la instauración de un programa de atención farmacéutica en la respuesta virológica e inmunológica de los pacientes.

5. Analizar la evolución en el tiempo del número de comprimidos de antirretrovirales y tomas diarias de medicación.

6. Analizar la influencia que tienen el número de comprimidos de antirretrovirales y tomas de medicación en el grado de adherencia de los pacientes a su tratamiento.

7. Analizar la evolución clínica y de adherencia en subgrupos de pacientes categorizados según el género, la edad, el tiempo en tratamiento y según sean naïve o pretratados.

CONCLVSIONES

Las conclusiones a las que se llega, a partir de la interpretación de los resultados de esta tesis, son las siguientes:

1. La aportación del farmacéutico en la individualización y optimización de los tratamientos es muy valiosa, tanto por sus conocimientos en farmacogenética y farmacocinética, como por su participación directa en el contacto con los pacientes dentro de los programas de atención farmacéutica.

2. Los resultados obtenidos muestran que existe relación entre los registros de dispensación de antirretrovirales y el cuestionario SMAQ, por lo que ambos métodos son adecuados para evaluar la adherencia al tratamiento antirretroviral.

3. Los resultados obtenidos permiten relacionar la adherencia al tratamiento antirretroviral con los dos indicadores más importantes de respuesta clínica, número de linfocitos CD4+ y carga viral plasmática. Por tanto, tasas de adherencia mayores o iguales al 95%, hacen posible un mayor tiempo de permanencia del paciente con cargas virales indetectables y en consecuencia un mejor recuento linfocitario.

4. Los resultados obtenidos muestran que existe asociación entre el número de entrevistas e intervenciones farmacéuticas realizadas a cada paciente y la adherencia al tratamiento antirretroviral. Esto evidencia la importancia de la instauración y permanencia de este servicio farmacéutico para los pacientes con VIH/sida.

5. En los 7 años de estudio, el número de comprimidos diarios de medicación antirretroviral ha descendido de 6 a 4, aproximadamente, y se ha incrementado la prescripción de regímenes que se administran una vez al día.

6. No se ha encontrado relación entre el número de comprimidos y tomas diarios de medicación antirretroviral con el nivel de adherencia del paciente a la terapia.

7. Las intervenciones realizadas en el marco de un programa de atención farmacéutica y la educación continua a los pacientes infectados por el VIH, han contribuido a mejorar las tasas de adherencia y la respuesta clínica de los pacientes, especialmente en pacientes pretratados, de género masculino y aquellos que llevaban menos tiempo en tratamiento con antirretrovirales.

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A pharmacist's role in the individualization of treatment of HIV patients

Review

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Review

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A pharmacist's role in the individualization of treatment of HIV patients

The pharmacological treatment of HIV is complex and varies considerably among patients, as does the response of patients to therapy, requiring treatment plans that are closely tailored to individual needs. Pharmacists can take an active role in individualizing care by employing their knowledge of pharmacokinetics and pharmacogenetics and by interacting directly with patients in counseling sessions. These strategies promote the following: maintenance of plasma concentrations of antiretroviral agents within therapeutic ranges, prediction of pharmacological response of patients with certain genetic characteristics, and clinical control of HIV through the correct use of antiretroviral treatments. Together, these strategies can be used to tailor antiretroviral therapy to individual patients, thus improving treatment efficacy and safety.

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AIDS was first identified in the USA in the summer of 1981, when the CDC announced the presence of unexplained pneumonia from the *Pneumocystis jirovecii* fungus (previously known as *Pneumocystis carinii*) and Kaposi sarcoma in five previously healthy homosexual men in New York and Los Angeles [1].

In the decades following this discovery, several treatment strategies have been developed to prolong the life expectancy and improve the quality of life of patients infected with HIV, the virus that causes AIDS. Nevertheless, it is still not possible to cure HIV infection, and patients today require prolonged pharmacological treatment that is complicated by adverse effects, drug resistance, drug interactions and the requirement for optimal and long-term adherence [2]. Furthermore, a patient's treatment plan may periodically change due to the appearance of drug toxicity and resistance resulting from mutations in the virus. These periodic treatment changes produce considerable uncertainty for clinicians and patients.

In addition to striving toward the development of a vaccine, therapeutic researchers have focused on finding new drugs or combinations of drugs that are less toxic, more cost effective and more tolerable to patients [3]. To achieve these goals, clinicians have implemented a number of strategies, including simplifying therapy [4,5], conducting genetic testing [6], and resistance testing [7] and maintaining antiretroviral plasma concentration within a range that has been deemed appropriate for each patient through personalized dosages [8].

Pharmacokinetics (PKs), pharmacodynamics (PDs) and pharmacogenetics must be carefully considered during antiretroviral treatment in order to reduce the variability of patient responses and determine the precise concentrations of antiretroviral agents needed to prohibit the replication

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of HIV [9–11]. Through therapeutic drug monitoring (TDM) of antiretroviral agents, it is possible to adjust dosages to maintain plasma concentrations within a therapeutic range, improving efficacy and reducing toxicity. Pharmacogenetics can help predict the pharmacological response in patients meeting certain genetic criteria, allowing clinicians to tailor antiretroviral therapy (ART) to individual patients. Additionally, adherence to ART affects the degree and duration of antiviral response [12–14], making patient education regarding the importance of adherence a key component of care.

This article reviews three principal tools that can be used by pharmacists to individualize HIV treatment: TDM, pharmacogenetics and personalized pharmaceutical care. Used together, these tools promote the optimized dosing of ART and improved clinical results.

PKs in the treatment of HIV patients

Monitoring antiretroviral plasma concentrations [15,16] plays a key role in the optimization of HIV treatment as evidenced by the relationship between drug exposure and efficacy and toxicity [17,18]. The primary objective of TDM in HIV patients is to tailor the dosage of antiretroviral agents for each patient in order to maximize the benefit of the prescribed treatment [19]. In some patients, TDM can be used to reduce the probability of drug toxicity, while in others it can be used to achieve desired therapeutic outcomes.

According to studies [20,21], 35–61% of patients receiving a standard dose of an antiretroviral agent do not achieve adequate plasma concentrations of the antiretroviral. The tendency to prescribe doses that are either too high or too low can be remedied by tailoring dosage according to the PK behavior of the drug in each patient.

Indications for TDM of antiretroviral agents

Treatment effectiveness can be reduced as a consequence of patient-related factors (e.g., lack of adherence and drug intolerance), drug-related factors (e.g., PK and PDs characteristics) and factors related to the virus (e.g., high levels of replication and mutation or the existence of latent reservoirs of virus). TDM can play a role in responding to each of these types of factors [4,5].

According to consensus documents [4–5,22–23], TDM is indicated for the treatment of HIV in order to promote adherence to ART, identify and control interactions, avoid toxicity, determine the initial ART treatment scheme and its modifications, establish unofficial or rescue doses, and optimize therapy in patients with renal or hepatic insufficiency, as well as in overweight, pregnant and/or pediatric patients. Given the evidence of TDM's effectiveness in meeting these objectives, many healthcare centers use TDM only in cases in which meeting these objectives is desired.

Antiretroviral agents suited for TDM

Generally speaking, dosage adjustments based on plasma concentration require the availability of tools capable of accurately measuring and analyzing plasma concentrations and are justified under certain pharmacological, PK and clinical criteria. These criteria include the availability of population PK data, high interpatient and low intrapatient variability in the relationship between dose and serum concentration, a close correlation between the plasma concentration of the agent and the concentration at the site of action, existence of a therapeutic range of plasma concentrations associated with maximum efficacy and minimal toxicity and a pharmacological effect dependent on plasma concentration [24].

The consensus among clinical pharmacists in the Europe and the USA [4,22] promotes the implementation of TDM for treatment with protease inhibitors (PIs) [25–27] and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [28–31]. Nevertheless, information regarding the relationship between concentrations and toxicities in these classes of antiretroviral agents is scarce; therefore, clinicians should consult up-to-date information regarding the therapeutic ranges for these agents.

In the case of entry inhibitors, only the CCR5 receptor antagonist maraviroc (MVC) has been demonstrated that minimal concentrations can be an important predictor of virological success [32]. However, clinical experience with TDM and MVC remains limited, as does the evidence available regarding TDM and integrase inhibitors (IIs). While there has been some evidence involving raltegravir (RAL) [33,34], it is not sufficient to make a concentration recommendation.

For nucleoside analog reverse transcriptase inhibitors (NARTIs), there is no solid or applicable evidence to date on PK/PD relationships in routine clinical practice. NARTIs are prodrugs that must be phosphorylated within cells in order to be activated; therefore, there is not a clear correlation between blood concentrations of these compounds and antiretroviral activity and potential toxicity [35]. Furthermore, these agents require a complex analytical technique and are associated with high intrapatient variability, complicating their use in clinical practice [5].

PK parameters

To date and for practical purposes, the minimum concentration at equilibrium (C^{ss}_{min}) appears to be the best PK indicator of suppression of viral replication accord-

ing to consensus among researchers [15,19,23,36–44]; however, the parameters of area under the curve and maximum concentration at equilibrium (C^{ss}_{max}) have also shown an acceptable correlation with clinical response [38–40]. When evaluating toxicity, measuring C^{ss}_{max} is preferred, as this parameter is more likely to be related with the presence of adverse effects.

Due to the difficulty associated with precisely measuring C^{ss}_{max} or C^{ss}_{min}, an estimation using the Bayesian method is most commonly used. In the context of clinical PKs, Bayes' theorem permits the identification of a quantitative relationship between the probability a priori of presenting certain values of PK parameters and the probability posteriori, once the concentrations of the drug are known [45]. Furthermore, the Bayesian method controls for diverse variables that influence the PK profile of a drug, such as pharmacological interactions.

Table 1 lists the principal PK parameters of each antiretroviral class that is suited for TDM; these parameters are updated periodically by the Liverpool HIV Pharmacology Group [43]. The characteristics that most influence PKs are also described for each family.

Non-nucleoside reverse transcriptase inhibitors

This class of antiretroviral agents has the benefit of a long half-life and low intrapatient variability. Monitoring these agents is particularly useful because dose adjustments help to avoid the rapid appearance of mutations that promote resistance [46], assuring longer lasting viral suppression. TDM also leads to a reduction of concentration-dependent side effects [4].

Protease inhibitors

This class of antiretroviral agents is characterized by low bioavailability, high affinity for plasma proteins and an extensive metabolism by the CYP3A4 enzyme [42]. Using a strategy called PK potentiation, PIs are typically administered along with ritonavir (RTV) or cobicistat (COBI), which inhibits the metabolic enzyme that metabolizes the PIs. RTV is a PI and it is administered in small doses (100–400 mg) for its inhibitory effect on the CYP450 enzyme, including predominately CYP3A4 and CYP2D6, and on P-gp. Due to this inhibitory effect, it is possible to obtain higher minimum concentrations of the antiretroviral agents and prolong their plasma half-lives [47]. This allows for lower and less frequent doses of the PIs, including at a frequency of once a day in the case of darunavir and atazanavir (ATV) [48,49].

With saquinavir (SQV) and lopinavir, the principal effect of RTV is to increase the bioavailability of PIs, while with amprenavir and indinavir (IDV), the principal effect is to prolong the PI's half-life [47].

COBI is a substrate and potent inhibitor of CYP3A, as well as a substrate and weaker inhibitor of CYP2D6; it is used in combination with elvitegravir (EVG). It is also used as a booster of some PIs as an alternative to RTV due to its ability to inhibit the membrane transporters P-gp, BCRP, OATP1B1 and OATP1B3 [50,51]. Both RTV and COBI interact with a high number of other drugs that are metabolized by the enzymes inhibited by the boosters.

Integrase inhibitors

This class of antiretroviral agents has been developed relatively recently with the exception of RAL; therefore, information on the PKs of these agents is limited. RAL and EVG are metabolized by UGT1A1, of which RAL is a weak inhibitor. EVG is also metabolized by the isoenzymes CYP3A and UGT1A3 and is weak inducer of CYP2C9. As previously mentioned, EVG is often boosted by COBI.

Dolutegravir (DTG) is also metabolized by UGT1A1 with minor contribution by CYP3A and is a substrate of P-gp. It is associated with few drug interactions [52]. While there are limited data available on TDM with DTG, its PK profile appears to be characterized by low variability [53]. A new II called cabotegravir may become the first long-acting parenteral drug of this class [54].

CCR5 receptor antagonists

MVC is one of the most sensitive metabolites of CYP3A4 with no significant involvement of the other CYP450 isoenzymes. MVC has a linear PK profile and therefore C^{ss}_{min} can be used as a reliable indicator of adequate drug dose [55].

Therapeutic index

The therapeutic index is the ratio between the maximum tolerated concentration and the minimum effective concentration [56]. Using PK/PD models, relationships between C^{ss}_{min} and virological failure [36–37,57–59] and between C^{ss}_{max} and toxicity have been established for a number of pharmacological classes [38–40]. These relationships are valid for naive patients, in other words, those who have not previously been treated by ART and are theoretically without resistance.

