## Editorial

# De aniversarios y realizaciones

**Kurt Frieder**

Los seres humanos otorgamos un valor simbólico de importancia a las cifras redondas y en especial cuando éstas se refieren a la medida del tiempo; también asignamos un significado diferente a los aniversarios cuando se cumplen lustros o décadas y los registramos especialmente. Más aún cuando se trata de períodos transcurridos en momentos trascendentales de nuestras vidas como ser el nacimiento o fallecimiento de seres queridos o cuando atañe a hitos o situaciones capaces de incidir en el rumbo de nuestras vidas y que no sólo nos trascienden sino que pueden tener algún impacto de importancia para terceros.

En tal sentido, el año 2004 es emblemático para la Fundación Huésped. No sólo porque se cumplen 15 años desde su creación, sino también porque algunos eventos puntuales que han marcado nuestra historia institucional sucedieron durante 1994, hace exactamente 10 años. En primer lugar, el 13 de enero de dicho año, fallecía Roberto Jáuregui, valiente y querido amigo, infatigable luchador por los derechos de las personas que viven con el virus y primer voluntario coordinador de nuestra entidad. Como decíamos en el obituario publicado en el número 3 de esta revista, "....Roberto vivió su vida plenamente y, al enterarse de su condición de infectado por HIV, desplegó la enorme capacidad de trabajo que lo caracterizaba y se puso a pelear...". Desafortunadamente él mismo no pudo cumplir con la consigna que acuñó de "estar aquí para el día de la cura".

Ya entonces decíamos que habíamos contraído el compromiso con Roberto de construir el Hospital de Día Roberto Jáuregui para la sección de infectología del Hospital Juan Fernández. Casi exactamente hace 10 años, el 1° de junio de 1994, poníamos la piedra basal para la edificación de un pabellón de 250 metros cuadrados que fue entregado a las autoridades del hospital exactamente a los seis meses, el 1° de diciembre del mismo año. Este proyecto edilicio, cuyo costo y equipamiento superó los USD 400.000, fue realizado íntegramente con fondos obtenidos de la sociedad civil y continúa siendo hasta la actualidad la mayor donación que —en el área de la lucha contra el sida— se ha realizado al hospital público desde una organización no gubernamental.

En la década transcurrida desde su creación, el Hospital de Día Roberto Jáuregui se ha transformado en uno de los centros de referencia nacional dando respuesta a alrededor de 1500 consultas mensuales. En su base de datos figuran alrededor de 6000 casos sida y se han realizado más de 15.000 testeos de HIV. Centro científico asistencial de excelencia, en el pabellón también se dicta el curso de médico especialista en enfermedades infecciosas y numerosos profesionales de todo el país hacen su capacitación para luego volver a sus centros asistenciales de origen. Pero nuestra tarea institucional en el Hospital continúa y durante todos estos años la Fundación ha estado presente con sus voluntarios y ha financiado parte de aquellos gastos que hacen a lo administrativo y a la mejor calidad de vida para sus numerosos pacientes.

Durante los 15 años transcurridos, Fundación Huésped ha acompañado las estrategias que, a nivel mundial, se han desarrollado por el crecimiento de la epidemia y ha incidido localmente tanto en tareas de prevención primaria dirigidas a informar y educar a la población, como así también asesorando a los legisladores que elaboraron las leyes nacionales destinadas a garantizar el acceso a la salud y el cuidado de los derechos humanos de todas las personas que viven con HIV/sida en nuestro país. A la vanguardia del sector civil, ya en 1992, a pocos años de su creación, la Fundación instalaba el primer servicio telefónico de ayuda y asistencia en sida, servicio que continúa brindándose a diario y que se ha complementado pocos años más tarde con la instalación de una página web de actualización permanente. Ha realizado innumerables actividades de capacitación destinadas a estudiantes y docentes así como simposios, jornadas y congresos de actualización para el equipo de salud. Con un compromiso de excelencia ha organizado un equipo de profesionales que desarrollan ensayos clínicos e investigaciones sociales para diversos financiadores que incluyen al Instituto Nacional de la Salud de los Estados Unidos (N.I.H.) y a la Unión Europea.

Desde el año 2001, y debido a la tremenda crisis socio-económica que atraviesa al país nos hemos propuesto que, ante las dificultades reales que dificultan e impiden a la gente acercarse a la Fundación, saldríamos con nuestros voluntarios y expertos sociales hacia los barrios y municipios más carenciados. Es así que estamos desarrollando tareas asistenciales y de capacitación a organizaciones de base y servicios de salud en Lanús, Florencio Varela, La Matanza, Moreno, San Fernando, Guernica y José C. Paz. Hoy en día, gran parte de nuestros 80 voluntarios se trasladan a diario a diversos hospitales del área metropolitana para llevar ayuda y asesoramiento a innumerables personas que se encuentran con dificultades en acceder a servicios de salud garantizados por la ley pero negados por sus circunstancias.

Cuándo un pequeño grupo de profesionales de la salud y sus amigos cercanos nos reunimos para dar inicio a este proyecto que llamamos Fundación Huésped, no sabíamos que la epidemia crecería con la velocidad que lo ha hecho y la importancia que tendrían para confrontarla las organizaciones no gubernamentales como la que estábamos creando. Tampoco pensábamos que 15 años más tarde tendríamos la oportunidad de recordar una historia tan vasta y plena de realizaciones. Nuestras tareas y responsabilidades han crecido ya que las necesidades aumentan mientras los recursos escasean. Cada vez debemos asistir con diversos servicios a más gente. Paralelamente y sin descanso, seguimos intentando que más gente se informe y menos gente se enferme. Y que a aquellos que conviven con el virus del HIV no se les sumen otros "efectos adversos", como la discriminación, el maltrato y la soledad.

# Estado actual del tratamiento de la Hepatitis C en pacientes co-infectados con HIV

**Claudia Ochoa***

## Resumen

*En los últimos años, se han producido significativos avances en el tratamiento de la hepatitis C. La combinación de interferón pegilado más ribavirina han mejorado significativamente el porcentaje de la respuesta viral sostenida (RVS) llevando los resultados de menos de un 10% a más del 50%. Esta mejoría en la respuesta virológica fue confirmada en dos extensos ensayos clínicos realizados en pacientes monoinfectados.*

*Desde el advenimiento de la terapia antirretroviral de alta eficiencia (HAART), la mortalidad y morbilidad asociada al HIV declinó marcadamente. Sin embargo, la morbi-mortalidad secundaria a enfermedad hepática crónica, especialmente asociada a la hepatitis C, ha sufrido un marcado incremento. Algunos estudios han demostrado, que los pacientes con co-infección HIV-HCV, tienen un riesgo aumentado de desarrollar cirrosis, enfermedad hepática terminal, hepatocarcinoma como manifestaciones extahepáticas relacionadas a esta infección. Los factores que contribuyen a esta evolución más acelerada de las complicaciones en pacientes co-infectados son: los niveles muy elevados de ARN-HCV basales, el abuso de alcohol, el recuento bajo de células CD4(<200cell/mm3) y la toxicidad secundaria a ciertos antirretrovirales*

*En Febrero del 2004, durante la 11ra CROI, se presentaron los resultados de los tres estudios más extensos conducidos a la fecha, en pacientes co-infectados, donde se evaluó la eficacia del interferón pegilado más ribavirina en esta población. Estos resultados, indicaron la ventaja de esta terapia frente a la standard aún en esta población. Sin embargo, la tasa de respuesta en estos ensayos fue menor que la previamente vista en pacientes HCV monoinfectados. Indicando estos resultados que la presencia de la infección HIV comprometería la eficacia del tratamiento HCV, aún en pacientes con un buen recuento de CD4(>500cells/mm3).*

*Area de Investigaciones Clínicas, Fundación Huésped. Angel Peluffo 3932. (C1202ABB) Ciudad de Buenos Aires. research@huesped.org.ar*

*A pesar de las dificultades que ofrece hoy el tratamiento de la hepatitis C tanto para el médico como para el paciente, el mismo puede resultar en una significativa mejoría de la sobrevida de estos pacientes. La mejor evolución y respuesta al tratamiento, dependerá en el futuro inmediato de lograr una mejor nivel de información en los pacientes, un mejor nivel de entrenamiento de los médicos y la posibilidad de mayor soporte psicosocial.*

La hepatitis crónica por el virus de la hepatitis C (HCV) evoluciona como una infección oportunista en el contexto de la enfermedad por el virus de la inmunodeficiencia humana (HIV). A favor de este concepto, se ha demostrado que los pacientes co-infectados con HCV y HIV presentan mayores niveles de replicación del virus C, mayor progresión a la fibrosis hepática, mayor frecuencia de enfermedad hepática descompensada y menor respuesta a la terapia antiviral especifica en comparación con los pacientes monoinfectados (1, 2). Más aún, un número de estudios poblacionales sustenta la noción de que la hepatitis C crónica es actualmente la causa más importante de morbimortalidad en pacientes con HIV en áreas geográficas con acceso irrestricto a la terapia antirretroviral de alta eficiencia (HAART) (3).

Un mayor conocimiento acerca de la historia natural de la infección por HCV en pacientes monoinfectados y datos recientes sobre la morbimortalidad asociada a la enfermedad hepática crónica en pacientes afectados con HIV/sida ha movilizado el interés de clínicos e infectólogos sobre los potenciales beneficios de tratar la infección por HCV en pacientes co-infectados con HIV. En ese contexto, la posibilidad de erradicar la infección por HCV es sin duda el mayor estímulo para explorar estrategias terapéuticas con los fármacos disponibles a la fecha.