For patients previously treated with ART, the therapeutic index is more difficult to establish, given that it cannot be extrapolated from one group of patients to another [60]. Table 2 shows the consensus values of therapeutic indices for the majority of antiretroviral agents [23,27,61–63]. While therapeutic indices have not yet been established for DTG, EVG and rilpivirina (RPV), techniques for quantifying the plasma concentration of EVG and RPV have been validated [64,65].

Table 1. The principal pharmacokinetic parameters of each antiretroviral class.

Drug	Bioavailability (%)	Volume of distribution (l)	Plasma half-live (h)	Protein binding (%)	Renal excretion (unchanged, %)	Transporters	Main metabolizers routes
Protease inhibitors							
Atazanavir	68	NA	6.5 (8.6 with RTV)	86	7	P-gP, MRP, BCRP	CYP3A4
Darunavir	37; 82 (with RTV)	131 ± 49.9 (with RTV)	15 (with RTV)	95	1.2	P-gP	CYP3A4
Fosamprenavir	NA	6†	7.7 (15–23 with RTV)	90	<1	P-gP	CYP3A4
Indinavir	65	1.74†	1.4–2.2	60	<20	P-gP, MRP1	CYP3A4
Lopinavir	NA	NA	5–6	98–99	<3	P-gP, MRP1, MRP2, hOATP	CYP3A4
Nelfinavir	70–80	2–7†	3.5-5	>98	1–2	P-gP, MRP1, MRP2	CYP3A4, CYP2C19, CYP2D6
RTV	NA	20–40	3–5	98–99	3.5	P-gP, MRP1	CYP3A4, CYP2D6
Saquinavir	4	700	7–12	97	1–3	P-gP, MRP1, MRP2, hOATP	CYP3A4
Tipranavir	NA	NA	5.5–6	>99.9	<5	P-gP	CYP3A
Non-nucleoside reverse transcriptase inhibitors							
Delavirdine	85	0.8–1.0†	5.8	98	<5	NA	CYP3A4, CYP2D6
Efavirenz	NA	252	55	>99	<1	NA	CYP3A4, CYP2B6
Etravirine	NA	NA	41	99.9	<1.2	NA	CYP3A4, CYP2C9, CYP2C19
Nevirapine	91–93	1.1–1.3†	25–30	60	<3	NA	CYP3A4, CYP2B6
Rilpivirine	NA	152	50	99.7	<1	NA	CYP3A, CYP2A19
Other classes							
Dolutegravir	NA	17.4	14	99	<1	P-gP, BCRP	UGT1A1, CYP3A
Elvitegravir	NA	NA	12.9	98–99	7 with RTV	NA	CYP3A, UGT1A1, UGT1A3
Maraviroc	23–33	194	13.2	76	8–23	P-gP	CYP3A4
Raltegravir	NA	NA	9	83	9	NA	UGT1A1

†l/kg.
NA: Data not available; P-gP: P-glycoprotein; RTV: Ritonavir.

Table 2. The consensus values of therapeutic indices for each antiretroviral agent.

Drug	MEC (μg/ml)			MTC (μg/ml) upper limit
	Lower limit		Upper limit	
	Naive patients	Pretreated patients		
Protease inhibitors				
Amprenavir (fosamprenavir)	0.4	1.2	–	–
Atazanavir	0.15	0.15	–	–
Darunavir	0.55	2.2	–	–
Indinavir	0.1	0.75	1	10
Lopinavir	1.0	5	8	–
Nelfinavir	0,8	–	–	–
Saquinavir	0.1	0.1	–	–
Tipranavir	–	20.5	–	–
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz	1	–	4	–
Etravirine	–	0.052	–	–
Nevirapine	3	–	8	–
Other classes				
Maraviroc	0.025	0.050	–	–
Raltegravir	–	0.015	–	–

MEC: Minimum effective concentration; MTC: Maximum tolerated concentration.

Pharmacogenetics in the treatment of HIV patients

Like PKs, pharmacogenetics is an applied clinical research methodology that has as its objective: the maximization of effectiveness and minimization of toxicity by tailoring treatment to individual patients [66]. Pharmacogenetics research explores the mechanisms by which variability in patient outcomes can be explained by genetic characteristics. The principal sources of variability in the human genome are SNPs. While 10 million SNPs have been identified, it is estimated that 20 million exist, equating roughly to one SNP per 100–300 nucleotides [67–69].

Patients undergoing ART for HIV/AIDS present a high level of variability in immune system recovery, as well as adverse drug events (ADEs). Given this variability, it is believed that individuals are genetically predisposed to developing certain ADEs. Accordingly, pharmacogenetics in ART has as its objectives to identify correlations between genotypes and clinical phenotypes, to identify patients at high risk of suffering ADEs or experiencing different treatment responses, to tailor treatment to individual patients – in other words, determine the right drug at the right dose for the right patient – and to improve the efficacy of antiretroviral agents and decrease the intensify of ADEs.

Recent advances in pharmacogenetics and pharmacogenomics have allowed for the identification of genetic markers that influence patient response to pharmacological agents and drug toxicity. Given these advances, in the near future it may be possible to tailor ART to individual patients considering their genetic profiles.

Pharmacogenetics in the response to ART

Variability in patient response to pharmacological agents has both PK and PDs components. Consequently, genetic variations in certain proteins involved in the transport, metabolism and mechanism of action of antiretroviral agents can influence both the efficacy and toxicity of these drugs.

Polymorphisms in drug-metabolizing enzymes

Polymorphisms in drug-metabolizing enzymes may have the following consequences: increase or decrease of the effective dose, lengthening or shortening of the duration of therapeutic effect, ADEs, drug toxicity and drug–drug interactions.

CYP450

The principal isoenzymes involved in the metabolism of antiretroviral agents are CYP1A2, CYP3A4, CYP3A5, CYP2C19, CYP2D6, CYP2A6 and CYP2B6. The

majority of polymorphisms are rare in the general population, and some are found only in certain ethnic groups.

Subclass CYP1A2

CYP1A2 is an important metabolizing enzyme in the liver, comprising approximately 13% of all CYP proteins. There are over 100 substrates identified for CYP1A2, including many clinically important drugs, procarcinogens and endogenous substrates. However, compared with other CYPs, there have been relatively few reports of pharmacogenetics relationships. However, a recent study suggests that the *CYP1A2* g.-163C>A polymorphism is associated with HIV disease progression in Zimbabwean HIV-infected patients treated with nevirapine (NVP) [70].

Subclasses CYP3A4 & CYP3A5

PIs are the principal class of antiretroviral agents metabolized by CYP3A4. PIs are also potent inhibitors of this enzyme. Additionally, some NARTIs are metabolized by these isoenzymes but to a lesser degree. The most relevant polymorphisms *CYP3A4*1B* (-392 A>G), *CYP3A5*3* (6986 A>G) and *CYP3A5*6* (14690 G>A) and their relationships with the PKs of efavirenz (EFV), nelfinavir (NFV), IDV, SQV and lopinavir/RTV have been evaluated in various studies. Studies to date have not yet demonstrated a significant effect of these polymorphisms on the PKs of EFV or NFV [71,72]. However, an association between *CYP3A5*3* and a decrease in the urinary excretion of SQV has been found but additional studies are needed to confirm this effect [73].

Subclass CYP2C19

Currently, the most relevant polymorphisms are *CYP2C19*2* and *CYP2C19*3*, which are responsible for 95% of the slow metabolizer phenotypes. These polymorphisms are more frequent in whites (3–13%) than in Asians or blacks. Regarding the PKs of antiretroviral agents, only *CYP2C19*2* (681G>A) and its involvement in the metabolism of EFV, etravirine (ETR) and NFV have been studied. In the case of EFV, no relationship has been found; however, plasma concentrations of NFV were found to be higher in individuals who were heterozygotes or homozygotes for the rare allele [72]. In the case of ETR, patients carrying the allele *CYP2C19*2* presented a 23% lower clearance compared with patients who were not carriers [74].

Subclass CYP2D6

The *CYP2D6* gene is highly polymorphic. Due to its genetic polymorphisms, it is possible to find individuals with different metabolizing capacities with race being one of the key factors influencing this variability. In this subclass only nonfunctional SNPs, which include *CYP2D6*3* (2549 A>del), *CYP2D6*4* (1846 G>A) and *CYP2D6*6* (1707 T>del), and their relationship with the PKs of EFV and NFV have been studied. The results of these studies demonstrate that individuals who are homozygotes or heterozygotes for these polymorphisms present elevated plasma concentrations of both drugs [75].

Subclasses CYP2B6 & CYP2A6

The isoenzyme CYP2B6 is involved primarily in the metabolism of NNRTIs and presents various genetic polymorphisms with higher frequency in blacks. Numerous SNPs have been identified in the gene that codes for CYP2B6 that are related with an increase in plasma concentrations of EFV and NVP. Those that have shown a higher clinical relevance include *CYP2B6*6* (516G>T) and *CYP2B6*16* (983 T>C), which can produce a 75% decrease in enzyme activity [76,77].

UDP-glucuronyl transferase (UGT or UDPGT)

Within this class, UGT1A1 is the specific enzyme that catalyzes the conjugation of bilirubin. In the case of antiretroviral agents, a number of polymorphisms have been studied to confirm their relationship with hyperbilirubinemia, a condition present in a considerable percentage of patients treated with ATV or IDV. The results of these studies show that the polymorphism most closely related with hyperbilirubinemia is *UGT1A1*28*, which reduces the activity of the enzyme in individuals who are homozygotes for the rare allele [78]. Recently, genetic polymorphisms of the isoenzyme UGT2B7 have also been studied. This enzyme has been observed to be the principal enzyme involved in the *N*-glucuronidation of EFV [79].

Polymorphisms in transporter proteins

Transporter proteins play a role in the oral absorption of drugs, as well as in their passage through the digestive system, the blood–brain barrier, excretion of bile and urine, and in the access to certain tissues.

P-glycoprotein

Key polymorphisms include 3435 C>T and 2677 G>T/A, which are associated with a decrease in the expression of P-gp. A number of studies have been conducted with the aim of establishing a relationship between these polymorphisms and the PKs of various PIs and EFV; however, the results of these studies have not been conclusive [80,81].

Multidrug resistance proteins

Multidrug resistance proteins (MRPs) are coded by the genes *ABCC1*, *ABCC2*, *ABCC3* and *ABCC4*.

MRP1 and MRP2 are charged with the transport of organic anions, including PIs, while MRP4 and MRP5 are charged with the transport of adefovir, tenofovir (TDF) and various NNRTIs (lamivudine, stavudine, among others). The most relevant polymorphism is 3463 A>G in the gene that codes for the MRP4 protein, which is related with the PKs of TDF [82].

Transporters of organic anions & cations

The transporters of organic anions and cations have as substrates a number of antiretroviral agents, including TDF, and different NNRTIs and PIs. These transporters are coded by the gene *OAT1* (SLC22A6), whose various polymorphisms, including 453 G>A and 728 G>A, and their relationship with the PKs of TDF have been studied [82]. Nevertheless, researchers have not yet identified a relationship.

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) [83] is a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene–drug associations and genotype–phenotype relationships. PharmGKB collects and disseminates knowledge about the impact of human genetic variation in drug response. Table 3 summarizes the most relevant genetic polymorphisms involved in the metabolism and transport of antiretroviral agents as a tool for individualizing HIV therapy in clinical settings (modified and updated version of Álvarez Barco and Rodríguez Nóvoa [84]).

Toxicogenetics of antiretroviral agents & their clinical application

One of the most important advances that has been made in the field of pharmacogenetics has been the identification of genetic markers associated with an individual's risk of developing certain adverse effects of ART. Accordingly, genetic markers have been identified that are related with the risk of developing neurotoxicity with EFV, hypersensitive reactions to abacavir (ABC) and NVP, hyperbilirubinemia with ATV and IDV, peripheral neuropathy and lactic acidosis with NARTIs, and renal toxicity with TDF. Table 3 summarizes the key polymorphisms in enzyme metabolizers and transporters that are related with adverse effects of antiretroviral agents [84].

Some of the most relevant gene-variant associations include:

- The hypersensitivity reaction to ABC is strongly associated with the presence of the *HLA-B*5701* allele and is the best example of the usefulness of employing pharmacogenetics in clinical settings. The mechanism underlying ABC hypersensitivity syndrome is related to the change in the *HLA-B*5701* protein product. ABC binds with exquisite specificity to *HLA-B*5701*, changing the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides that can bind to *HLA-B*5701*. In this way, ABC guides the selection of new endogenous peptides, inducing a marked alteration in 'immunological self'. The resultant peptide-centric 'altered self' activates ABC-specific T-cells, thereby driving polyclonal CD8 T-cell activation and a systemic reaction manifesting as a hypersensitivity reaction [85]. The genetic test for this allele has been demonstrated to be cost effective, and current guidelines for ART recommend screening for *HLA-B*5701* prior to initiating treatment with ABC [4,5]. However, among sub-Saharan black Africans, *HLA-B*5701* is virtually absent [86], so for this group, genetic testing is not recommended;

- In the case of ATV, the most relevant polymorphisms are those affecting UGT1A1 and P-gp activity. Polymorphisms in the P-gp influence ATV plasma concentrations, which are related with clinical response and increases in bilirubin plasma levels [78,87,104,133]. This is particularly important when ATV is administered in those pretreated patients for whom greater ATV concentrations may be required to inhibit virus replication, as well as in those patients with Gilbert's syndrome. Genotyping for *UGT1A1*28* and screening for the *ABCB1* 3435C>T polymorphism would identify HIV-infected individuals at risk of developing hyperbilirubinemia, which could decrease episodes of jaundice;

- Regarding NNRTIs, *CYP2B6* 516G>T, 983T>C, 785A>G and 21563C>T SNPs have been associated with greater EFV plasma exposure and the development of more severe CNS effects in different HIV-infected populations. The identification of patients who are slow metabolizers of EFV would allow for reduced doses, which could prevent toxicity [105–107,125] and the appearance of resistance following drug discontinuation [102]. Being a carrier of the class II allele *HLA-DRB1*0101* has been linked with NVP-associated hepatotoxicity and hypersensitivity reactions in HIV-infected western Australians, especially in those individuals with a CD4 cell count >25% [134];

- In the case of TDF, while the precise mechanism that produces renal tubular dysfunction has yet to be established, it is possible that genetic factors

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity.

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
PIs	ATV	*UGT1A1* (UGT1A1)	*28	8175347	No	Yes	Higher risk of hyperbilirubinemia	[77,85–87]
				887829		Gilbert's syndrome. Increased levels of bilirubin		
		ABCB1 (P-gp)	3435C>T	1045642	Yes	No	ATV minimum effective concentration = 0.15 µg/ml. Risk of subtherapeutic levels in TT carriers	[85,88–89]
			2677G>T	2032585	Lower ATV plasma levels			
		NR1I2 (PXR)	63396C>T	2472677	Yes		Risk of subtherapeutic levels in TT carriers	[90,91]
					Lower ATV plasma levels			
	LPV	*SLCO1B1* (OATP1B1)	521T>C	4149056	Yes	No	–	[92–95]
					Higher LPV plasma levels with CC genotype			
NARTIs	ABC	*HLA-B* *HLA-B*57:01*	NA	–	No	Yes	Abacavir HSR	[96,97]
		HLA complex P5 (HCP5)	335T>G	2395029	No	Yes	Alternative marker for screening of individuals at risk for ABC-HSR	[98–101]
	TDF	*ABCC2* (MRP2)	CATC haplotype (-24, 1249, 3563, 3972) -24CC	717620	No	Yes	*CATC* haplotype associated with greater risk of KTD -*24CC* associated with higher risk of KTD	[102,103]
				2273697	No	Yes		
				8187694				
				3740066				
				717620				
		ABCC4 (MRP4)	3463A>G	1751034	Yes	No	–	[81]
					Higher intracellular TFV-DP			
		ABCC4 (MRP4)	-669C>T	899494	No	Yes	Risk for KTD	[102]
		ABCC10 (MRP7)	Intron-4	9349256	No	Yes	Urine phosphate wasting and β2-microglobulinuria	[102]

ABC: Abacavir; ATV: Atazanavir; EFV: Efavirenz; HSR: Hypersensitivity reaction; II: Integrase inhibitor; KDF: Kidney tubular dysfunction; LPV: Lopinavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NARTIs: Nucleoside analog reverse transcriptase inhibitors; NA: Not applicable; NVP: Nevirapine; P-gP: P-glycoprotein; PIs: Protease inhibitors; RAL: Raltegravir; TDF: Tenofovir.
Data taken from [84].

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity (cont.).

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
NNRTI	EFV	*CYP2B6* (CYP2B6)	516G>T	3745274	Yes Higher plasma levels	Yes CNS adverse effects	EFV range: 1-4 µg/ml TT genotype associated with more risk for CNS adverse events	[104–108]
			785A>G	2279343	Yes Higher plasma levels	Yes CNS adverse effects	Genotype 516/983 associated with increased CNS events	[108–112]
			983T>C	28399499	Yes Higher plasma levels	Yes CNS adverse effects	Genotype 516/983 associated with increased CNS events	[108,111–112]
			*1/*1 haplotype		Yes Lower plasma levels	No	In patients receiving antituberculosis treatment	[113]
		ABCB1 (P-gp)	3435C>T	1045642	Controversial influence in plasma EFV levels	Yes Higher HDL-cholesterol in Spanish populations	Decreased likelihood of virologic failure and decreased emergence of resistant virus	[74,114–117]
		CYP2A6	-48T>G	28399433	Yes Higher plasma levels	Yes CNS adverse effects	In black and white, but not in Hispanic individuals from the USA	[78]
		UGT2B7	735A>G	28365062	Yes Higher plasma levels	Yes CNS adverse effects	In black and white, but not in Hispanic individuals from the USA	[78]
	NVP	*CYP2B6* (CYP2B6)	516C>T	3745274	Yes Higher plasma levels	No	–	[104,118–120]
			983T>C	28399499	Yes Higher plasma levels	Yes	Stevens–Johnson syndrome or toxic epidermal necrolysis, but no other HSR	[112,121–122]

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Data taken from [84].

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity (cont.).

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
NNRTI (cont.)		*ABCB1* (P-gp)	3435C>T	1045642	No	No	T allele associated with lower risk of hepatotoxicity	[123,124]
		HLA-DR	*HLA-DRB1*0101*	–	No	Yes HSR	Greater risk for HSR	[125,126]
		HLA-C	*HLA*-Cw*8	–	No	Yes HSR	Greater risk for HSR	[127,128]
		HLA-B	*HLA*-B3505	–	No	Yes	NVP skin rash	[129]
II	RAL	*UGT1A1*28* [A(TA7)TAA]	**28*	8175347	No	No	–	[130,131]
		ABCB1 (P-gp)	3435C>T	1045642	Yes	No	T allele is associated with lower RAL plasma exposure	[132]

ABC: Abacavir; ATV: Atazanavir; EFV: Efavirenz; HSR: Hypersensitivity reaction; II: Integrase inhibitor; KDF: Kidney tubular dysfunction; LPV: Lopinavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NARTIs: Nucleoside analog reverse transcriptase inhibitors; NA: Not applicable; NVP: Nevirapine; P-gP: P-glycoprotein; PIs: Protease inhibitors; RAL: Raltegravir; TDF: Tenofovir.
Data taken from [84].

may facilitate this dysfunction, whose main clinical consequence is phosphate waste that can ultimately lead to osteopenia and osteoporosis. It has been recently demonstrated that certain genetic polymorphisms in the regions that code for the transporter proteins MRP2 (*ABCC2*) and MRP4 (*ABCC4*) are associated with differences in urinary excretion of TDF and the probability of development renal failure [82,135–136]. In this regard, information derived from pharmacogenetics studies may help to identify the subset of individuals at greater risk for developing more severe renal injury and loss of bone density.

Pharmaceutical care of HIV patients

The objective of pharmaceutical care of HIV patients is to achieve adequate clinical control of the virus through the proper use of prescribed antiretroviral agents [137]. To achieve this objective, a pharmacist should possess deep knowledge of pharmacotherapy, the physiopathology of the disease, the methodology of pharmaceutical care and the methodology of clinical interviewing. However, the acquisition of this knowledge does not guarantee success; it is necessary to possess communication and team-working skills and to assume a proactive, empathetic and convincing attitude. To provide quality care to patients with HIV/AIDS, procedures should be established that promote care that is tailored to the characteristics and needs of each patient.

Pharmaceutical care activities

The American Society of Hospital Pharmacists has established in a document of recommendations of the principal actions that can be taken by pharmacists working as members of clinical care teams [138]. These recommendations are supported by a number of previous documents of consensus and apply to both ambulatory patients in general and HIV patients specifically [139–142]. These documents recommend that pharmacists complete systematic evaluations of drug interactions, adherence and adverse effects, and take actions aimed at detecting, preventing and resolving other problems related with the effectiveness and safety of prescribed medications.

Both ART and strategies to tailor treatments to individual patients have advanced continually over the past 30 years [143], leading to a base of evidence regarding the actions that pharmacists can take to anticipate the needs of their increasingly informed and inquisitive patients [144]. The actions of pharmacists caring for patients with HIV have been associated with improved patient outcomes, including enhanced adherence [145], reduced pill burden and dosing frequency, greater

increases in CD4 cell counts, higher rates of viral suppression [146–148] and reduction of medication errors [149,150].

Promotion of adherence in ART

Patient adherence to prescribed treatment involves a complex process that first includes a patient accepting his/her diagnosis and recognizing the need to take his/her medication correctly. It also requires education to assure that the patient is able to correctly administer the medication and respond to any difficulties that may arise during treatment [151].

Medication adherence is a crucial factor affecting the extent and duration of response to combination ART [4]. Suboptimal adherence to any component of HIV therapy may produce lasting consequences, including increased viral load, development of resistance, reduced efficacy of future combination therapy, increased risk of hospital admission, more rapid progression to AIDS and decreased survival [4,152–153]. Data obtained from studies following patients treated with the first combination therapies used in the treatment of HIV (which included nonpotentiated PIs) showed that obtaining maximum efficacy requires near perfect adherence (>95%) [154]. However, recent studies suggest that with lower levels of adherence (75%), it is still possible to reach the therapeutic index during treatment with NNRTIs or PIs boosted with RTV [155–157]. Despite this, all studies agree that with each increment in adherence level, viral suppression increases and progression of the disease slows. These studies also emphasize the importance of maintaining adherence over the long term.

In a worldwide meta-analysis of 84 observational studies, only 62% of adults with HIV achieved adherence to ART of at least 90% [158]. Therefore, a major goal is to increase adherence rates, and pharmacists are uniquely positioned to help patients achieve this objective. However, a number of factors may complicate a patient's ability to take their combination ART as prescribed; therefore, it is essential that pharmacists recognize these factors and develop strategies to overcome them. Effective strategies may include utilization of once-daily regimens, single-tablet fixed-dose combinations, reminder alarm devices, text message alerts, pill organizers, dose planners and one–one–one support in an interdisciplinary team environment [159,160].

A number of studies [146–148] have shown significant gains in the level of adherence and clinical response of patients participating in dedicated pharmaceutical care programs. Furthermore, a recent meta-analysis [161] that evaluated four randomized controlled trials indicated that improvements in ART adherence and treatment efficacy may be greater in populations with initially lower adherence and greater vulnerability, when these patients participate in pharmaceutical care interventions. Considering this evidence, the implementation of pharmaceutical care programs that include adherence evaluation and long-term personalized care is essential to increasing adherence to ART and improving patient outcomes.

Counseling & patient education

The Global AIDS Program of the WHO defines counseling as the dynamic communication process through which one person helps another in an atmosphere of mutual understanding. This process relies on communication abilities and strategies to facilitate decision-making and problem-solving. Pharmacists need to be aware of these issues and take into account the communication style and literacy level of each patient when providing counseling. The ultimate goal of a counselor is to develop a more personal and trusting relationship with the patient, so that the patient feels comfortable and cared for and thus more willing to discuss any and all issues regarding his or her diseases and treatment in a confidential, nonjudgmental, nonpunitive relationship with the pharmacist [162].

Counseling should address practical topics and include advice, for example, on whether to take a medication with or without food and on which foods could affect absorption. Discussions about the adverse effects of medications should be presented in a balanced manner with emphasis on the benefits of therapy and strategies for managing nuisance side effects. Patients benefit from counseling regarding proactive strategies to minimize the risk of resistance if doses are missed. Written materials can also help patients retain the information [4].

The pharmacist can also be a referral source for other support and educational tools that may be of interest and useful to the patient, such as websites with drug information or other patient-related information and community support groups. Furthermore, a number of mobile applications have been developed that aim to improve adherence by educating patients and facilitating communication with the healthcare team [163–166].

From providing counseling on vitamins, alternative medicine and safer sex practices to educating patients on treatment, aging and lifestyle changes to manage co-morbidities, pharmacists can act as the healthcare providers who consolidate information and relay it simply and efficiently to patients in counseling sessions.

Complementary strategies to individualize care of HIV patients

The pharmacological treatment of HIV is complex and specific to each patient, requiring cooperation

among a multidisciplinary healthcare team. In these teams, pharmacists play an important role, employing knowledge of PKs and pharmacogenetics and interacting directly with patients through pharmaceutical care programs.

As previously mentioned, TDM of antiretroviral agents is useful for detecting drug interactions [167], optimizing patient exposure to the medications, avoiding and controlling adverse effects and maintaining treatment efficacy [168]. Furthermore, TDM is a direct indicator of adherence [151] and can be used in conjunction with other adherence evaluation tools used in routine pharmaceutical care, such as self-administered questionnaires and dispensation records. Pharmaceutical care, by providing the pharmacist with a more exhaustive knowledge of the patient, allows for a more accurate interpretation of plasma concentrations obtained through TDM and for dosage adjustments to optimize treatment. Additionally, pharmaceutical care can promote patient education regarding dosage changes and the need to strictly follow therapy during these times.