Las drogas aprobadas para el tratamiento de la hepatitis C son el interferón alfa 2 y la ribavirina. Los estudios preclínicos de otras proteínas terapéuticas pegiladas, demuestran que los polímeros de polietilenglicol (PEG) optimizan la actividad farmacológica de la proteína original. El PEG aumenta la vida media de la proteína conjugada por disminución del clearance renal e intracelular, así como por la disminución de la lisis proteica. En el caso del interferón, estudios clínicos controlados han demostrado la mayor eficacia del interferón alfa 2 pegilado con respecto al interferón alfa 2 estándar (4,5).

A la fecha se encuentran disponibles dos formulaciones de interferón alfa 2 pegilado:

1. PEGASYS " (Roche). El PEGASYS es el resultado de la unión covalente de una proteína mono metoxi ramificada de PEG al IFN alfa-2 a. Esta molécula ramificada de interferón alfa-2a de 40KD conserva la misma actividad que la molécula original. El producto se presenta en jeringas prellenadas de 180 microgramos para ser administrado una vez por semana (6).
2. Intron A-PEG (Schering Plough): Este compuesto consta de una única molécula lineal de PEG de 12 KD. Las presentaciones que actualmente se comercializan son: polvo liofilizado para solución inyectable con 50, 80, 100 y 120 microgramos para ser administrado a la dosis de 1,5 microgramos/kg una vez por semana (7).

Ambas formas farmacéuticas se aplican por vía subcutánea con un perfil de seguridad semejante. La eficacia y toxicidad comparativa de ambas formulaciones se encuentran en evaluación en un estudio clínico (IDEAL).

Durante la XI Conferencia sobre Retrovirus e Infecciones Oportunistas realizada en la ciudad de San Francisco (USA) en Febrero del 2004, se comunicaron datos recientemente obtenidos de estudios observacionales y clínicos sobre el manejo de los pacientes co-infectados con HCV-HIV. Este artículo intenta revisar y comentar desde una perspectiva clínica los datos expuestos durante esta conferencia, los conceptos presentados en foros internacionales de expertos sobre el tema y opiniones obtenidas en reuniones de especialistas en la unidad de infectología del Hospital Fernández.

## Evaluación inicial

Debido a la alta frecuencia de infección por HCV, existe consenso en realizar una serología (ELISA) para el HCV en todos los pacientes infectados con HIV. Los pacientes que presentan una serología positiva deberán ser confirmados con una técnica de PCR cuali o cuantitativa (limite mínimo de detección 50 copias/ml).

Hasta un 15 % de los pacientes con serología positiva pueden presentar una PCR negativa. Por otro lado, pacientes con recuentos bajos de células CD4 pueden presentar serología negativa en el contexto de replicación viral cuantificable (PCR positiva). En los pacientes con RNA HCV detectable se deberá evaluar su elegibilidad para el tratamiento específico. En ausencia de contraindicaciones para la terapia con interferón + ribavirina la indicación del tratamiento se basa en el análisis de los factores del huésped y los factores virales asociados a una respuesta virológica, como así también en los potenciales beneficios versus la potencial toxicidad de los regímenes actualmente disponibles.

## Factores del huésped

A. La inmunodeficiencia asociada al HIV estimada con el recuento de CD4 es un determinante mayor de respuesta al tratamiento. En un consenso de expertos realizado durante Febrero del 2003 se reconocieron tres posibles escenarios (8):
   1. En pacientes naïve de terapia antirretroviral con recuentos de CD4 estables superiores a 350 células/mm3 y marcadores bioquímicos y virológicos de infección viral activa se recomienda iniciar la terapia de la hepatitis C previamente al inicio de la terapia antirretroviral.
   2. En pacientes con recuentos de CD4 entre 200 y 350 células/mm3, se prefiere iniciar el tratamiento antirretroviral y diferir el tratamiento de la hepatitis C por considerarse que la progresión de la inmunodeficiencia es más rápida que la progresión de la hepatopatía. Además, la respuesta virológica a la terapia anti HCV es más favorable en pacientes con CD4 > 200 células/mm3.
   3. En pacientes con < 200 CD4 se recomienda diferir la terapia de HCV hasta obtener una respuesta virológica e inmunológica al HAART.

   Es posible que pacientes que iniciaron HAART con recuentos muy bajos de CD4 no presenten una respuesta inmunológica adecuada aun cuando presenten una supresión prolongada de la viremia por HIV. Además, debe tenerse en cuenta que en los pacientes co-infectados la respuesta de los CD4 al HAART es menor cuando se compara con aquella de pacientes sin infección por HCV. Un numero de estudios poblacionales, y un estudio observacional recientemente conducido en la Fundación Huésped demostró que el incremento de células CD4 luego de 48 semanas de terapia HAART es menor y más lento en pacientes co-infectados versus pacientes sin infección por HCV (9). Estudios que evaluaron la dinámica del incremento de células CD4 han determinado que el aumento proporcional en las células CD4 con respecto a los valores basales se observa dentro del primer año de iniciada la terapia HAART. En aquellos pacientes que no aumentan el recuento de CD4 por encima de 200 células a pesar de una adecuada supresión virológica, es posible que un año de terapia HAART adecuada sea un intervalo de espera prudente para el inicio del tratamiento para la hepatitis C.

B. Estadio de la hepatopatía: Un Consenso de Expertos Europeos ha recomendado recientemente ofrecer tratamiento a aquellos pacientes con fibrosis hepática de grado 1 a 4. Los pacientes con cirrosis compensada deben ser evaluados para un transplante hepático. En estos pacientes, el tratamiento con interferón + ribavirina, aunque pobremente tolerado, podría evitar la descompensación a corto plazo y reducir el riesgo de hepatocarcinoma (4,5)

   El estadio de la hepatopatía se valora por el grado de fibrosis observado en una biopsia hepática. Sin embargo el rol de la biopsia hepática en la evaluación pre terapia no esta claramente definido. Un numero de estudios han tratado de encontrar subrogantes bioquímicos para evaluar la fibrosis hepática. Mehta y colaboradores seleccionaron 96 pacientes con una muestra de sangre tomada en el mismo momento de una biopsia de hígado. La histología hepática fue analizada con el score modificado de Ishack. Los marcadores subrogantes explorados fueron los niveles de ALT, AST, albúmina, bilirrubina y ácido hialurónico. Un score de fibrosis > 2 fue 12 veces mas frecuente en individuos que presentaron niveles de ácido hialurónico > 85 ng/dL y tres veces mas frecuente en los pacientes con niveles de ácido hialurónico entre 42 y 85 ng/dl. Los niveles de albúmina y AST presentaron una menor correlación. Por el contrario, los pacientes con menores niveles de ácido hialurónico y AST y mayores niveles de albúmina mostraron un score de fibrosis igual o menor a 2 (10). La aplicación de este y otros scores de fibrosis en la práctica clínica deberían ser validados en un mayor número de pacientes.

   Es de notar que las enzimas hepáticas no reflejan el nivel de replicación viral ni la magnitud del daño histológico. Por consiguiente el riesgo de progresión a una enfermedad hepática descompensada no puede evaluarse por los niveles de enzimas hepáticas. En un estudio retrospectivo, Uberti-Foppa y colaboradores analizaron 354 biopsias hepáticas de pacientes co-infectados de acuerdo a los niveles de transaminasas. En este estudio se observaron cambios histológicos significativos en la biopsia hepática a pesar de niveles normales de ALT hasta en un 20% de los casos, como ha sido previamente descrito en pacientes monoinfectados (11)

Un beneficio clínico adicional de practicar una biopsia hepática es la posibilidad de detectar otras enfermedades asociadas (infecciones oportunistas, hepatopatía alcohólica, toxicidad a drogas, etc) sin expresión clínica especifica.

### Factores Virológicos

El genotipo del HCV y la carga viral pretratamiento son dos determinantes de respuesta al tratamiento:

Genotipo: Existen 6 genotipos identificables por técnicas de hibridización molecular. Se recomienda caracterizar el genotipo del HCV antes de iniciar el tratamiento con interferón + ribavirina. Las infecciones por los genotipos 2 y 3 presentan tasas de respuesta superiores a las infecciones por genotipos 1 y 4. Aunque la duración del tratamiento es tema de reciente controversia es posible tratar las infecciones por genotipos 2 y 3 por un menor periodo de tiempo y con menores dosis de interferón y ribavirina en comparación a las necesarias para tratar los genotipos 1 y 4. Tasas de respuesta virológica del 80 % al interferón pegilado + ribavirina en pacientes con genotipo 2 y 3 sustentan el inicio del tratamiento independientemente de la evaluación de otros factores de respuesta (12).

Carga viral: Niveles de HCV RNA superiores a 2.000.000 de copias/mL se han asociado a una subóptima respuesta a la combinación interferón + ribavirina (13).

## Objetivos de la terapia anti-HCV

El objetivo del tratamiento combinado con interferón + ribavirina es la remisión virológica y eventualmente la erradicación o cura de la infección por HCV. La erradicación de la infección se correlaciona con la respuesta virológica sostenida (RVS) definida por niveles de HCV RNA inferiores a 50 copias/ml luego de 6 meses de finalizado el tratamiento. No todos los pacientes que alcanzan una respuesta virológica completa al finalizar 24-48 semanas de terapia (ETR= respuesta al final del tratamiento) sostienen niveles de carga viral no detectable luego de la suspensión del mismo. Es de notar que una reducción igual o mayor a 2 log de los valores basales dentro de las 12 semanas de iniciada la terapia (EVR = respuesta virológica temprana) indica una alta probabilidad de alcanzar una RVS. Secundariamente, el objetivo del tratamiento es mantener valores normales de enzimas hepáticas y prevenir el riesgo de progresión a la cirrosis y/o cáncer hepático.

## Toxicidad

Los efectos adversos secundarios al tratamiento de la hepatitis C con interferón-ribavirina en pacientes con HIV son frecuentes. Mientras que estos se observan en el 12 al 15% de los pacientes monoinfectados, esta proporción asciende a un 20 al 25% en pacientes co-infectados. Para una revisión mas practica, los eventos adversos relacionados a la medicación se clasifican en las siguientes categorías.

#### Síntomas pseudogripales

Fiebre, cefalea, dolores articulares, astenia y anorexia, son los eventos más frecuentes y pueden llegar a ser muy severos. Sin embargo, tienden a reducirse a medida que transcurre el tratamiento. Estos síntomas puede aliviarse con la administración de paracetamol o antiinflamatorios no esteroides administrados en forma preventiva. Se recomienda además mantener una buena hidratación, para tratar estos síntomas.

#### Náuseas, diarrea y anorexia

La ribavirina puede causar nauseas si se administra en ayunas o con comidas ricas en grasas. Se ha observado diarrea asociada al interferón que puede controlarse aumentando la hidratación y con dieta pobre en residuos y antidiarreicos. Los pacientes pueden perder peso como consecuencia de las náuseas, la anorexia y la diarrea.

#### Reacción en el sitio de aplicación

Se describe en un 5% a 12% de los pacientes, pero raramente limitan la terapia. Se ha descripto con mayor frecuencia con el Intron-A PEG. Se puede minimizar aplicando hielo local previamente a la inyección. Es conveniente realizar la aplicación en un ángulo de 40 a 90 grados y no mover la jeringa una vez que se encuentra en el tejido subcutáneo. Es recomendable además, rotar el sitio de inyección.

#### Depresión

Se describe este evento con una frecuencia del 21 y el 31% en los dos estudios más extensos de terapia combinada de PEG Interferón y ribavirina . Esta es la toxicidad mas frecuente luego de los síntomas pseudo gripales; Puede asociarse a irritabilidad e insomnio. Es recomendable advertir al paciente sobre la posibilidad de estos síntomas y enseñarle a identificar los mismos precozmente. Aun es tema de debate el uso de terapia preventiva (antidepresivos) antes del inicio del tratamiento. Se han comunicado cuadros de psicosis y ataques de pánico durante la combinación de terapia HAART e interferón / ribavirina. Es recomendable una consulta con un especialista en salud mental si se sospechan síntomas depresivos, previamente o durante el tratamiento

**Hematológicos**

La anemia es por lo general inducida por la ribavirina por un mecanismo de hemólisis extravascular. El grado de reducción de la hemoglobina, es directamente proporcional la dosis de ribavirina. Algunos pacientes pueden experimentar una reducción de la hemoglobina de 3 a 4 gramos dentro de las primeras ocho semanas de iniciado el tratamiento, En el contexto de ensayos clínicos, la ribavirina se debió reducir por anemia moderada a severa en el 13 a 22% de los pacientes (4,5). Una guía practica para el manejo clínico de la anemia sugiere:

- Si el paciente no tiene antecedentes de enfermedad cardiaca y la hemoglobina es menor a 10 g/dl, se indica reducir la dosis diaria de ribavirina en 200 mg (un comprimido). Si los niveles de hemoglobina persisten por debajo de 8,5 g/dl, se deberá interrumpir la ribavirina.
- En pacientes con antecedentes de enfermedad coronaria, la ribavirina deberá ser reducida si la hemoglobina desciende mas de 2 gramos (<12 g/dl). Si los niveles de hemoglobina persisten por debajo de 12 g/d luego de reducir la dosis, la ribavirina deberá ser interrumpida. Una vez que los niveles de hemoglobina aumenten, la ribavirina podrá ser re-introducida.

Datos recientes sugieren que la reducción de la dosis de ribavirina podría afectar la RVS (14). Por este motivo, resulta razonable explorar estrategias con el uso de eritropoyetina. En un estudio controlado de etiqueta abierta, 52 pacientes con anemia (Hb <12 g/dl o disminución > 2 g/dl del basal), durante la terapia con interferon/ribavirina fueron randomizados a recibir eritropoyetina -( 40000 UI por vía subcutánea una vez a la semana o controles habituales más terapia standard. En un análisis interino sobre 41 pacientes, la mediana de cambio de la Hb a la semana 16 del estudio fue de 2.8 +/- 0.3 g/dl en el grupo eritropoyetina versus 0.4 +/-0.3 en el grupo control ( $p < 0.01$) (15). Una estrategia complementaria en evaluación es la utilización de eritropoyetina en forma de profilaxis antes del inicio de la ribavirina.

La neutropenia y plaquetopenia se asocian con el interferón pegilado y requieren reducción de la dosis en el 18 a 20% de los pacientes (4,5). Generalmente la neutropenia es leve y no obliga a interrumpir o modificar la dosis. Si la neutropenia es severa (menos de 500 neutrófilos/mm3 ) la terapia se interrumpe. El recuento de glóbulos blancos suele retornar a las cifras basales dentro de las siguientes cuatro semanas. En el caso que el recuento de neutrófilos se encuentre por encima de los 750 células/mm3, es posible reducir la dosis en un 50%. Algunos especialistas utilizan además factores estimulantes de colonia (GCS-F) a la dosis de 300 ug subcutáneos por semana.

La linfopenia se asocia con una reducción de los linfocitos T CD4 totales. La misma es transitoria y rara vez tiene significado clínico en pacientes que mantienen una respuesta virológica al HAART. En el caso de recuentos basales inferiores a 200 células debe considerarse las profilaxis para infecciones oportunistas asociadas al SIDA. Durante la terapia con interferón, es conveniente monitorear la respuesta de los CD4 al HAART de acuerdo a su porcentaje.

**Daño mitocondrial.**

El daño mitocondrial es el resultado de la inhibición de la polimerasa gamma por los análogos nucleósidos y el mismo podría verse exacerbado cuando la ribavirina se utiliza en combinación con algunos análogos nucleósidos como el ddI y el D4T. La ribavirina podría incrementar los niveles intracelulares de didanosina fosforilada aumentado de esta manera el riesgo de toxicidad (16,17,18) . Se han descrito casos de pancreatitis y acidosis láctica en pacientes que recibían la combinación de didanosina y ribavirina, por tal motivo no se aconseja su administración conjunta. Si esto no fuera posible, se deberá controlar a intervalos regulares la amilasa y el lactato venoso además de interrogar al paciente sobre síntomas asociados a toxicidad mitocondrial . Estos últimos incluyen dolor abdominal, nauseas, vómitos, disnea, fatiga y perdida de peso. Perrone y col. describieron episodios de descompensación hepática en pacientes con hepatopatía avanzada que recibían ddI en conjunto con ribavirina en el contexto del estudio RIBAVIC. Estos pacientes padecían cirrosis y la interacción del ddI con la ribavirina puede haber precipitado el fallo hepático de un órgano con limitada reserva funcional (19).

**Disfunción tiroidea**

Aunque poco frecuente, se han reportado casos de hipo e hipertiroidismo asociados a la terapia con interferón. Por esta razón, se recomienda la evaluación de la función tiroidea basal y a intervalos semestrales durante el tratamiento.

**Interacciones medicamentosas**

Diversos efectos adversos son el resultado de interacciones farmacológicas entre la combinación de interferón-ribavirina y algunas drogas antirretrovirales. Se sugiere utilizar con precaución combinaciones con AZT porque podrían incrementar el riesgo de anemia asociado a la ribavirina. Como se indico previamente, el ddI incrementa el riesgo de acidosis láctica, pancreatitis y descompensación hepática. También se ha sugerido que la administración conjunta de d4T y ribavirina podría potenciar la lipoatrofia y perdida de peso inducida por los nucleósidos de la transcriptasa reversa.

Finalmente, debe considerarse que la enfermedad hepática avanzada puede limitar la capacidad de los pacientes de tolerar la terapia antirretroviral. Moya J y colaboradores, demostraron una estrecha relación entre el grado de fibrosis hepática y la posibilidad de desarrollar toxicidad asociada a los antirretrovirales. En pacientes con estadios leves a moderados de fibrosis la toxicidad a los ARV fue mas baja (18%), que en los pacientes con fibrosis severa (35%) (20) La limitación en la tolerancia de los antirretrovirales en pacientes con hepatitis C crónica debe ser un factor a considerar para decidir la terapia precoz de la hepatopatía.

# Ensayos Clínicos

## Pacientes monoinfectados

Los resultados obtenidos en estudios de terapia combinada con interferón y ribavirina en pacientes monoinfectados pavimentaron el camino para avanzar en el tratamiento de la hepatitis crónica C en pacientes coinfectados con HIV. Observaciones clínicas iniciales mostraron en forma consistente que la terapia combinada con interferón mas ribavirina fue superior en eficacia a la monoterapia con interferón. En esos estudios, la proporción de pacientes con RVS fue del 10 al 15 % en los pacientes tratados con interferón standard versus 40 % de los pacientes tratados con combinaciones de interferón mas ribavirina (21,22).