Pharmacists can also use information regarding the presence of alleles associated with drug disposition and response to certain antiretroviral agents to guide dosage adjustments and the selection of appropriate alternative therapies [66], leading to better treatment designs and predictive profiles for certain genotype-identified patient subpopulations.

The three tools discussed in this paper are complementary and can be used together to individualize care. For example, pharmaceutical care can serve as the initial point of detection of problems with ART, while TDM and pharmacogenetics can allow pharmacists to identify the causes of the problems and develop solutions tailored to each patient [169]. Furthermore, pharmacogenetics tests combined with TDM and pharmaceutical care can be used to individualize dosing regimens, maximize drug efficacy and enhance drug safety.

Conclusion

Combining PKs, pharmacogenetics and pharmaceutical care in the context of a comprehensive and individualized care program appears to be the most effective strategy for allowing pharmacists to best evaluate the efficacy of the therapeutic plan for each patient. This information, when relayed to the medical care team, can support clinical decision-making aimed at optimizing the efficacy and safety of antiretroviral treatments.

Future perspective

The individualization of ART represents an important component of day-to-day practice in the care of HIV patients, given the diversity of drugs available, viral factors and an increasingly diverse HIV patient population. It is expected that in the future TDM will be a common practice in the control of HIV, especially if the development of new pharmaceuticals fails to keep pace with drug resistance – while the number of antiretroviral agents may appear to be high, the number of effective combinations is considerably more limited.

Nevertheless, TDM has some limitations that require continued research aimed at developing further studies of inhibition coefficients that consider the susceptibility of HIV to treatment; developing improved systems of PK interpretation that consider all components of ART, including polypharmacy; determining the population PK parameters for all antiretroviral agents; and developing pharmacoeconomic evaluations to demonstrate the cases for which TDM is cost-effective in routine clinical practice.

In terms of pharmacogenetic analyses, the International Society of Pharmacogenomics has stated that knowledge of pharmacogenetics is necessary for incorporating personalized treatment into routine clinical practice. Evidence suggests that pharmacogenetics will play an increasingly important role in healthcare services. In fact, some health authorities predict that in the future it will be considered unethical not to conduct genetic testing on patients exposed to certain medications that may provoke adverse reactions depending on patient phenotype [170].

To facilitate translation into clinical practice, it is essential that pharmacists are fully prepared to use pharmacogenetics diagnostic tools; however, insufficient education and the resulting lack of knowledge and contextual awareness of these tools may pose severe barriers to the widespread incorporation of personalized medicine in daily clinical practice [88,171-172]. Other factors, such as ethical considerations, the costs associated with utilizing the tools and the complexities of genetic variation among populations and geographies, will further complicate the incorporation of these data into determining patient risk and treatment decision-making.

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Executive summary

Pharmacokinetics in the treatment of HIV patients

- The percentage of patients who do not achieve adequate plasma concentrations when given a standard dose of antiretroviral agents is 35–61%.
- The principal objectives of therapeutic drug monitoring (TDM) of antiretroviral agents are to control patient adherence to antiretroviral treatment (ART), to identify and control drug interactions, to avoid toxicity, to establish unofficial or rescue dosing regimens, and to optimize treatment outcomes for overweight, pregnant and pediatric patients, as well as for patients with hepatic or renal insufficiency.
- Evidence supports the use of TDM for protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Pharmacogenetics in the treatment of HIV patients

- Genetic variations in the proteins involved in the transport, metabolism and mechanism of action of antiretroviral agents can influence the efficacy and toxicity of treatments.
- The objectives of employing pharmacogenetics in ART include to correlate genotypes with clinical phenotypes, to identify patients at higher risk of suffering adverse drug events or different treatment responses, to individualize therapy, to improve efficacy and to reduce the intensity of adverse effects.
- Genetic markers have been identified that are related with the risk of developing neurotoxicity with efavirenz, hypersensitivity reactions with abacavir and nevirapine, hyperbilirubinemia with atazanavir and indinavir, peripheral neuropathy and lactic acidosis with nucleoside analog reverse transcriptase inhibitors and renal toxicity with tenofovir.
- Screening for *HLA-B*5701* is recommended prior to administering abacavir in order to avoid the development of a delayed hypersensitivity reaction.
- It is recommended to evaluate other well-established pharmacogenetics associations, including that of *CYP2B6* 516G>T with greater efavirenz plasma exposure and the development of more severe CNS effects and that of polymorphisms in *UGT1A* with a higher risk of hyperbilirubinemia in patients treated with atazanavir.

Pharmaceutical care of HIV patients

- The systematic evaluation of interactions, adherence and adverse effects, as well as the detection, prevention and resolution of other problems associated with ART are key components of the pharmaceutical care of HIV patients.
- The actions of pharmacists treating HIV patients have been associated with improved patient outcomes, including enhanced adherence, reduced pill burden and dosing frequency, greater increases in CD4 cell counts, higher rates of viral suppression and decreases in medication errors.

Complementary strategies to individualize care of HIV patients

- Pharmaceutical care often serves as the initial point of detection of problems with ART, and TDM and pharmacogenetics allow pharmacists to postulate the causes of these problems and develop solutions based on the characteristics of individual patients.
- Available pharmacogenetics tests can complement TDM and pharmaceutical care to individualize dosing regimens and maximize drug efficacy and safety.

Future perspective

- It is expected that in the future TDM will be a common practice in the control of HIV, especially in cases in which the development of new pharmaceuticals fails to keep pace with the drug resistance.
- Some health authorities predict that in the future, it will be considered unethical not to conduct genetic testing on patients exposed to certain medications that may provoke adverse reactions depending on patient phenotype.
- Combining pharmacokinetics, pharmacogenetics and pharmaceutical care in the context of a comprehensive and individualized care program appears to be the most effective strategy for allowing pharmacists to best evaluate the therapeutic plan for each patient and to support the clinical decision-making of the healthcare team.

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Resumen Artículo I

Papel del farmacéutico en la individualización de los tratamientos en pacientes infectados por el VIH

Objetivos: Revisar las principales herramientas de las que dispone el farmacéutico hasta la fecha para contribuir a la individualización de los tratamientos en pacientes infectados por el VIH.

Material y métodos: Se realizó una revisión bibliográfica en Julio de 2015, realizando búsquedas en la base de datos MEDLINE® utilizando los siguientes términos de vocabulario controlado (MeSH): ”pharmacogenetics”, “pharmacokinetics”, “therapeutic drug monitoring”, “pharmaceutical care”, “human immunodeficiency virus” y “antiretroviral therapy”. Se incluyó literatura gris mediante búsqueda manual y se revisaron las referencias de los artículos examinados.

Resultados: Se han discutido las tres principales estrategias de individualización y optimización de la terapia antirretroviral en pacientes infectados por el VIH: determinación de concentraciones plasmáticas (TDM) de antirretrovirales, análisis farmacogenéticos y atención farmacéutica personalizada. La TDM de antirretrovirales permite detectar interacciones entre fármacos, optimizar la exposición de los pacientes a los medicamentos, evitar y controlar efectos adversos y mantener la eficacia virológica. Además, es un indicador directo del cumplimiento correcto del tratamiento, por lo que complementa a otros métodos de medida de adherencia utilizados rutinariamente en la atención farmacéutica. La atención farmacéutica, por su parte, permite interpretar correctamente los valores de concentraciones plasmáticas obtenidos con la TDM y diseñar los mejores ajustes posológicos en cada caso, ya que proporciona un conocimiento exhaustivo de la situación del paciente. Su objetivo es conseguir un adecuado control clínico a través del uso correcto de los medicamentos antirretrovirales, para lo cual, el farmacéutico debe tener un profundo conocimiento de la farmacoterapia, de la fisiopatología de la enfermedad, de la metodología de atención farmacéutica y de la entrevista clínica. Por otro lado, la existencia de variaciones genéticas en proteínas implicadas en el transporte, metabolismo o mecanismo de acción de los fármacos antirretrovirales, pueden influir en la eficacia y toxicidad de la terapia. Por ello, su identificación permite guiar ajustes posológicos y seleccionar la

terapia alternativa más apropiada en cada caso, mejorando tanto la eficacia y seguridad de los tratamientos, como el pronóstico de la enfermedad en subpoblaciones de pacientes identificados genotípicamente.

Conclusiones: La interrelación de la farmacocinética, la farmacogenética y la atención farmacéutica, en el contexto de un programa de seguimiento integral e individualizado del paciente infectado por el VIH, parece ser la estrategia más efectiva que ofrezca al farmacéutico una visión completa del funcionamiento del plan terapéutico en cada paciente. Esta información, trasladada al equipo médico, sirve de apoyo en la toma de decisiones clínicas dirigidas a optimizar la eficacia y seguridad de los tratamientos.

Impact of a pharmaceutical care program on the clinical evolution and antiretroviral treatment adherence: a 5-year study

Original Research

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ORIGINAL RESEARCH

Impact of a pharmaceutical care program on clinical evolution and antiretroviral treatment adherence: a 5-year study

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Background: Antiretroviral treatments (ART) form the basis of adequate clinical control in human immunodeficiency virus-infected patients, and adherence plays a primary role in the grade and duration of the antiviral response. The objectives of this study are: (1) to determine the impact of the implementation of a pharmaceutical care program on improvement of ART adherence and on the immunovirological response of the patients; and (2) to detect possible correlations between different adherence evaluation measurements.

Methods: A 60-month long retrospective study was conducted. Adherence measures used were: therapeutic drug monitoring, a simplified medication adherence questionnaire, and antiretroviral dispensation records (DR). The number of interviews and interventions related to adherence made for each patient in yearly periods was related to the changes in the adherence variable (measured with DR) in these same yearly periods. The dates when the laboratory tests were drawn were grouped according to proximity with the study assessment periods (February–May, 2005–2010).

Results: A total of 528 patients were included in the study. A significant relationship was observed between the simplified medication adherence questionnaire and DR over the 60-month study period ($P < 0.01$). Improvement was observed in the mean adherence level ($P < 0.001$), and there was a considerable decrease in the percentage of patients with CD_{4+} lymphocytes less than 200 cells/mm^3 ($P < 0.001$). A relationship was found between the number of patients with optimum adherence levels and the time that plasma viral load remained undetected. The number of interviews and interventions performed in each patient in the first 12 months from the onset of the pharmaceutical care program (month 6), was related to a significant increase in adherence during this same time period.

Conclusion: The results suggest that the establishment and permanence of a pharmaceutical care program may increase ART adherence, increase permanence time of the patient with undetectable plasma viral loads, and improve patients' lymphocyte count.

Keywords: pharmaceutical care, antiretroviral treatment adherence, undetectable PVLs, CD_{4+} lymphocyte count, adherence measures, HIV/AIDS

Introduction

Acquired immunodeficiency syndrome (AIDS) was first identified in the United States in the summer of 1981 when the Centers for Disease Control and Prevention reported the appearance of an unexplained pneumonia due to *Pneumocystis jiroveci* (previously named *P. carinii*) and Kaposi's sarcoma in five previously healthy male homosexuals in New York and Los Angeles.[1] Since then, its control has become one of the most important public health challenges because of the nature of this epidemic, its impact on health, economics, and on social and political matters, as well as due to the virus's epidemiological characteristics. Different solutions have been sought, including the

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development of a possible vaccine. However, mainly drug treatments have been developed in order to improve and increase the quality of life and expectancy of those infected by the human immunodeficiency virus (HIV) that may lead to the development of AIDS.

Current antiretroviral treatments (ART) form the basis of adequate virological and immunological control in HIV-infected patients. The rates of hospitalization, opportunistic infections, and mortality associated with HIV infection have been reduced. This has given rise to chronification of the infection and to a significant increase in survival.

ART adherence plays a primary role in the grade and duration of the antiviral response. This patient adherence is the result of a complex process developed through acceptance of the diagnosis, perception of the need to correctly carry out the treatment, motivation to do so, disposition and training of the skills to do it, capacity to overcome the difficulties that appear, and maintenance of the achievements reached over time. Several studies have demonstrated that medication adherence is second only to CD_{4+} count in accurately predicting progression to AIDS and death.[2,3]

Adherence is not the only determinant of ART failure or success. Other factors include genetic differences in drug metabolism, severe baseline immunosuppression, prior drug resistance, and concurrent opportunistic infections, among others. Adherence to ART, however, is one of few potentially alterable factors determining outcomes for patients with HIV.

The data obtained during the first available combined treatments based on unboosted protease inhibitor (PI) drugs showed that maximum efficacy was obtained with almost perfect adherence, usually superior to 95%.[4] However, recent studies suggest that the therapeutic objectives can be achieved in regimens based on ritonavir-boosted PIs (PI/r) or on non-nucleoside reverse transcriptase inhibitors with adherence rates of approximately 75%.[5,6] In spite of this controversy, there is general agreement that although viral suppression may be possible with moderate adherence levels, the probability of viral suppression and, more importantly, reduced disease progression and mortality, improves with every increase in adherence level.