Posteriormente, la introducción de la molécula pegilada de interferón, permitió mejorar la eficacia de la terapia combinada. En un estudio controlado sobre 1530 pacientes con hepatitis crónica por virus C la proporción de pacientes con RVS fue del 54% para la rama que recibía 1.5 ug/kg/semana de interferón pegilado en combinación con ribavirina (800 mg OD) versus un 47% para los pacientes asignados a recibir interferón standard (3 millones UI 3 veces por semana) más ribavirina 1200 mg OD (p=001). La RVS en los pacientes con el genotipo 1 y en los pacientes con genotipo 2/3, fue del 42% y 80 % respectivamente.

En un segundo estudio sobre 1121 pacientes monoinfectados, la RVS fue del 56 % para la rama de interferón-alfa-pegilado (180ug) /ribavirina (1000-1200mg) versus el 44 % para la rama de interferón-alfa-standard/ ribavirina (1000-1200mg) (p=0.001). La RVS en los pacientes con genotipo 1 fue 46 % en la rama interferón pegilado versus el 36% en la rama con interferón standard. La RVS para los genotipos no-1, también fue mejor en la rama de PEG-interferón (76% y 61% respectivamente (p< 0.005) (5).

**Tabla 1. Paceintes monoinfectados**

| Estudio | RVS PEG-INF/ RVB | RVS INF/ RVB | RVS G1 PEG-INF vs standard | RVS no G1 PEG-INF vs standard | P |
|---|---|---|---|---|---|
| Manns M & col | 54% | 47% | 42%/34% | 80%/80% | 0.01 |
| Fried MW & col | 56% | 44% | 46%/36% | 76%/61% | 0.001 |

## Pacientes co-infectados

A la fecha, tres estudios clínicos controlados evaluaron comparativamente la eficacia y seguridad de combinaciones de interferón alfa 2 standard o interferón alfa 2 pegilado con o sin ribavirina en pacientes coinfectados con HCV y HIV. Los resultados preliminares de estos estudios fueron presentados recientemente en la Conferencia sobre Retrovirus y se resumen a continuación (ver también tabla 2).

### APRICOT

Este fue un estudio multicéntrico realizado en 19 países que incluyo 868 pacientes adultos randomizados a uno de los siguientes regímenes durante 48 semanas:

- interferón alfa 2 standard (3 millones de UI tres veces por semana) + ribavirina (RBV) 800 mg/día (n=285)
- interferón alfa 2 pegilado (Pegasys): 180 microgramos una vez por semana) (n=286)
- interferón alfa 2 pegilado (Pegasys): 180 microgramos una vez por semana) + ribavirina (RBV) 800 mg/ día (n=289)

Las características basales de los pacientes fueron semejantes en las tres ramas de tratamiento. Aproximadamente un 60% presentaban una infección por genotipo 1 y un 40 % por genotipo "no 1" (5% por el genotipo 2; 27% por el genotipo 3 y el 7% por el genotipo 4). La mediana de CD4 fue de 500 células/mm3 y el 84 % de los pacientes recibía terapia antirretroviral al iniciar el estudio. Todos los pacientes tenían una biopsia hepática previa al tratamiento y aproximadamente en un 16% presentaban puentes de fibrosis o cirrosis. Los análisis de eficacia (ITT: intención de tratar) mostraron una RVS del 40% en los pacientes con interferón alfa 2 pegilado/ RBV versus 12% en los pacientes con interferón alfa 2 standard/RBV y 20% en la rama de monoterapia con interferón alfa 2 pegilado. La RVS estratificada según genotipo fue superior en los pacientes infectados con genotipos 2 y 3: 62 % con la combinación de interferón alfa 2 pegilado, 20 % con interferón alfa 2 standard y

36 % con monoterapia de interferón alfa 2 pegilado. En los pacientes con genotipo 1, la RVS fue 29%, 7 %, y 14% en las ramas de interferón alfa 2 pegilado/RBV, interferón alfa 2 standard y monoterapia con interferón alfa 2 pegilado respectivamente.

El numero de pacientes que discontinuo el estudio según la rama de tratamiento fuero: 39% en la rama de INFstandard/RBV , 31% en la rama de peg-INF monoterapia y 25% para la rama peg-INF/RBV. Los eventos adversos y anormalidades de laboratorio fueron de alrededor del 15%. en las tres ramas y los eventos adversos severos fueron del 5%, 10% y 8% respectivamente. La neutropenia fue mas frecuente en la rama de interferón pegilado (12%)(23)

### ACTG A5071

En este estudio se comparo la eficacia y seguridad del interferón alfa 2 standard (dosis de 6 MUI tres veces por semana durante tres meses, seguido de dosis de 3MUI en los meses subsiguientes) versus el interferón alfa 2 pegilado (Pegasys() (180ug en una dosis semanal), ambos en combinación con ribavirina. Es importante notar que los pacientes iniciaron ribavirina a una dosis de 600 mg/día y la misma fue incrementada a 800 mg/día de acuerdo a la tolerancia. El 80 % de los pacientes eran de sexo masculino y el 50 % de raza negra. La mediana de CD4 al inicio era de 400 células/mm3. Un 70 % de los pacientes tenían un genotipo 1 y las biopsias hepáticas mostraron un score de 5 y 2 en la actividad inflamatoria y fibrosis respectivamente (mediana). Los análisis de eficacia mostraron una RVS del 27 % en los pacientes randomizados a recibir interferón alfa 2 pegilado versus 12% en la rama de interferón alfa 2 standard ($p< 0.03$). La RVS a la combinación de Peg-interferón 180ug + RBV para el genotipo “no 1” y genotipo 1, fue del 73 y 14% respectivamente ($p: 0.0007$). El 52 % de los pacientes con respuesta virológica también obtuvieron mejoría histológica. Es de notar que un 36 % de los “no respondedores” presentaron respuesta histológica al tratamiento. La incidencia de eventos adversos fue similar en ambas ramas y un 12% de pacientes discontinuo prematuramente la terapia (24).

### RIBAVIC

En este estudio multicéntrico conducido en Francia, aproximadamente 400 pacientes fueron randomizados a recibir interferón alfa 2 standard (3 millones de UI trisemanal) o interferón alfa 2 pegilado (Peg-Intron(: 1.5 microgramos/Kg/semana), ambos en combinación con ribavirina 800 mg por día. Los participantes debían tener al comienzo del estudio una infección HIV estable con o sin tratamiento antirretroviral. Al igual que en el estudio APRICOT la mediana de CD4 fue de 500 células y el 82% de los pacientes recibía HAART. Una característica sobresaliente en la población de este estudio fue que el 79 % los pacientes eran usuarios de drogas y que un 40% de los mismos tenia un estadio 3-4 de fibrosis, en la biopsia hepática basal. En el 58% de los pacientes presentaba el genotipo 1.La RVS fue del 27% y 15 % para los pacientes asignados al tratamiento con interferón alfa 2 pegilado e interferón alfa 2 standard respectivamente. Al igual que en los otros dos estudios la RVS fue muy pobre para el genotipo 1 (15 % en la rama de interferón alfa 2 pegilado). Un 40% de los pacientes discontinuaron la terapia y un 30% de los pacientes experimentaron eventos adversos severos incluyendo seis casos de hiperlactatemia sintomática. También se comunico una significativa reducción en los niveles de hemoglobina y las plaquetas pero no de los leucocitos. (25)

En resumen, los resultados preliminares de estos tres estudios demuestran mayor eficacia del interferón alfa 2 pegilado sobre el interferón alfa standard en la terapia combinada con ribavirina en pacientes co infectados con HCV y HIV. Sin embargo, existen diferencias substanciales en las tasas de respuesta observadas en cada estudio. Es posible que estas diferencias reflejen variaciones en el diseño de los ensayos clínicos y de la población enrolada y no diferencias en la potencia intrínseca de los regímenes evaluados. La pobre respuesta observada con Peg-Intron en el estudio RIBAVIC (15 % de RVS en pacientes con genotipo 1) es consistente con una mayor proporción de participantes con una enfermedad avanzada y usuarios activos de drogas endovenosas en este ensayo clínico. Es de notar que este estudio presenta la mayor frecuencia de abandono del tratamiento y perdidas de seguimiento. En el estudio ACTG A5071, la utilización de dosis crecientes de ribavirina con la intención de mejorar la tolerancia a esta droga podría haber afectado el predictor más robusto de eficacia que es la respuesta virológica temprana al tratamiento combinado. Observaciones clínicas sugieren que dosis iniciales máximas de ribavirina se asocian a una mejor respuesta virológica temprana. En el estudio APRICOT se obtuvo la tasa de respuesta viral sostenida más alta comunicada a la fecha en pacientes co-infectados. Este estudio, se caracterizo por rigurosos criterios de selección de los pacientes en cuanto a medicaciones concomitantes y uso de substancias, reflejado en una tasa relativamente baja de eventos adversos serios a la medicación evaluada.

Estos resultados comunicados confirman tasas de respuesta entre el 40 y 65 % previamente observadas en series no controladas de pacientes tratados con interferón mas ribavirina (26, 27, 28).

En todos los estudios el genotipo viral retiene un alto valor predictivo para estimar la respuesta terapéutica como ha sido observado en pacientes monoinfectados. Sin embargo, los pacientes co-infectados parecen presentar mayores diferencias entre ETR y RVS sugiriendo una mayor proporción de recaídas en los pacientes coinfectados. El significado de estas observaciones sobre la duración del tratamiento como así también en la optimización de las dosis de interferón y ribavirina esta actualmente bajo evaluación.