According to a study conducted in the Spanish population, adherence in 20% to 50% of the patients receiving ART is inadequate.[7] A meta-analysis has recently been published in Spain on ART adherence and concluded that the global percentage of ART adherence is 55%.[8] Studies from the United States, Canada, and developed countries in Latin America and Europe have demonstrated similar rates of suboptimal adherence.[9–12] The average rate of adherence appears to be approximately 70%. In light of this evidence, global care programs need to be established for the patient. These should include both the evaluation of ART adherence and the elaboration of action strategies aimed at optimizing these results.

Up to now, there is no known intervention method superior to the others to improve patient adherence. However, the best levels of evidence come from randomized and controlled studies. The easiest and most common intervention is based on providing the patients with information and knowledge in an attempt to achieve their maximum commitment with the proposed treatment. This commitment will be possible if the patient understands the purpose of the ART and the importance of adherence; this shows how important it is for the patient to feel like a participant in treatment-related decisions. Pharmacotherapy follow-up of the patient, included within the context of a pharmaceutical care program, comprises follow-up of the patient, the interventions themselves, as well as continuing education, among others. The principal objective of this study was to evaluate the impact of the implementation of a pharmaceutical care program on the evolution of ART adherence over the course of 60 months in a cohort of HIV outpatients from our hospital, and to determine the repercussion of ART adherence on the patients' virological and immunological evolution. Equally, we hoped to detect possible correlations between the different adherence evaluation measurements used in this study: therapeutic drug monitoring (TDM), a simplified medication adherence questionnaire (SMAQ),[13] and ART dispensation records (DRs).

Methods

Patient screening

A 60-month-long retrospective study with data from 528 HIV-infected subjects treated in the outpatient unit of the Pharmacy Service of the University Hospital of Salamanca, Salamanca, Spain was conducted. The patients were invited to participate voluntarily.

Inclusion criteria included patients with confirmed HIV infection and who had been receiving active ART in our hospital for more than 6 months (either naïve or pretreated patients).

Adherence measures

The scientific literature recommends using and combining several adherence evaluation methods. If not, the results obtained only by one of these methods would not be reliable.[14]

Three strategies were used in our case: TDM (direct method), DR, and SMAQ (the latter two being considered as indirect methods). These three adherence evaluation tools are routinely included in our pharmaceutical care program. There are TDM and SMAQ data for each pharmaceutical interview or clinical control. These records correspond to the measurements obtained around the month of April (February–May) of the year in question (2005–2010) since this is the month that corresponds to the study initiation point. The data for DR were obtained twice a year (April and October of each year).

- Antiretroviral plasma concentrations were determined with the high-performance liquid chromatography–ultraviolet validated technique that permits the measurement of atazanavir, darunavir, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, and saquinavir.[15,16] The analyzed samples had been drawn when fasting and before the administration of the next medication dose. In every case, the plasma trough concentrations (C^{ss}_{min}) of the monitored antiretroviral therapy were estimated individually using Bayesian algorithms, based on previously published population pharmacokinetics models using PKS® software (Abbott Diagnostics, Abbott Laboratories, Abbott Park, IL, USA). The C^{ss}_{min} obtained in this way were classified into three groups – according to whether they were within (therapeutic), low (subtherapeutic), or above (supratherapeutic) the therapeutic range – in accordance with the therapeutic margins collected previously.[17,18]
- The SMAQ questionnaire, which was validated in a Spanish population, was used to evaluate treatment adherence. The questionnaire consists of six questions with previously defined short answers that the patients are asked to answer. Based on the patients' answers, each patient is classified as being either adherent or nonadherent to the pharmacological treatment.[13]
- The DR is an indirect method of measuring adherence based on the assumption that a patient cannot take medication that has not been dispensed, and that those that are dispensed to him/her are taken adequately. An adherence calculation was made using the dispensation dates that were included in 6-month periods beginning from the initiation of the study. Adherence was calculated as the number of pills taken during the previous 6 months divided by the number of pills prescribed during the same period. Levels that exceeded 100% were rounded down to 100%. Patients who consumed ≥95% of the medication prescribed were considered "adherent patients." Adherence values were dichotomized into two levels: ≥95% versus <95%. However, since some studies consider 90% as the cutoff of adherence,[8,19–21] this percentage was also considered.

Pharmaceutical care

The comprehensive follow-up program for patients with established HIV includes pharmaceutical care activities, TDM of antiretroviral drugs, and pharmacogenetic analysis. The latter two tools make it possible to individualize the PI, PI/r, and non-nucleoside reverse transcriptase inhibitor doses according to the needs of each patient because these are the antiretroviral drug families that have a demonstrated correlation between plasma concentrations and response.[22] This comprehensive follow-up program has been established and developed based on close collaboration among the pharmacists, physicians, and nurses who attend this patient population.

The interviewer always consults the DR adherence data at the onset of pharmaceutical care in order to intervene during the program, if necessary. Furthermore, the adherence results measured by DR are communicated to the prescribers twice a year.

During the interview, the SMAQ questionnaire was used and the evolution of the plasma viral load (PVL), CD_{4+} lymphocyte count, and antiretroviral C^{ss}_{min} was monitored. Possible analytic alterations that could be due to adverse drug events and possible interactions of the antiretroviral drugs with other drugs, food, natural products, abuse drugs, and so on were also reviewed.

During the study period, information regarding HIV and its treatment as well as the importance that adherence has in clinical outcomes and the prevention of resistance was specifically provided to the patients. In addition, a personalized dosing schedule was developed with the patient, and strategies on how to manage side effects were made. During follow-up visits, recommendations were made to solve any problems encountered; adherence was verbally reinforced and plans were developed to solve the problems that had appeared up to that time.

In this study, the number of interviews and interventions related to adherence made for each patient was determined in yearly periods (2005–2010), beginning with the implementation of the pharmaceutical care program in month 6, and then related to changes in the adherence variable (measured with DR) in these same periods. Pharmaceutical interventions related to adherence were considered as providing both oral and written information regarding the treatment, giving a

weekly medication pill organizer, and making posological adjustments if the patient had supratherapeutic levels associated with adverse drug events that could decrease treatment adherence.

Clinical evolution

CD_{4+} counts and PVLs are indicators of immune status and HIV viral activity; both are expected to improve with ART adherence. However, the intended effect of ART (that of preventing viral replication) is more directly assessed by the PVL.[23–25] We used data extracted from participants' medical records. Dates at which laboratory tests were obtained were grouped according to proximity to the study assessment periods. For the analysis, we used the CD_{4+} count and the PVL, which was considered undetectable when the number of copies per milliliter was less than 50.

The number of months in which undetectable PVL levels were maintained in each patient during the study was determined. This information was then contrasted with the patients' average adherence.

Statistical analysis

The IBM SPSS Statistics for Windows (version 19.0.0.1, released 2010; IBM Corporation, Armonk, NY, USA) was used for the statistical analyses. Chi-square tests were used to compare categorical variables. The Mann–Whitney test was used to assess differences between two independent samples, and the Wilcoxon signed-rank test was used to compare two related samples. The Kruskal–Wallis test was used to compare $k > 2$ independent samples. Spearman's correlation was used to study the relationship between quantitative or ordinal variables.

Results

A total of 528 patients were included in the study, 259 of whom received pharmacological treatment during the entire study period. The remaining patients were either lost to follow-up during this period (due to transfers, exitus, and so on), and/or they entered the study after the established initiation date. The mean patient permanence time in the study was 3.56 ± 1.68 years. Demographic and baseline clinical characteristics of the total study population are shown in Table 1.

Association among adherence measurements

All three methods were used to collect the adherence data, and the results were grouped into periods of 6 months (DR) and 12 months (SMAQ and TDM) for each of the patients.

Table 1 Demographic and clinical characteristics of study population (n = 528)

Characteristics	Values
	Mean ± SD or n (%)
Age (years)[a]	40.48 ± 8.94
Male	371 (70.3)
Therapy-naïve[b]	187 (35.6)
Number of years on ART[c]	5.49 ± 3.41
CD_{4+} counts (cells/mcL)[c]	381.63 ± 245.93
Undetectable plasma viral load[c]	251 (83.7)

Notes: [a]Age at which the patient entered the study; [b]number of total naïve patients who entered the study; [c]variable measured at onset of the study (n = 332).
Abbreviations: n, number; SD, standard deviation; ART, antiretroviral treatment.

Not all of the three measurements were available for the entire population at each of the cutoff levels because this was a retrospective study. Associations among the three methods used to measure adherence (TDM, SMAQ, and DR) were analyzed (Table 2).

A significant association was found between TDM (therapeutic/subtherapeutic/supratherapeutic) and SMAQ ($P = 0.013$) in the first 6 months after the pharmaceutical care program was initiated. However, no association was found during this period when TDM was categorized into subtherapeutic and nonsubtherapeutic. No significant correlations were found between these two adherence measurements in the remaining periods analyzed; however, there was a clear tendency for adherent patients to reach therapeutic levels (50.0% in month 12 versus 77.9% in month 60) according to the SMAQ questionnaire.

A significant association ($P < 0.01$) was found between DR and SMAQ when the cutoff for adherent patients was 95% during the entire study period. Nonetheless, if the cutoff was established at 90%, this association was only observed in some periods. Furthermore, mean adherence obtained by DR was greater in those who were adherent according

Table 2 Association among adherence measurements

Time (months)	0	12	24	36	48	60
N	332	377	398	410	411	398
Adherent patients (%)						
TDM[a]	–	78.95	81.61	84.45	95.51	93.77
SMAQ	–	65.20	75.26	80.25	84.62	90.44
DR[b]	64.8	70.16	76.01	73.69	78.41	76.36
Agreement between adherence measurements (%)						
SMAQ–TDM[a]	–	53.57	69.66	75.00	83.18	88.17
SMAQ–DR[b]	–	69.40†	77.64†	76.39†	78.51†	80.58†
TDM[a]–DR[b]	–	60.70	72.73	68.67	81.36	76.21

Notes: [a]TDM categorized into subtherapeutic or not subtherapeutic; [b]DR categorized into: <95%; ≥95%; †$P < 0.01$ (Chi-square test and kappa coefficient).
Abbreviations: N, number; TDM, therapeutic drug monitoring; SMAQ, simplified medication adherence questionnaire; DR, dispensation record.

to the SMAQ than those who were nonadherent during the entire study.

There was no significant association between DR and TDM, regardless of the cutoff level used (90% or 95%) or the TDM variable category (subtherapeutic/therapeutic/supratherapeutic or subtherapeutic/not subtherapeutic).

Antiretroviral treatment adherence

Mean global adherence of the patients during the 60 months of the study was 94.98% when the DR was used to measure adherence.

Mean adherence at the implementation of the pharmaceutical care program was 92.69%; at month 60, adherence was approximately 96.04%, with this difference being very significant ($P < 0.001$) (Figure 1).

In addition, statistically significant differences ($P < 0.001$) were detected in the mean patient adherence level between the first 6 months of the study (prior to the initiation of the pharmaceutical care program) and second 6 months of the study. All the differences were highly significant ($P < 0.003$) when the first 6 months of the study were compared with the 6-month adherence measurements evaluated during the entire period. Similarly, it stands out that statistically significant differences were not observed when adherences measures after the first 6 months of the study were compared with each other.

There were 107 nonadherent patients in the baseline measurement. The follow-up of this subgroup showed that 43 of them had good adherence at 1 year after the implementation of the pharmaceutical care program, and this number increased to 75 at the end of the study period (while the remainder continued to be nonadherent or were lost to follow-up).

Regarding the evolution of the percentage of patients with optimum adherence (≥95%), this number increased from 64.80% at baseline to 76.36% at the end of the study. The number of patients with adherence levels greater than 90% also increased significantly (73.36% at baseline versus 86.68% at the end of the study).

Plasma viral load (PVL)

The percentage of patients with undetectable PVL remained practically unchanged during the study period with a mean of 76.7%. Statistically significant differences were found between the number of patients with optimum adherence levels and those who did not have these levels in regards to the amount of time they remained with undetectable PVL. This occurred when both the cutoff level of 95% adherence was considered and when adherence was grouped into four different levels ($P < 0.002$ and $P < 0.001$, respectively) (Figure 2).[26]

CD_{4+} lymphocyte count

CD_{4+} lymphocyte levels were recorded at the onset and end of the study. The proportion of patients who had $CD_{4+} < 200$ cells/mm^3 was compared. Statistically significant differences were found between both values (27.8% versus 14.9%, respectively; $P = 1.992 \times 10^{-5}$). Furthermore, the mean count of CD_{4+} lymphocytes significantly increased ($P < 0.001$) from 381.6 cells/mm^3 (baseline) to 458.5 cells/mm^3 (month 60).