**Tabla 2. Características sobresalientes de los estudios clínicos APRICOT, ACTG A5071 y RIBAVIC**

| | APRICOT | ACTG A5071 | RIBAVIC |
|---|---|---|---|
| N | 868 patients | 133 | 412 |
| CD4 (mediana) | 500cells/ml | 400cells/ml | 500cells/ml |
| fibrosis/cirrosis | 16% | F2/HAI-score:5 (mediana) | F3-4 40% |
| genotipo 1 | 60% | 75% | >58% |
| medicación estudiada | Interferón+RBV Pegasys+RBV Pegasys mono | Interferón+RBV Pegasys+RBV | Interferon+RBV Peg Intron+RBV |
| RVS total | 40% | 27% | 27% |
| RVS genotipo 1 | 29% | 14% | 15% |
| SAE | 8% | -.- | 30% |
| Discontinuación | 25% | 12% | 40% |

# Referencias

1. *Bica I, Mc Govern B, Dhar R et al. Increasing mortality due end-stage liver disease in patients with HIV Infection. Clin Infect Dis 2001; 32:492-7.*
2. *Martin-Carbonero L, Benhamou Y, puoti M, et al. Incidence and predictors of severe liver fibrosis in HIV-infected patients with chronic hepatitis C: European collaborative study Clin Infect Dis 2004; 38:128-33.*
3. *Sulkowki M, Thomas D. Hepatitis C in the HIV-infected person. Ann Intern Med 2003, 138:197-207.*
4. *Manns MP McHutchison JG, Gordon SC,et al. Peg-interferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001; 358(9286):958-65.*
5. *Fried MW, Shiffman ML, Reddy KR, et al. Peg-interferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med, vol 347, No 13. september 26, 2002.*
6. *Pegasys , package insert. Nutley, NJ: Roche Pharmaceuticals, 2002.*
7. *Peg-Intron, package insert; Kenilworth, NJ: Schering Plough Corporation, 2001.*
8. *Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV co-infection. AIDS 2004, 18:1-12.*
9. *Zala C, Patterson P, Ochoa C, et al. The Impact of Hepatitis C virus on CD4 Response Post Initiation of HAART among Patient Enrolled in Clinical Trials. 11th Conference on Retrovirus and Opportunistic Infections. Abstract #817.*
10. *Mehta S, Braskar K, Sulkowski M, et al. Serum Markers of Liver fibrosis in HIV/HCV-infected Adults. 11th Conference on Retrovirus and Opportunistic Infections. Abstract# 809*
11. *Uberti-Foppa C, De Bona A, Galli L, et al. Fibrosis Damage in Liver Biopsy specimens From 354 HIV-HCV Co-Infected Patients: Role of Persistently Normal Alanineaminotransferase. 11th Conference on Retrovirus and Opportunistic Infections. Abstract #814.*
12. *NIH Consensus Development Conference Statement: management of hepatitis C. Gastroenterology 2002; 123:2082-99.*
13. *E.Daar and others. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. Journal of Infectious Diseases 2001; 589-95.*
14. *MShiffman. The HALT-trial investigators. Retreatment of HCV no-responders with peginterferon and ribavirin: results from the lead-in phase of hepatitis C anti-viral long-term treatment against cirrhosis trail. Hepatology 2002; 36: abstract 527.)*
15. *Dietrich D, Sulkowski M, Bini E, et al. Epoentin -( Administered Once Weekly Improves Anemia in HIV/HCV Co-infected patients treated with Interferon/Ribavirin therapy: A prospective randomized study. 11th Conference on Retrovirus and Opportunistic Infections. Abstract # 824,*
16. *Lafeuillade A, Hittinger G, Chapadaud S et al. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. Lancet 2001, 357:280-281.*
17. *Kakuda T, Brinkman K. Mitochondral toxic effects of ribavirin. Lancet 2001: 357:1803*
18. *Mauss S, Larrey D, Valenti W. Risk factors for hepatic descompensation in cirrhotic patients with HIV-HCV coinfection treated with PEG interferon or interferon and ribavirin or placebo.*
19. *Perrone C, Carrat F, Banisadr F, Morand P, et al. ANRS HCO2-ribavic.A Randomized controlled trials of Pegylated Interferon alfa-2b plus ribavirin versus interferon alfa-alfa2b plus ribavirin as primary treatment of chronic hepatitis C in HIV-coinfected patients. Hepatology 2002, 36:283.*
20. *Moya J, Aranzabal L, Casado L, et al. HAART-associated hepatotoxicity in HIV/HCV Co-infected patients: correlation with liver histologic Stage. 11th Conference on Retrovirus and Opportunistic Infections. Abstract #747*
21. *Poynard T, Marcellin P, Lee SS, et al Randomized Trial of Interferon alfa-2b plus ribavirin for 48 weeks or for 24weeks versus interferon alfa-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352:1426-32.*
22. *Mc Hutchinson JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C.N Engl J Med 1998; 339:1485-92.*
23. *Torriani FJ, Rockstroh J, Dietrich D, et al. Final results of APRICOT: A randomized partially blinded international Trial Evaluating Peg-interferon b+ribavirin vs. interferon-(-2b+ribavirin vs. in the treatment of HCV in HIV/HCV Co-infection.11th Conference on Retrovirus and Opportunistic Infections. Abstract #112LB*
24. *Chung R, Andersen J, Volberding P, et al. A randomized, controlled trial of PEG-interferon-(-2b plus Ribavirin vs. Interferon-(-2b plus ribavirin for chronic hepatitis C virus infection in HIV Co-infected persons: follow up results of ACTG A5071. 11th Conference on Retrovirus and Opportunistic Infections. Abstract #110LB*
25. *Perrone C, Carrat F, Bani-Sadr F et al. Final results of ANRS HCO2-RIBAVIC: a Randomized Controlled Trial of Pegilated-*

*Interferon-(-2b plus Ribavirin vs. Interferon-(-2b plus Ribavirin for the initial treatment of chronic hepatitis C in HIV co-infected patients 11th Conference on Retrovirus and Opportunistic Infections. Abstract #117LB*

26. *Soriano V, Camino N, Pérez M, et al. Hepatitis C Virus RNA clearance in HIV co-infected patients with chronic hepatitis C treated with pegylated interferon plus ribavirin. 11th Conference on Retrovirus and Opportunistic Infections. Abstract 819.*
27. *Hopkins S, Lyons F, Brannig E, et al. Tolerability of pegylated interferon and ribavirin in the HIV/HCV co-infected population. In XIV World AIDS Conference. Barcelona, Spain, 7-12 July 2002abstract ThPeC7531.*
28. *Rockstroh J, Schulz C, Mauss S, et al. Pegylated Interferon-alfa and ribavirin therapy for hepatitis C in HIV-coinfected patients: 24 weeks results. In XIV World AIDS Conference. Barcelona, Spain, 7-12 July 2002abstract wePeB6025.*

## Summary

In the past few years, significant advances have been made in the treatment of HCV infection. The combination of pegylated interferon plus ribavirin has significantly increased the percentage of patient achieving a sustained virologic response (SVR) from less than 10% to more than 50%. These improved success was reported in two large studies involving HCV monoinfected patients in which pegylate interferon plus ribavirin was compared to treatment with standard interferon plus ribavirin.

Since highly active antiretroviral therapy (HAART) became widely available in 1996, morbidity and mortality related to HIV infection have remarkably declined. However, the proportion of patients suffering morbidity or mortality related to liver disease, much of it related to chronic HCV, has risen significantly. Studies have demonstrated that HIV/HCV confected patients are at a higher risk of cirrhosis, end stage liver disease, hepatocellular carcinoma and extra hepatic manifestation of HCV. Factors that may contribute to these higher rates of HCV-related complications include: higher baseline HCV viral loads, continued Alcohol abuse, CD4 count <200 cells/mmm3, and liver toxicities from certain antiretroviral therapies.

On February 2004 the results at 72 weeks of the three largest studies conducted to evaluate the pegylate interferon and ribavirin treatment in HIV/HCV co infected patients were presented at the 11th CROI,. These results indicate a high rate of response, especially in patients with the more difficult to treat HCV genotype 1. It should be noted, however, that rates of response seen in those trials were lower than those seen in the HCV-mono-infected patients, indicating that the presence of HIV infection compromises the efficacy of HCV treatment even in patients with relatively high CD4 counts.

While HCV treatment is cumbersome for physicians and patients, it may provide a significant improvement in the health of HIV-HCV co-infected patients. Improved outcomes and better responses to therapy are likely to result from improving awareness among patients, medical education and psychosocial supports.

# Leucoencefalopatía multifocal progresiva*

**Iñigo Corral Corral†, Carmen Quereda Rodríguez-Navarro‡**

## Resumen

*La leucoencefalopatía multifocal progresiva (LMP) es una enfermedad desmielinizante del sistema nervioso central causada por la infección de oligodendrocitos por parte del virus JC (VJC), un virus ADN de la familia de los poliomavirus (1, 2). Aunque más del 80% de los adultos padece una infección asintomática por el VJC, definida por la presencia de anticuerpos frente al virus (3), la LMP sólo se desarrolla en pacientes con alteración de la inmunidad celular, y únicamente en una minoría de ellos.*

*Con la epidemia del sida, la incidencia de LMP, antaño una enfermedad muy rara, se multiplicó hasta 20 veces (4). Esta enfermedad puede afectar al 4% de los pacientes con sida, y en la actualidad hasta el 90% de los casos de LMP se asocian a la infección por el HIV (4). La incidencia de LMP en los pacientes con otras patologías asociadas a una alteración de la inmunidad celular, como enfermedades malignas hematológicas y transplantes, es mucho menor que en el sida: 0,07% frente a 5,1% en un estudio (5).*

## Patogenia

En la mayor parte de los individuos sanos, la infección por el VJC permanece activa de forma crónica, tal como se demuestra por la excreción crónica del virus en orina, detectable mediante técnicas de reacción en cadena de la polimerasa (PCR) (6). La respuesta inmunitaria específica frente al virus en los individuos sanos podría tolerar su replicación en algunos tejidos, como el riñón, pero no en el cerebro (6). Se desconoce cuál es el mecanismo de reactivación del virus que produce la LMP (2).