Evolution of adherence, PVL, and CD_{4+} lymphocyte count over the 60 months of the study is shown in Figure 3. The data

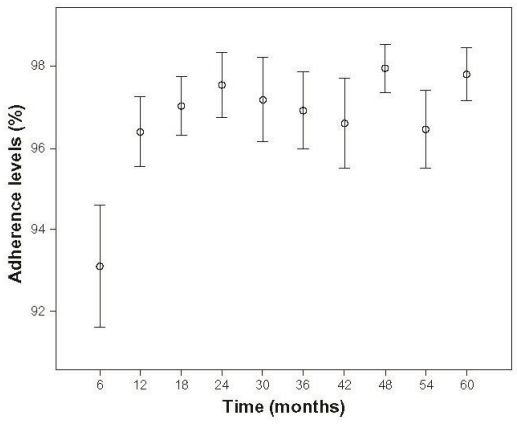

Figure 1 Evolution of the means (95% confidence interval) of antiretroviral treatment adherence during the 60 months of the study.

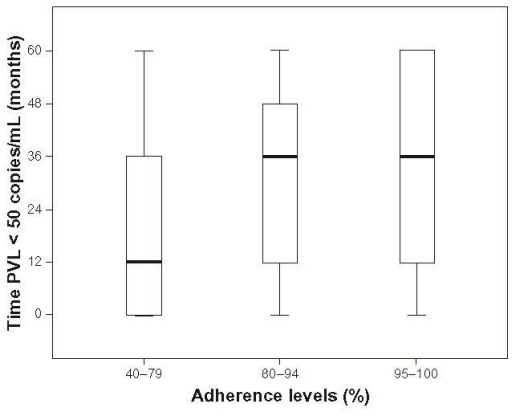

Figure 2 Influence of antiretroviral treatment patient adherence on permanence time in virological suppression.
Note: No patients had adherence <40%.
Abbreviation: PVL, plasma viral load.

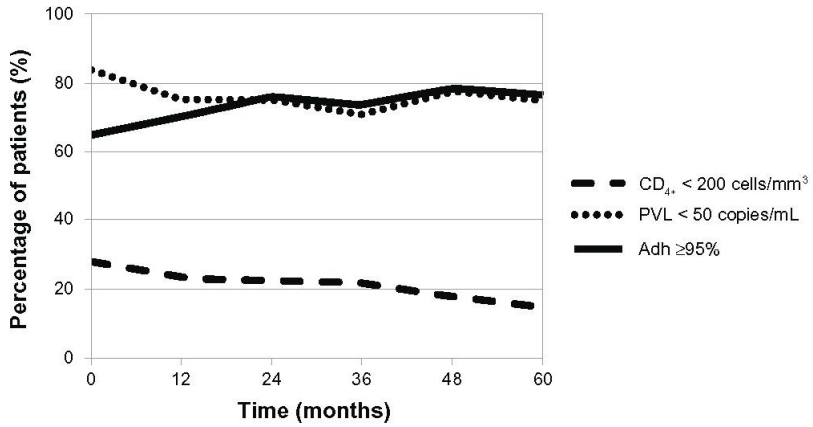

Figure 3 Evolution of patients in terms of adherence, virological status, and immunological status over the 60 months of the study.
Abbreviations: PVL, plasma viral load; Adh, adherence to antiretroviral therapy.

are represented as the percentage of patients with adherence levels ≥95%, PVL < 50 copies/mL, and CD_{4+} lymphocyte count <200 cells/mm^3.

Effect of interviews and interventions on adherence

During the study period, 2,199 interviews (4.2 ± 3.3 interviews/patient) and 3,100 interventions related to adherence (5.9 ± 4.4 interventions/patient) were conducted in the 528 patients studied. In accordance with the DR data collected, the number of interviews made for each patient in the first 12 months from the onset of the pharmaceutical care program was significantly related to an increase in his/her adherence levels in this same period ($P < 0.05$) (Figure 4).

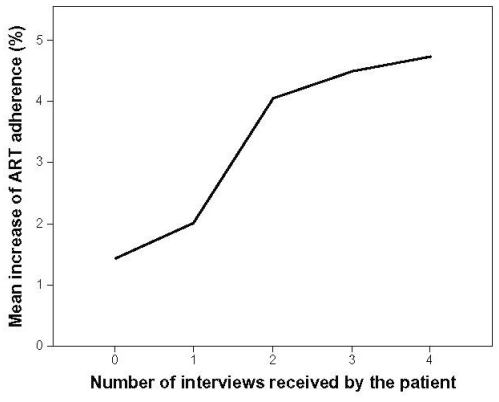

Figure 4 Relation between the mean increase of ART adherence in the first year after the pharmaceutical care program was initiated and the number of interviews made in this period.
Abbreviation: ART, antiretroviral treatment.

The same was found for the number of interventions conducted during the same year ($P < 0.002$) and the following year ($P < 0.05$). This relation was not found during the remainder of the study period.

In regard to adherence determined by the SMAQ questionnaire, it was observed that the mean number of interviews conducted among the adherent patients was higher than among the nonadherent patients in all of the time periods, although these results are not statistically significant.

Discussion

In regard to the baseline characteristics of the population, it is evident that most of the patients were males (70.3%), a little more than one-third of patients were treatment-naïve when they entered into the study, the mean age was 40 years, and mean time in ART was approximately 5 years.

Association among adherence measurements

Adherence should be evaluated and optimized periodically during the ART in order to achieve the expected clinical response and to be able to make pertinent therapeutic decisions. Many studies have demonstrated that there is no single reliable method for its evaluation;[7,27] therefore, consensus has been reached that at least two methods should be used. Included among the most important methods are administering a structured questionnaire during the interview, recording the collection of medication from the pharmacy, and determine the plasma concentrations of the antiretroviral drugs that can be monitored. Some authors have proposed that the immunovirological course of the patient could be considered

a direct adherence evaluation method;[28] however, subsequent studies have demonstrated that this is a consequence of the adherence grade of the patient with their treatment.[29]

In relation to the above, it would be advisable to know how the different adherence measurement methods are interrelated to see if there is a correlation between their results, or to see if they are different. For this reason, the present study has applied three different methods and has analyzed the relations between them.

TDM versus DR

DR is an indirect method that correlates positively with virological evolution,[20,24,30,31] and it has acceptable specificity and sensitivity.[11,32] However, this method requires the dispensation of ART in a single center, as is done in both this study and in Spanish hospitals. However, this centralized dispensation is not also performed in every country. Its principal limitations are that dispensation of the medication is not synonymous with correct adherence and, on the other hand, that mobility of the patients and sharing medication with their close relations may induce biases in the evaluation.

Although TDM is considered to be the most objective method to evaluate adherence, it has many and important limitations. Some of these limitations include elevated inter- and intraindividual variability, the lack of establishment of a standard cutoff to classify the patients as adherent or nonadherent, providing information only from the recent adherence level, and so on. Furthermore, evaluation of compliance could be affected by whether the medication is taken with or without meals, since this considerably affects bioavailability,[33,34] as well as the C^{ss}_{min} reached by the antiretroviral agent. The growing importance of pharmacogenetics in the field of HIV/AIDS must also be mentioned. It has been possible to demonstrate how the presence of a single nucleotide polymorphism in an individual patient causes considerable variation of drugs plasma levels.[35,36] Thus, for example, patients who are rapid metabolizers could be classified as nonadherent in spite of having optimum adherence.

Consequently, the limitations of both evaluation methods could be responsible for the fact that a significant relation has not been found between both measurements.

TDM versus SMAQ

Over the 60 months of the study, a statistically significant relation was only found between TDM (subtherapeutic, therapeutic, and supratherapeutic) and SMAQ in the first 6 months after the pharmaceutical care program was initiated ($P = 0.013$). In the remainder of the study period, no association was observed.

The SMAQ is one of the many questionnaires existing to evaluate treatment adherence.[7,13,37–39] In this questionnaire, it is the patient who, based on a reduced number of short response questions – normally dichotomous ones (yes/no) – states if he/she has been adherent in regards to taking the medication as indicated by the health care staff, or if this adherence has been occasional or nonexistent. The results provided by the SMAQ are generally overestimated,[39,40] and consequently their reliability will depend on the communication skills of the interviewer.[41,42] However, it will also significantly depend on how much confidence the patient has in the interviewer.

It is important to mention that the implementation of the monitoring program of antiretroviral plasma levels (TDM) coincided with the initiation of the pharmaceutical care program. Therefore, the patient was not familiar with this analytic measurement at the onset of the study period. For this reason, many undiscovered adherence problems surfaced with it. Over time and after the patients with low drug concentrations in their blood were warned by the health care personnel, some of the patients decided to take their medication prior to the analytic control to avoid new warnings. However, this was only done in specific situations which, in no case, implied permanent improvements in adherence.[43]

Due to the previously mentioned limitation of TDM, it is necessary to measure patients' plasma concentrations of antiretroviral therapy several times, so as to carry out population pharmacokinetic studies and to have a profound knowledge of those factors affecting the kinetic profile of the drugs to assure that the results obtained with this tool are reliable.

SMAQ versus DR

As commented on in the previous section, the results provided by the SMAQ depend both on the communication ability of the health care worker and of the trust the patient has in health care professionals. This will depend, among other factors, on the continuity of the program and on the interviewer.[41–44] Both circumstances were taken into account when analyzing the data in this study.

In relation to the DRs, although it is true that they have some limitations, it seems to be the most widely used method in pharmacy departments to evaluate patient treatment adherence. Furthermore, many publications use it as the reference method, not only to measure adherence, but to also compare it with other variables for which some type of relationship is studied.[3,19,24,26,30,45–47] In our study, a significant

relation was found between both adherence measurement methods during the 60 months of the study ($P < 0.002$). For this reason, both the DR and SMAQ seem to be equally reliable in patients with ART.

Evolution of adherence

Given the correlation found between SMAQ and DR, and considering that the latter allows us to quantify adherence easily, DR was used as a reference method to measure the evolution of adherence.

The implementation and continuity of the pharmaceutical care program over the 60 months of the study improved the mean adherence level (92.7% to 96.0%; $P < 0.001$), increased the percentage of patients with adherence ≥95% (64.8% to 76.4%), as well as increased the percentage of patients with adherence equal to 100% (39.7% to 50.8%). The results reached in the present study are similar to, and even better than, those obtained in previous studies.[30,31,48–50]

It would be well to comment that mean adherence did not decrease during the study. This may be because the pharmaceutical care program remained in force during this period. In fact, there are many scientific references that establish that adherence is a continuous process, and therefore, motivation and permanent education is also necessary to maintain the adherence levels reached with the first interventions.[44,51,52] The above would explain why no statistically significant differences were found between the different adherences obtained after the 6th month.

Indicators of clinical evolution

Different studies have searched for a relationship between adherence and the principal indicators of clinical evolution. Thus, some authors have found a relationship between adherence and PVL,[4,20,31,40,53,54] others between adherence and CD_{4+} lymphocyte count,[47,55] and others have found a relationship with both parameters.[30] Our study has found significant differences in the virological as well as the immunological evolution of patients ($P < 0.002$ and $P < 0.0001$, respectively).

In the case of PVL, statistically significant differences were found between the number of patients with optimum adherence levels and those who did not have these levels in regard to time they remained with undetectable PVL. This indicates a direct correlation between better adherence rates and longer time with undetectable PVL. Although it is true that this correlation is quite logical, it has not always been possible to establish it.[56] Furthermore, the patients need to be aware of this reality since this knowledge, by itself, would provide motivation to achieve and maintain optimal adherence rates. Maintenance of virological success may increase the time that the patients continue with the same treatment. This would avoid changes and exposure to new drugs with another profile of adverse effects and toxicity. This aspect gains even more importance in these current times of economic restrictions in health care costs since most of the time, changes in treatment entail a considerable increase in costs.

The evolution of the number of CD_{4+} lymphocytes over the 60 months of this study was examined in regard to the immunological status of the patients. The cutoff point was considered at 200 cells/mm^3 – a limit that was established in agreement with many international guidelines for the follow-up and control of HIV/AIDS patients. These guidelines relate this level as a cutoff point to assure absence of opportunistic diseases.[57–59] The outcomes obtained showed a significant decrease in the percentage of patients with CD_{4+} lymphocytes inferior to 200 cells/mm^3 from the onset until the end of the study. This difference is highly significant ($P < 0.001$). This result demonstrates the successfulness of the pharmaceutical care program implemented, and specifically illustrates the development of a continuous pharmacotherapeutic follow-up. It is very likely that improved adherence has contributed to the virological improvement of the patients which, in turn, has been responsible for the increases observed in the immunological response.

Interviews and interventions

Pharmaceutical care, understood as pharmacotherapy follow-up, is based on carrying out personalized interviews with the patient. In these interviews, the patient is educated and reinforced regarding subject matters related to adherence. Furthermore, when pertinent, interventions can be made. This is why a positive relation between both the number of interviews and interventions received by the patient and improvement in adherence can be expected. This has been evidenced for both variables (interviews and interventions) during the first year of implementation of the pharmaceutical care program. The reason for this may be that the number of patients with poor adherence (35.2%) was greater when the study was being initiated, so that greater opportunities existed to educate the patients and to intervene. On the other hand, interviews and subsequent interventions would not improve adherence in those who were already adherent; however, interviews and interventions would make it possible for the adherence levels to remain elevated over time.

A highly significant change is observed in those patients who entered at the beginning of the study and were classified as nonadherent at that time (n = 107), since 40.2% of them had optimum adherence levels at 6 months after initiation of the pharmaceutical care program; this percentage increased up to 55.1% at the end of the study. On the other hand, 62.8% of those patients who improved their adherence in the first year of follow-up (n = 43) continued with this improved adherence until the end of the study. These results show the need for patients to have access to a pharmacotherapeutical follow-up program where they will be educated and motivated in terms of both their disease and the correct taking of their antiretroviral medication. This program will play a principal role enabling patients to change their behavior and to perceive and appreciate their treatment.[51,60]

For those patients who did not show improvements in antiretroviral medication adherence during the first 6 months after initiation of the pharmaceutical care program, 45.8% did so during the remaining months of the study. This seems to demonstrate how the continuous interviews and messages patients received in this program allowed some patients with inadequate adherence to become aware of the risks entailed, and they subsequently changed their behavior.

As expected, some individuals need more time than others to be able to internalize concepts, messages, and recommendations. However, everyone should have the opportunity to receive detailed and personalized information adjusted to their sociocultural and educational reality, as well as tailored to their clinical profile and history.

Included within the principal limitations of this investigation are the facts that (1) some patients withdrew during the 60 months of the study due to transfers to other hospital centers, treatment abandonments, exitus, and others; and (2) some patients entered the study after it had been initiated (from transfers, new treatments, and so on). Although it is true that one could consider that treatment abandonments are related to noncompliance, it has been observed that these abandonments are significantly due to toxicity problems related to the ART; in turn, this is directly related to elevated adherence rates. These limitations have complicated the data collection and interpretation. However, it is estimated that of the population studied, 22.5% dropped out and 25.6% entered into it. Thus, this probably has not significantly affected the results and conclusions obtained.

Another limitation to keep in mind is that interprofessional work was begun with the physicians, nurses, and pharmacists in order to optimize treatments when the pharmaceutical care program was established. The purpose of this interprofessional work was to not only optimize the treatment, but to also improve antiretroviral therapy adherence. Therefore, improvements in the levels of adherence observed in this study cannot be exclusively attributed to the pharmaceutical intervention. They should also be attributed to the participation of the remaining members of the health care team.

Finally, improvement in adherence and evolution of the patients may be partially due to the improvements introduced in the medications available during the years of the study. Medications that require fewer daily doses, medications that have fewer side effects, or medications that exhibit better efficacy with lower adherence requirements have been incorporated into the current treatment. This contributes to obtaining better results with less effort by the patient. A more comprehensive study on the relation of these and other variables with the grade of adherence or efficacy of the different treatment regimes is needed, since it must be remembered that treatment adherence is, by definition, multifactorial.[57,59]

Conclusion

Both DR and SMAQ may be considered as adequate measurements of treatment adherence because of the good correlation observed between them. The SMAQ is the easiest method and, in our opinion, its validity is based on the existence of a long, continuous, and permanent pharmacist–patient relationship over 5 years. This makes it possible for the patient to openly admit the times when his/her adherence has fluctuated. The advantage of DR is that it has more objectivity, which makes it possible to quantify this variable.

The correlation observed between treatment adherence and the two most important indicators of clinical response (number of CD_{4+} lymphocytes and PVL) shows how adherence rates equal to or greater than 95% make it possible for the patient to maintain undetectable PVLs for a longer period of time, and consequently, patients can have a better lymphocyte count.

Finally, the correlation observed between both the number of interviews and the number of pharmaceutical interventions with adherence should be emphasized. This shows the importance of the establishment and permanence of this pharmaceutical service for HIV/AIDS patients.

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here on behalf of the Tormes Team: Carmen Bustos, Miguel Cordero, Aurelio Fuertes, and Guillermo Luna.

Disclosure

The authors report no conflicts of interest in this work.

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Resumen Artículo II

Impacto de un programa de atención farmacéutica en la evolución clínica y en la adherencia al tratamiento antirretroviral: 5 años de estudio

Introducción y objetivos: Los tratamientos antirretrovirales conforman la base del adecuado control clínico en los pacientes infectados por el VIH, y la adherencia juega un papel primordial en el grado y duración de la respuesta antiviral. Los objetivos del estudio son: (1) determinar el impacto de la instauración de un programa de atención farmacéutica en la mejora de la adherencia al tratamiento antirretroviral y en la evolución inmunovirológica de los pacientes; y (2) detectar posibles asociaciones entre diferentes medidas de valoración de la adherencia.

Material y métodos: Estudio retrospectivo de 60 meses de duración. Se utilizaron como medidas de adherencia: determinación de la concentración plasmática de los fármacos antirretrovirales, un cuestionario estructurado (SMAQ) y los registros de dispensación (RD) de los antirretrovirales. Se determinó el número de entrevistas y de intervenciones relacionadas con adherencia, realizadas a cada paciente en periodos anuales y se relacionaron con cambios en esta variable (medidos con RD) en esos mismos periodos. Los datos de laboratorio se agruparon de acuerdo a la proximidad de sus fechas con los periodos de evaluación del estudio (Febrero–Mayo, 2005–2010).

Resultados: Se incluyeron en el estudio 528 pacientes. Se encontró una asociación significativa entre SMAQ y RD a lo largo de los 60 meses de estudio ($p<0.01$). Tras la puesta en marcha del programa de atención farmacéutica mejoró el nivel de adherencia medio (92.7% a 96.0%; $p<0.001$), se produjo un considerable descenso en el porcentaje de pacientes con linfocitos CD4+ inferiores a 200 cels/mm^3 (27,8% vs 14,9%; $p=1,992 \times 10^{-5}$) y se encontró relación entre el número de pacientes con niveles óptimos de adherencia y el tiempo que permanecieron con carga viral plasmática indetectable. El número de entrevistas e intervenciones realizadas a cada paciente en los primeros 12 meses tras el inicio del programa de atención farmacéutica, se relacionó con un aumento significativo de su adherencia en ese mismo periodo ($p<0.05$ y $p<0.002$, respectivamente).

Conclusiones: Los resultados sugieren que la instauración y continuidad de un programa de atención farmacéutica permiten incrementar la adherencia al tratamiento antirretroviral, aumentar el tiempo de permanencia del paciente con cargas virales indetectables y mejorar su recuento linfocitario.

Influence of the number of daily pills and doses on adherence to antiretroviral treatment: A seven-year study

Original Research

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Influence of the number of daily pills and doses on adherence to antiretroviral treatment: a 7-year study

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SUMMARY

What is known and objective: **Antiretroviral treatment (ART) is hampered by complicated regimens, high pill burden, drug–drug interactions, and frequent short- and long-term adverse effects, leading to decreased adherence. Over recent years, considerable effort has been directed at developing regimens that are less burdening. We undertook a 7-year retrospective study of the records of 264 HIV-infected subjects enrolled in a pharmaceutical care programme to document the progress made and to study the influence of the number of ART pills and doses on the level of treatment adherence.**

Methods: **Antiretroviral dispensing records were analysed for the number of pills and doses administered and the ART adherence rate estimated.**

Results and discussion: **In 2005, the patients took a mean of 6·2 pills daily (CI 95%: 5·9–6·6), and 92·9% of them were on a twice-a-day (BID) dosage regimen. By 2012, the mean number of pills was reduced to 4·1 (CI 95%: 3·8–4·4), and only 50·9% were on a BID regimen. No statistically significant relation was observed between number of daily pills and doses and ART adherence reached by the patients in any of the analyses performed.**

What is new and conclusions: **There has been a continuous reduction in the number of pills and doses of antiretrovirals taken by individual patients over the last 7 years due largely to the introduction of improved treatments and regimens. More daily pills or doses was not associated with worse ART adherence in our pharmaceutical care programme.**

WHAT IS KNOWN AND OBJECTIVE

Antiretroviral treatment (ART) aims to improve survival and quality of life of the patients with HIV infection and reduce transmission of the infection. These are achieved by maintaining the CD^{4+} lymphocytes count within the normal range and obtaining complete control of viral replication.[1]

ART has been steadily improving particularly since the introduction of potent combination therapy in 1996. New drugs with new mechanisms of action, improved potency and activity even against multidrug-resistant viruses, dosing convenience, and tolerability have been approved. These newer drugs have dramatically reduced HIV-associated morbidity and mortality and have transformed HIV infection from a rapidly lethal condition into a chronic one.[1] However, the success of ART has been hampered by complicated regimens, high pill burden, drug–drug interactions, and frequent short- and long-term adverse effects, leading to decreased adherence to prescribed regimens. Currently, lack of adherence to ART continues to be one of the principal factors in therapeutic failure and the development of viral resistance.[2,3]

Adherence is the result of a complex process that involves acceptance of the diagnosis, perception of the need to correctly carry out the treatment, and motivation to do so. Furthermore, possession of appropriate skills, ability to overcome any difficulties that appear and maintenance of the level of achievement reached over time are necessary.[4] The development of strategies for improving ART adherence requires knowledge of the influential factors and how these factors exert their effects. In general, it is accepted that motivational and daily-habit-modifying strategies are the most effective ones.[5–7]

Several studies have shown that the characteristics of the antiretroviral regimens may affect ART adherence. These studies have described a direct association between antiretroviral treatment non-adherence and burden in the number of pills.[8,9] Higher adherence levels have been reported in patients on a once-daily (OD) vs. twice-daily (BID) or three-times-a-day (TID) regimens.[10–13] Due to these findings, a concerted effort has been made to reduce both pill burden and dosing frequency.[14,15] Two types of improvements are possible. The first is based on optimizing the presentation of each medication by increasing the amount of drug contained in each pill or increasing its half life. The second involved including two or more antiretrovirals into one pill.

This study aimed to analyse the evolution over time of the number of ART pills and doses taken by individual patients and the influence of these factors on the level of treatment adherence by a group of HIV-infected patients participating in a pharmaceutical care programme.

METHODS

A 7-year long retrospective study with data from HIV-infected patients treated in the Pharmacy Service outpatient unit of the

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University Hospital of Salamanca, Spain was conducted (April 2005–April 2012). Inclusion criteria were as follows: patients with confirmed HIV infection who had been receiving ART in our hospital during the entire study period.

Adherence measures

Many scientific studies and consensus documents have recommended the use and combination of at least two adherence evaluation methods to yield reliable results.[1,16] Therapeutic drug monitoring (TDM) (direct method), antiretrovirals dispensing records (DR) and simplified medication adherence questionnaire (SMAQ)[17] (indirect methods) are routinely used in our care practice.

A previous 5-year study of ours showed a correlation between DR and SMAQ (measurement of self-reported adherence by the patient) during the study period.[18] The current study used the DR method because it makes possible the quantification of adherence as a continuous variable. Adherence was calculated, for 6-month periods beginning from the initiation of the study (April 2005). The adherence level for each period was obtained from the number of pills taken during that period divided by the number of pills prescribed during the same period. Levels that exceeded 100% were rounded down to 100%. Patients who consumed ≥95% of the medication prescribed were considered 'adherent patients'.[19]

Daily pills and doses

Antiviral treatment was characterized by the number of pills and doses that the patient needed per day. This number was obtained from the DR for each patient using 6-month periods beginning at the onset of the study. This was compared with adherence in these same periods. For patients who had switched treatment, the number of pills and doses corresponding to the longest period within the 6-month period evaluated was used.

The analysis strategies were based on the study of the following relationships:

1Relationship between the number of daily pills or doses with the level of adherence. Adherence was used as a continuous variable and categorized into two levels: ≥95% vs. <95%.

2Relationship between the change in the number of daily pills or doses with the change in adherence level.

3Relationship between the number of daily pills or doses with adherence level stratified into four categories at the start and end of the study (<60%, 60–79%, 80–94%, 95–100%).[19] The percentage of patients in the total population with the same number of pills or doses was calculated in each case. The cut-off for number of pills corresponds to the number that optimized sampling sizes: four and three for the baseline and final situation, respectively. Cut-off for dose number was one.

Statistical analyses

The chi-square test for independence, also called Pearson's chi-square test, was used to study if there was a relationship between categorical variables. Spearman's correlation was used to study the relationship between quantitative or ordinal variables and Bonferroni correction was conducted. The Z test was used for the comparison of proportions. Furthermore, logistic regression models were constructed to investigate the association of the number of pills or doses with the dichotomous outcomes of adherence (<95% vs. ≥95%). IBM SPSS Statistics for Windows version 20.0.0.2[20] and Epidat 3.1[21] were used for the statistical analyses.

RESULTS

A total of 264 patients who received pharmacological treatment during the entire study period were included. Baseline demographic and clinical characteristics of the total study population are given in Table 1.

Evolution of the number of daily pills and doses during the study

During the 7 years of the study, 3610 records of the number of pills and the same number of records for doses in the patients enrolled were obtained. Evolution of the number of daily pills or doses during the study is shown in Fig. 1(a) and Table S1.

In addition, the evolution in the number of pills at the beginning and end of the study based on whether treatment was administered in a OD, BID or TID regimen was studied. The results are shown in Table 2.