Sin embargo, en situaciones de inmunosupresión, la pérdida de linfocitos específicos que controlan la infección activa o la replicación vírica parece desempeñar un papel decisivo. En pacientes con infección por el HIV y LMP activa no se observa una respuesta específica al VJC por parte de las células T CD4+, con lo que tampoco existe una respuesta específica efectiva de los linfocitos T CD8+ citotóxicos (6). En estas condiciones

**Reproducido con la autorización exclusiva de TTM Cyber Journal AIDS.* *†Servicio de Neurología. ‡Servicio de Enfermedades Infecciosas. Hospital Ramón y Cajal, Madrid. España.*

podría permitirse la replicación y diseminación de cepas de VJC patogénicas, y la infección del sistema nervioso central por parte de éstas.

Las cepas de virus encontradas en cerebros de pacientes con LMP presentan reordenamientos y mutaciones en la región reguladora del ADN vírico (TCR, región de control de transcripción) que parecen desempeñar un papel patogénico (7). Estos mismos reordenamientos de las TCR se observan también en los linfocitos plasmáticos de los pacientes con LMP, pero no en su orina, donde sólo se detectan formas arquetípicas (sin reordenamientos) y no patogénicas del VJC (8). Esto indica que los reordenamientos se producirían fundamentalmente en la médula ósea y en otros órganos linfoides. Por diseminación hematógena, el virus puede infectar el sistema nervioso central y otros órganos. En pacientes con LMP, se detecta ADN del VJC en linfocitos de sangre periférica en el 75% de los casos, frente a sólo el 10% de los pacientes con sida sin LMP. Estos linfocitos circulantes atravesarían la barrera hematoencefálica y a partir de ellos se infectarían las células gliales (3).

El VJC infecta específicamente células gliales (astrocitos y oligodendrocitos) debido a la presencia en ellas de proteínas de transcripción específicas (2). La infección y lisis de los oligodendrocitos producen la desmielinización del sistema nervioso central. Recientemente, se ha demostrado por primera vez la infección activa de neuronas por el VJC en un paciente con LMP (9). Mediante hibridación in situ e inmunohistoquímica se detectó una infección productiva de células granulares del cerebelo que condicionaba una pérdida neuronal y, clínicamente, un síndrome cerebeloso, en ausencia de desmielinización a ese nivel. Se desconoce la incidencia de estos hallazgos y la repercusión que pueden tener en las manifestaciones clínicas de la mayoría de los pacientes con LMP.

Se ignoran los factores que pueden condicionar un mayor riesgo de LMP en pacientes con sida frente a otros pacientes inmunodeprimidos. La inflamación resultante de la infección por el HIV del sistema nervioso central facilita la entrada de los linfocitos B infectados por el VJC en este sistema nervioso y activa la replicación del VJC (1). El herpesvirus humano 6 (HHV-6) puede ser un cofactor en el desarrollo de la LMP (10).

## Anatomía patológica

Desde el punto de vista macroscópico, la LMP se caracteriza por la presencia de lesiones desmielinizantes, que pueden ser únicas o múltiples, así como de tamaño muy variable (desde 1 mm a varios centímetros). Las lesiones de mayor tamaño se forman por la confluencia de otras menores. Estas lesiones se pueden localizar en cualquier región de la sustancia blanca, tanto supratentorial como infratentorial, o incluso en la médula espinal. Podría existir una predilección por las regiones parietooccipitales. Es frecuente la afectación de tronco o cerebelo, en algunos casos de forma aislada. En ocasiones puede quedar afectada la sustancia gris.

Las alteraciones microscópicas características son la presencia de desmielinización, oligodendrocitos con núcleos hipercromáticos y agrandados, y astrocitos anómalos y grandes, con núcleos hipercromáticos y lobulados (1). En la microscopia electrónica pueden verse los viriones en los núcleos de los oligodendrocitos, bien de forma aislada o en formaciones cristalinas. La presencia de ADN vírico o proteínas del VJC en los oligodendrocitos se demuestra mediante hibridación o PCR in situ, o mediante inmunohistoquímica, respectivamente. La reacción inflamatoria en las lesiones suele ser escasa o nula. Sin embargo, en algunos pacientes existe una respuesta inflamatoria prominente, con infiltrados mononucleares de predominio perivascular, que se asocia a un mejor pronóstico (11).

## Manifestaciones clínicas

Desde el punto de vista clínico, la LMP se presenta como un cuadro neurológico focal de curso subagudo. Con frecuencia constituye la primera manifestación del sida (47% de los casos) (12). Las manifestaciones iniciales más frecuentes son, según las series, paresia de extremidades, alteraciones cognitivas y síntomas visuales (1, 12). En el curso de la enfermedad, aparece paresia de extremidades en la mayoría de los pacientes. Los trastornos cognitivos que pueden desarrollarse son muy variados. Asociado a otros síntomas focales se produce un deterioro mental en el que pueden notarse alteraciones de memoria, de atención, de cálculo o de conducta (1). Muy rara vez se produce demencia aislada sin síntomas focales. Pueden aparecer alteraciones neurooftalmológicas en el 50% de los pacientes: hemianopsia, ceguera cortical o alteración de la movilidad ocular. Otros síntomas focales son: alteraciones sensitivas, afasia, ataxia de la marcha o de extremidades, y síntomas extrapiramidales. Se han descrito casos aislados de síndrome de Gertsmann o de Balint. Son raras las crisis epilépticas, que pueden presentarse como epilepsia parcial continua.

## Diagnóstico

En el contexto clínico, los estudios de neuroimagen constituyen el apoyo fundamental para sospechar el diagnóstico. En la tomografía computarizada (TC), las lesiones características son hipodensas, sin efecto masa y sin captación de contraste, de localización periventricular o subcortical (12). Las lesiones subcorticales pueden tener una forma geográfica como consecuencia de la afectación de las fibras en U. La resonancia magnética nuclear (RMN) es más sensible que la TC para mostrar las lesiones. Las lesiones son hiperintensas en imágenes ponderadas en T2, e hipointensas en imágenes en T1. La captación de contraste es una excepción (5%-10% de los casos), y cuando sucede, es débil y periférica (12).

La espectroscopia por RMN muestra un patrón característico que puede ser útil en el diagnóstico de la LMP: se objetiva un descenso de N-acetilaspartato y un incremento de colina y lípidos, así como un incremento de mio-inositol, como consecuencia de la pérdida neuronal, la ruptura de membranas y la proliferación glial (13). La RM con transferencia de magnetización también puede ayudar al diagnóstico, al presentar las lesiones de LMP una relación de transferencia de magnetización más reducida que la desmielinización por el HIV (14). En la tomografía por emisión de fotón único (SPECT) lo habitual que es que no haya captación.

El líquido cefalorraquídeo (LCR) puede ser normal o mostrar una discreta elevación de proteínas. Puede detectarse proteína básica de mielina en el LCR. Los parámetros inmunológicos en el LCR (IgG, índice de IgG, índice de Tourtelotte, bandas oligoclonales) no muestran ningún patrón específico en la LMP.

Hasta hace poco, la confirmación del diagnóstico de LMP se basaba exclusivamente en la demostración de las alteraciones anatomopatológicas características y en el hallazgo del VJC en el cerebro mediante biopsia cerebral o en autopsia. Para demostrar la existencia de VJC en muestras patológicas, la inmunocitoquímica y la hibridación in situ tienen un valor diagnóstico similar. Dado que la biopsia cerebral es un procedimiento cruento, y considerando el mal pronóstico de la enfermedad hasta hace pocos años, el diagnóstico se ha establecido frecuentemente de forma presuntiva por clínica y radiología, ya que el diagnóstico por biopsia no aportaba beneficios para el paciente (15).

Numerosos estudios realizados en los últimos 12 años han puesto de manifiesto la utilidad de la demostración del ADN del virus JC en LCR para el diagnóstico de la leucoencefalopatía multifocal progresiva (16). Los resultados han variado mucho en las diferentes investigaciones por diferencias en la metodología, bien en lo que respecta a los criterios diagnósticos usados, bien en cuanto a la técnica de PCR utilizada. En los estudios iniciales, la sensibilidad de esta técnica fue baja (12%-30%). Sin embargo, en los trabajos posteriores, la sensibilidad ha estado siempre por encima del 65%, con una especificidad comprendida entre el 90% y 100%. Los valores predictivos positivo y negativo se han situado entre el 88%-100% y 88,5%-95%, respectivamente. Cuando el diagnóstico de LMP se ha basado en la clínica, sin confirmación histológica, la sensibilidad ha descendido hasta el 42%. Con el grado habitual de detección de las técnicas usadas (entre 10 y 100 genomas del VJC), la sensibilidad rara vez es mayor del 75%. Con una técnica capaz de detectar un solo genoma del VJC, la sensibilidad alcanzó el 92%, pero a costa de reducir la especificidad al 92%. Esta sensibilidad relativamente baja puede deberse a que el VJC es estrictamente intracelular, por lo que pudiera existir una liberación muy escasa de viriones en LCR. Se ha visto que la probabilidad de obtener un resultado positivo es mayor cuando el LCR se extrae poco antes del fallecimiento, lo que sugiere que en estadios avanzados de la enfermedad podrían liberarse más virus al LCR, probablemente en relación con la extensión de las lesiones desmielinizantes.