The evolution in time of the percentage of the patients who were using the less complex regimens, that is less than five antiretroviral pills per day and/or a single dose per day, was also analysed [Fig. 1(b)].

Relation between pills and doses with adherence

Three different strategies were used to analyse the possible relation between the number of pills or doses and adherence:

Relation between the number of daily pills or doses with adherence in each studied period. No significant relation was observed when adherence was studied as a continuous variable. However, all the estimated correlations have the expected sign ($\hat{\rho} < 0$), indicating a decrease of adherence when the number of daily pills or doses increases.

On the other hand, when adherence was categorized into two levels, no clear pattern was found in the logistic regression analysis to relate number of daily pills and doses with adherence or non-adherence.

Relation between the change in number of daily pills and doses with the change in adherence in each studied period. No statistically significant relation was found between the change in number of pills and

Table 1. Baseline demographic and clinical characteristics of study population

Characteristics	Values Mean ± SD (range) or *n* (%)
Age (years)	40·58 ± 8·81
Male	180 (68·2)
Number of years on ART	5·35 ± 3·60
CD_{4+} counts (cells/mcL)[a]	398·16 ± 240·57
Undetectable plasma viral load[a]	191 (85·3)

SD, standard deviation; *n*, number; ART, antiretroviral treatment.
[a]The variable only refers to those patients for whom these clinical data were available.

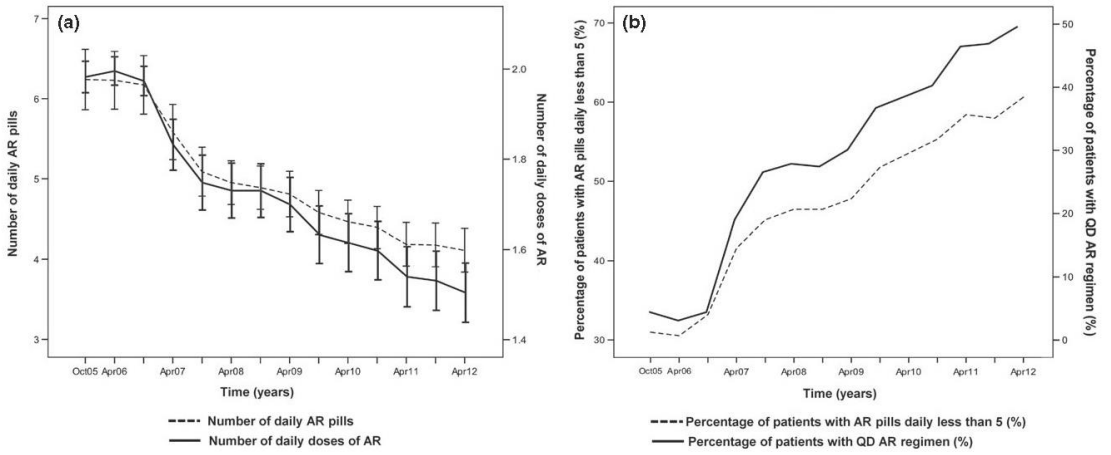

Fig. 1. Mean number of daily pills and doses during the study period (a) and percentage of patients taking less than five pills daily and that of patients on the OD regimen (b). AR, antiretrovirals; OD, once a day.

Table 2. Number of patients and number of daily pills at the beginning and end of the study, based on type of administration regimen (OD, BID or TID)

	Administration regimen					
	OD		BID		TID	
	Baseline	Final	Baseline	Final	Baseline	Final
Number of patients	10	129	221	134	7	0
Number of daily pills Mean (range)	3·5 (2–5)	2·8 (1–6)	6·2 (2–15)	5·4 (2–10)	8·1 (4–12)	–

OD, once a day; BID, twice a day; TID, three times a day.

doses in each patient with the change in adherence in the period studied or in the period immediately follow it.

Relation between number of daily pills and doses with adherence stratified into four categories at the onset and end of the study. Regarding number of pills, 157 patients showed high pill burden at the beginning of the study (>4 pills) and 140 patients at the end of it (>3 pills). It can be observed that: (i) the percentage of adherent patients was greater than the non-adherent, both globally and by the number of pills; (ii) the percentage of patients with optimal adherences was slightly greater in the patients who took fewer pills; and (iii) there were no statistically significant differences between the two groups in any of the four adherence sections (Fig. 2).

No statistically significant differences were observed between both groups in any of the four adherence sections in relation to dose (Fig. 3).

The results of analysis at the end of the study established that: (i) there was no patient group in which adherence was less than 60%, (ii) the percentage of patients in the ≥95% adherence range increased considerably ($P = 0{\cdot}0015$), and (iii) number of daily pills or doses did not affect adherence reached by the patients.

DISCUSSION

Adequate antiretroviral treatment adherence is undoubtedly one of the fundamental requirements for success.[19,22] For this reason, the study of the different factors that may improve patient adherence with the pharmacotherapy has led to great interest within the scientific and health care setting.[23,24]

The patients included in the study had a mean antiretroviral treatment time (at the onset of the study) of approximately 5 years. Globally, the clinical status of the patients was good, with an approximate mean CD^{4+} lymphocyte count of 400 and undetectable plasma viral load in 85% of the cases.

Evolution of the number of daily pills and doses during the study

The study was initiated in 2005. As can be seen in Table 2, at that time, the patients were taking a mean of 6·2 pills daily, 92·9% of

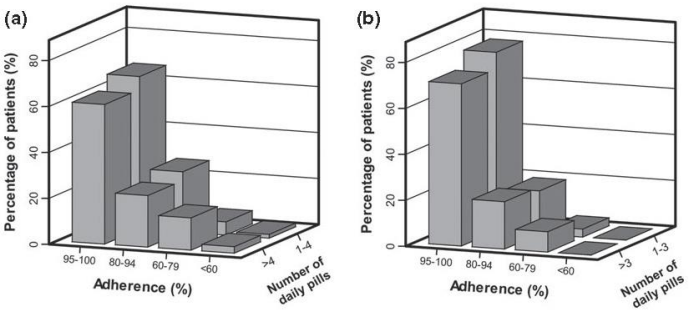

Fig. 2. Percentage of patients, at each adherence level, based on number of daily pills, at the beginning (a) and end of the study (b). Note: patients for whom baseline and final data of number of daily pills and adherence were available (n = 229 and n = 246, respectively).

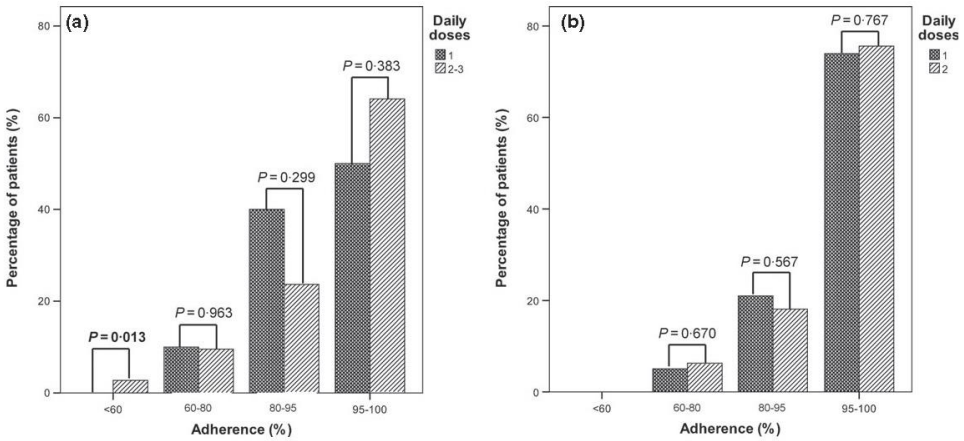

Fig. 3. Percentage of patients, at each adherence level, based on number of daily doses, at the beginning (a) and end of the study (b). Note: patients for whom baseline and final data of number of daily doses and adherence were available (n = 230 and n = 246, respectively).

them with a BID regimen. At the end of the study (2012), mean number of pills that the patients were taking decreased to 4·1 [Fig. 1(a)] and only 50·9% of them with a BID regimen. The reduction observed in the frequency of use of BID regimens was associated to a considerable increase in the OD regimens. This latter increased from 4·1% in the year 2005 to 49·1% in 2012. The tendency observed in the reduction of the number of doses was been observed in the TID regimens too. These went from 2·9% at the onset of the study to disappearing at the end of it. As can be seen in Fig. 1(b), it should also be stressed that only 32·0% of the patients in 2005 were taking less than five pills and that this amount practically doubled by the end of the study (60·4%).

The spectacular increase of simpler regimens in our population in the period studied can be explained by the marketing of new formulations, by the low frequency of drug resistance mutations in our patient population, and a high proportion of patients on their first treatments. People with first-line regimens are more likely to receive a reduced number of pills and doses. This may in turn have accounted for the high rates of adherence recorded in our population, even at baseline measurement and the prolonged efficacy of treatment.

Consensus does exist that patients prefer the simpler regimens, ideally OD, and those with only one pill.[25–28]

However, no consensus has been found on whether this reduction in the number of pills and doses objectively leads to improvement in patient adherence with their antiretroviral medication.[11,12,29]

Relation between daily pills and doses with adherence

Based on the existing controversy in the literature on the influence of the number of pills and doses on adherence to ART, we carried out this study over a 7-year period. Bearing in mind that the results obtained often depended on the type of analysis performed, on the criteria used and even on the statistical analyses chosen, we considered that it was necessary to analyse the possible influence from different points of view in order to obtain general conclusions that attempt to clarify the information existing up to date:

When the relation between number of pills or doses with adherence was studied, no statistical significance was observed in any of the periods studied. When the changes in the number of pills or doses were compared with changes in adherence, no statistically significant relation between them was observed.

Finally, no relation was observed between number of pills or doses and whether the patient was ART adherent or non-adherent.

For the number of pills, it appears that the number of times the patient takes the pills per day is more important than the number of pills as more frequent dosing may interfere with the patient's daily activities. Our results on number of pills and doses are similar to those reported in a recent meta-analysis.[30]

Finally, we would like to think that the good results observed reflect positively on the continuous 7-year pharmaceutical care programme. Thus, the patients were instructed on the importance of taking their antiretroviral medication correctly and about not forgetting to take it. In this sense, it is possible that these results cannot be extrapolated to care centres in which this type of follow-up does not exist or to settings in which the antiretroviral drugs are not dispensed centrally in hospital pharmacies. However, our study design does not allow the impact of our programme to be independently estimated.

Many factors influence ART adherence, including demographic factors, clinical management and drug adverse effects and again these could not be assessed independently in our study.

Currently, due to important and growing economic restrictions on health care costs, there is a tendency to 'break up' fixed-dose combinations of antiretrovirals[31] to enable the use of antiretroviral drugs individually, especially with less expensive generic drugs.[32] The savings can be considerable. Our study results suggest that this strategy is unlikely to affect patient adherence, at least in our setting.

WHAT IS NEW AND CONCLUSION

The number of daily pills during the 7-year study period decreased from about six to four. An increase was observed in the frequency of OD regimens instead of BID regimens. No relationship was found between number of daily pills or doses of the antiretroviral medication and adherence in our pharmaceutical care programme.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Evolution of the number of daily pills or doses during the study.

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Resumen Artículo III

Influencia del número de comprimidos y tomas diarias en la adherencia al tratamiento antirretroviral: 7 años de estudio

Introducción y objetivos: La adherencia al tratamiento antirretroviral con frecuencia se ve dificultada por la presencia de efectos adversos a corto y largo plazo, interacciones con otros fármacos, alta carga de comprimidos y complicados regímenes de dosificación, lo que ha obligado, en los últimos años, a introducir mejoras en los tratamientos que ayuden a simplificar la terapia. Con el fin de estudiar la evolución en el tiempo del número de comprimidos y tomas diarias del tratamiento antirretroviral y su influencia en el grado de cumplimiento de los pacientes con su tratamiento, se realizó un estudio retrospectivo de siete años de duración, con datos de 264 pacientes infectados por el VIH, incluidos en un programa de atención farmacéutica.

Material y métodos: Se utilizaron los registros de dispensación de antirretrovirales para determinar el número de comprimidos y tomas diarios administrados en cada paciente y estimar la tasa de adherencia al tratamiento antirretroviral.

Resultados: En 2005, los pacientes tomaban una media de 6,2 comprimidos diarios (IC95%: 5,9-6,6), y 92,9% de ellos lo hacían con una pauta de administración de dos veces al día. En 2012, el número medio de comprimidos se redujo a 4,1 (IC95%: 3,8-4,4), y sólo un 50,9% los tomaban dos veces al día. No se encontró asociación estadísticamente significativa entre el número de comprimidos y tomas diarios y la adherencia al tratamiento antirretroviral alcanzada por los pacientes en ninguno de los análisis realizados.

Conclusiones: A lo largo de los últimos siete años se ha reducido de forma continua y progresiva el número de comprimidos diarios y la frecuencia de administración de antirretrovirales. En nuestro programa de atención farmacéutica, un mayor número de comprimidos y tomas no se asoció con peor adherencia al tratamiento antirretroviral.