Dado el alto valor predictivo positivo de la PCR en LCR, el diagnóstico de la LMP puede basarse en esta técnica, evitando la necesidad de realizar una biopsia cerebral (16). Utilizando criterios clínico-radiológicos junto con un resultado positivo de la PCR, la probabilidad de diagnosticar correctamente la LMP llega hasta el 99% (17). Sin embargo, un resultado negativo no permite excluir el diagnóstico en un 20% a 30% de los casos, si bien la realización de estudios repetidos de LCR puede aumentar la sensibilidad.

## Diagnóstico diferencial

El diagnóstico diferencial de la LMP incluye muchas otras posibles causas de leucoencefalopatía en pacientes con infección por el HIV. La leucoencefalopatía asociada al complejo demencia-sida es el cuadro que da lugar con más frecuencia a confusión con la LMP. El cuadro clínico presenta un curso más insidioso, con alteraciones cognitivas (raras de forma aislada en la LMP), y habitualmente sin signos focales. En la neuroimagen, la leucoencefalopatía por el HIV, a diferencia de la LMP, suele ser isointensa en RMN potenciada en T1 y no suele afectar a regiones subcorticales. Es raro que la leucoencefalopatía por el HIV afecte a la fosa posterior, hecho frecuente en la LMP, aunque se ha

descrito algún caso de leucoencefalopatía infratentorial asociada a la infección por el HIV.

Otros tipos de leucoencefalopatía que pueden ser muy similares a la LMP desde el punto de vista clínico y radiológico son la asociada a virus varicela zoster (VVZ) y la leucoencefalopatía recurrente similar a la esclerosis múltiple (18). Aunque descrita fundamentalmente en etapas precoces de la infección por el HIV, esta enfermedad similar a la esclerosis múltiple puede afectar también a pacientes con inmunosupresión avanzada. Deben incluirse también en el diagnóstico diferencial la encefalitis por citomegalovirus, la leucoencefalopatía por inhalación de heroína, los accidentes cerebrovasculares isquémicos y los astrocitomas de bajo grado.

## Pronóstico

La LMP progresa hasta la muerte en una media de cuatro meses. Una cifra de CD4 baja se asocia a una supervivencia más corta (19). No obstante, existe un porcentaje de pacientes que presenta estabilización o mejoría clínica espontánea, con prolongación de la supervivencia, e incluso con remisión completa. Estos pacientes han representado el 10% de los casos de LMP atendidos por algún autor (1). Los pacientes con supervivencia prolongada presentan un recuento de CD4 mayor que el resto, algunos con CD4 mayores de 300; en ellos, la LMP es más a menudo la primera manifestación de sida, presentan con más frecuencia captación de contraste en las pruebas de imagen (como reflejo de una mayor reacción inflamatoria en la anatomía patológica) y pueden tener remisiones parciales clínicas o radiológicas (11). La presencia de afectación de tronco o cerebelo es un factor de mal pronóstico.

La determinación de la carga viral del VJC en LCR mediante PCR cuantitativa puede tener valor pronóstico en la LMP. La carga viral baja del VJC se ha correlacionado con una mayor supervivencia (20-22). La cifra de 50-100 copias/_l podría ser el punto de corte más predictivo de mayor o menor supervivencia (20).

## LMP y tratamiento antirretroviral

Aunque se han comunicado casos de LMP con aparente mejoría con zidovudina (AZT), la experiencia general con monoterapia antirretroviral no ha sido satisfactoria. Desde la introducción del tratamiento antirretroviral de gran actividad (TARGA), la supervivencia de los pacientes con LMP ha aumentado significativamente (23-27). Las diferencias en cuanto a supervivencia en los pacientes tratados y no tratados con TARGA han sido llamativas: 545 y 60 días respectivamente en un estudio (26). Muchos pacientes han mejorado o se han estabilizado desde el punto de vista clínico, considerándose la enfermedad en remisión o inactiva. Sin embargo, algunos autores no han hallado una mayor supervivencia en los pacientes tratados con TARGA (19). Las lesiones en RMN se estabilizan o mejoran en la mayoría de los pacientes que reciben TARGA (26). En aquéllos con LMP que sobreviven con TARGA, este tratamiento restaura la respuesta específica de las células CD4+ al VJC (6).

A pesar de prolongar la supervivencia, la eficacia del TARGA en la LMP es limitada. En muchos pacientes no se produce una recuperación del daño neurológico establecido (25). En una revisión reciente de 118 pacientes tratados con TARGA, un tercio falleció en una media de 14 semanas y la mitad de los supervivientes no presentó una mejoría neurológica tras un seguimiento de 114 semanas (24). Se han identificado algunos factores que influyen en la respuesta de la LMP al TARGA. Una cifra de CD4 inicial menor de 100 células/ml se asocia a una mayor mortalidad (24). La carga viral alta del VJC en LCR en el momento del diagnóstico también es un factor de mal pronóstico para la respuesta al TARGA (28). Por el contrario, la reducción de la detección por PCR y la negativización de la carga viral del VJC mediante PCR cuantitativa en LCR se asocian a la prolongación de la supervivencia en pacientes tratados con TARGA (21, 26).

## LMP como síndrome de reconstitución inmunológica

Muchos pacientes han presentado LMP al poco tiempo de iniciar el TARGA, coincidiendo con una reducción de la carga viral del HIV y con una elevación de la cifra de linfocitos CD4+ (29, 30). Estos pacientes pueden representar casi el 20% de los casos de LMP de diagnóstico reciente (29). En otros casos, pacientes con diagnóstico previo de LMP han sufrido un deterioro neurológico al introducirse el TARGA. Este deterioro puede preceder a una mejoría neurológica subsiguiente, pero a veces es fatal (31, 32). En todos estos casos existe un componente inflamatorio aumentado en las pruebas de neuroimagen, con captación de contraste en las lesiones. Estos casos se han considerado cuadros de reconstitución inmunológica. Así, mientras que el TARGA eficaz iniciado de forma precoz se considera indispensable para la mejoría de los pacientes con LMP, se puede dar la paradoja de que esto resulte fatal para algunos pacientes por motivos que aún se desconocen.

## Otros tratamientos

Ningún fármaco ha demostrado ser eficaz en ensayos clínicos aleatorizados sobre el tratamiento de la LMP. En estos pacientes se han evaluado como opciones terapéuticas la citarabina, el interferón alfa, el cidofovir y el topotecán.

Los resultados del tratamiento con citarabina (arabinósido de citosina, Ara-C) han sido muy variables. En el estudio del AIDS Clinical Trial Group, en el que se comparaban el tratamiento con citarabina por vía intravenosa o intratecal asociada a tratamiento antirretroviral -el estudio es anterior a los inhibidores de la proteasa- frente a tratamiento antirretroviral solo, no se encontraron diferencias en cuanto a la supervivencia entre los tres grupos. El estudio se interrumpió cuando se habían reclutado 60 pacientes. Según los datos del estudio, el efecto de la citarabina en la LMP es muy pequeño o bien es inexistente (33). Otra serie de 27 pacientes se trató con citarabina intratecal, asociada en algunos casos a tratamiento intravenoso, junto con terapia antirretroviral en la mayoría de los pacientes. La mayor parte de ellos progresaron, con una supervivencia media de 60 días (34).

El tratamiento con interferón alfa, que ejerce un efecto antivírico probablemente por la activación de las células natural killer, no produjo ninguna mejoría neurológica en 17 pacientes tratados en un estudio abierto (35).

El topotecán (camptotecina) es un antitumoral inhibidor de la topoisomerasa tipo I. Se ha demostrado que inhibe la replicación tanto del VJC como del propio HIV, y atraviesa bien la barrera hematoencefálica. En un estudio piloto, 4 de 12 pacientes tratados con topotecán y TARGA mejoraron (36).

Se han descrito casos aislados de mejoría con cidofovir, un fármaco con actividad frente a poliomavirus in vitro. Sin embargo, en muchos de estos casos, el cidofovir se añadió a TARGA tras una aparente falta de respuesta inicial, y no se puede descartar una respuesta tardía a TARGA. Un estudio abierto reciente con 24 pacientes concluyó que el cidofovir no prolongaba la supervivencia más allá de lo previsto por la historia natural de la LMP (37).

## Bibliografía

1. *Berger, J.R., Gallo, B.V., Concha, M. Progressive multifocal leukoencephalopathy. En: Berger, J.R., Levy, R.M. (Ed.). AIDS and the nervous system. Lippincott-Raven, Philadelphia 1997; 569-594.*
2. *Seth, P., Díaz, F., Major, E.O. Advances in the biology of JC virus and induction of progressive multifocal leukoencephalopathy. J Neurovirol 2003; 9: 236-246.*
3. *Major, E.O., Amemiya, K., Tornatore, C., Houff, S., Berger, J. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev 1992; 5: 49-73.*
4. *Holman, R.C., Torok, T.J., Belay, E.D., Janssen, R.S., Schonberger, L.B. Progressive multifocal leukoencephalopathy in the United States, 1979-1994: Increased mortality associated with HIV infection. Neuroepidemiology 1998; 17: 303-309.*
5. *Power, C., Gladden, J.G., Halliday, W. y cols. AIDS and non-AIDS-related PML association with distinct p 53 polymorphism. Neurology 2000; 54: 743-746.*
6. *Gasnault, J., Kahraman, M., de Goer de Herve, M.G. y cols. Critical role of JC virus-specific CD4 T-cell responses in preventing progressive multifocal leukoencephalopathy. AIDS 2003; 17:v1443-1449.*
7. *Atwood, W.J. Genotypes, archetypes, and tandem repeats in the molecular epidemiology and pathogenesis of JC virus induced disease. J Neurovirol 2003; 9: 519-521.*
8. *Fedele, C.G., Ciardi, M.R., Delia, S. y cols. Identical rearranged forms of JC polyomavirus transcriptional control region in plasma and cerebrospinal fluid of acquired immunodeficiency syndrome patients with progressive multifocal leukoencephalopathy. J Neurovirol 2003; 9: 551-558.*
9. *Du Pasquier, R.A., Corey, S., Margolin, D.H. y cols. Productive infection of cerebellar granule cell neurons by JC virus in an HIV+ individual. Neurology 2003; 61: 775-782.*
10. *Mock, D.J., Powers, J.M., Goodman, A.D. y cols. Association of human herpesvirus 6 with the demyelinative lesions of progressive multifocal leukoencephalopathy. J Neurovirol 1999; 5: 363-373.*
11. *Berger, J.R., Levy, R.M., Flomenhoft, D., Dobbs, M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. Ann Neurol 1998; 44: 341-349.*
12. *Whiteman, M.L., Post, M.J., Berger, J.R., Tate, L.G., Bell, M.D., Limonte, L.P. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: Neuroimaging with clinical and pathologic correlation. Radiology 1993; 187: 233-240.*
13. *Iranzo, A., Moreno, A., Pujol, J. y cols. Proton magnetic resonance spectroscopy pattern of progressive multifocal leukoencephalopathy in AIDS. J Neurol Neurosurg Psychiatry 1999; 66: 520-523.*
14. *Ernst, T., Chang, L., Witt, M. y cols. Progressive multifocal leukoencephalopathy and human immunodeficiency virus-associated white matter lesions in AIDS: Magnetization transfer MR imaging. Radiology 1999; 210: 539-543.*
15. *Karahalios, D., Breit, R., Dal Canto, M., Levy, R.M. Progressive multifocal leukoencephalopathy in patients with HIV infection: Lack of impact of early diagnosis by stereotaxic brain biopsy. J Acquir Immune Defic Syndr 1992; 5: 1030-1038.*
16. *Cinque, P., Scarpellini, P., Vago, L., Linde, A., Lazzarin, A. Diagnosis of central nervous system complications in HIV-infected patients: Cerebrospinal fluid analysis by polymerase chain reaction. AIDS 1997; 11: 1-17.*
17. *Antinori, A., Ammassari, A., De Luca, A. y cols. Diagnosis of AIDS-related focal brain lesions: A decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. Neurology 1997; 48: 687-694.*

18. Berger, J.R., Tornatore, C., Major, E.O. y cols. Relapsing and remitting human immunodeficiency virus-associated leukoencephalomyelopathy. Ann Neurol 1992; 31: 34-38.

19. Enting, R.H., Portegies, P. Cytarabine and highly active antiretroviral therapy in HIV-related progressive multifocal leukoencephalopathy. J Neurol 2000; 247: 134-138.

20. Yiannoutsos, C.T., Major, E.O., Curfman, B. y cols. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. Ann Neurol 1999; 45: 816-821.

21. De Luca, A., Giancola, M.L., Ammassari, A. y cols. The effect of potent antiretroviral therapy and JC virus load in cerebrospinal fluid on clinical outcome of patients with AIDS-associated progressive multifocal leukoencephalopathy. J Infect Dis 2000; 182: 1077-1083.

22. García de Viedma, D., Díaz Infantes, M., Miralles, P. y cols. JC virus load in progressive multifocal leukoencephalopathy: Analysis of the correlation between the viral burden in cerebrospinal fluid, patient survival, and the volume of neurological lesions. Clin Infect Dis 2002; 34: 1568-1575.

23. Antinori, A., Cingolani, A., Lorenzini, P. y cols. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: Data from the Italian Registry Investigative Neuro AIDS (IRINA). J Neurovirol 2003; 9(Supl. 1): 47-53.

24. Berenguer, J., Miralles, P., Arrizabalaga, J. y cols. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. Clin Infect Dis 2003; 36: 1047-1052.

25. Gasnault, J., Taoufik, Y., Goujard, C. y cols. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. J Neurovirol 1999; 5: 421-429.

26. Miralles, P., Berenguer, J., García, V. y cols. Treatment of AIDS-associated progressive multifocal leukoencephalopathy with highly active antiretroviral therapy. AIDS 1998; 12: 2467-2472.

27. Clifford, D.B., Yiannoutsos, C., Glicksman, M. y cols. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. Neurology 1999; 52: 623-625.

28. Taoufik, Y., Delfraissy, J.F., Gasnault, J. Highly active antiretroviral therapy does not improve survival of patients with high JC virus load in the cerebrospinal fluid at progressive multifocal leukoencephalopathy diagnosis. AIDS 2000; 14: 758-759.

29. Cinque, P., Bossolasco, S., Brambilla, A.M. y cols. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: Study of 43 cases with review of the literature. J Neurovirol 2003; 9(Supl. 1): 73-80.

30. Hoffmann, C., Horst, H.A., Albrecht, H., Schlote, W. Progressive multifocal leukoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry 2003; 74: 1142-1144.

31. Miralles, P., Berenguer, J., Lacruz, C. y cols. Inflammatory reactions in progressive multifocal leukoencephalopathy with highly active antiretroviral therapy. AIDS 2001; 15: 1900-1902.

32. Safdar, A., Rubocki, R.J., Horvath, J.A., Narayan, K.K., Waldron, R.L. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: Impact of antiretroviral therapy-associated immune reconstitution. Clin Infect Dis 2002; 35: 1250-1257.

33. Hall, C., Dafni, U., Simpson, D. y cols. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. N Engl J Med 1998; 338: 1345-1351.

34. De Luca, A., Giancola, M.L., Cingolani, A. y cols. Clinical and virological monitoring during treatment with intrathecal cytarabine in patients with AIDS-associated progressive multifocal leukoencephalopathy. Clin Infect Dis 1999; 28: 624-628.

35. Berger, J.R., Pall, L., McArthur, J. y cols. A pilot study of recombinant alpha-2a interferon in the treatment of AIDS - related progressive multifocal leukoencephalopathy. Neurology 1992; 42(Supl. 3): 257.

36. Royal, W., Dupont, B., McGuire, D. y cols. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. J Neurovirol 2003; 9: 411-419.

37. Marra, C.M., Rajicic, N., Barker, D.E. y cols. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. AIDS 2002; 16: 1791-1797.

## Summary

Progressive multifocal leucoencephalopathy (PML) is a demyelinating disease that affects the central nervous system and results from an infection of oligodendrocytes by the JC virus (JCV), an DNA virus of the polyomavirus family (1, 2). Although over 80% of the adults suffer an asymptomatic JCV infection, defined by the presence of virus antibodies (3), PML does only develop in patients with cellular immunity alterations and only in a small number of them.

After the aids epidemic, the incidence of PML -which was formerly a very rare disease- became twenty times greater (4). The disease can affect 4% of the aids patients and, currently, 90% of the PML cases are associated with HIV infections (4). The incidence of PML in patients with other pathologies related to alterations in cellular immunity, such as malign haematological diseases and transplants, is far lower than in aids: 0.07% as compared with 5.1%, according to a study (5).

# Abstracts seleccionados
# 11th Conference on Retroviruses and Opportunistic Infections

**February 8-11, 2004 - San Francisco, CA, USA**

## 23 - Effect of Treatment during versus after Acute Retroviral Syndrome (ARS) on HIV Viral Load and CD4 Cell Counts within 3 Years of Infection

**N Voirin*[1], D Smith[2], J P Routy[3], M Legault[3], D Baratin[4], C Trepo[1,5], L Cotte[5], J M Livrozet[4], J L Touraine[4], D A Cooper[2], A Gayet-Ageron[4], J Ritter[4], J Fabry[4], and P Vanhems[1,4]**

**[1]INSERM U271, Lyon, France; [2]Univ. of New South Wales, Sydney, Australia; [3]McGill Univ., Montreal, Canada; [4]Edouard Herriot Hosp., Lyon, France; and [5]Hotel Dieu Hosp., Lyon, France**

**Background:** Starting antiretroviral therapy (ART) during ARS might influence immediate immunological response and control of virological replication but it is unknown if this benefit persists over time. We therefore compared the HIV viral load and the CD4 cell counts at different time points from the initiation of ART among patients treated during or treated after ARS.

**Methods:** Data from patients enrolled from 1995 to 2003 in 3 prospective primary HIV infection cohorts with similar follow-up (Lyon, Montreal, and Sydney) were analyzed. We compared mean HIV viral load and CD4 counts at initiation of therapy, 6 months and 1, 2, and 3 years after start of therapy between patients with documented ARS treated during or after ARS, using Kruskal-Wallis rank sum test.

**Results:** Of a total of 203 patients, 188 (93%) were male, mean age 34.5 years. The presumed route of HIV infection was men who had sex with men for 148 (73%), heterosexual contact for 21 (10%), and injecting drug use for 33 (16%). ART was started after ARS for 117 (58%) (Gr1), during ARS for 51 (25%) (Gr2), and 35 (17%) received no therapy during the follow-up (Gr0). The mean time between onset of ARS and start of therapy was 164 days for Gr1 and 27 days (p = 0.001) for Gr2. No difference was observed between the 3 groups for gender (p = 0.65) and age (p = 0.47). The table shows the HIV viral load and CD4 count for each group at the various time points. Similar results persist after adjustment on ARS severity score.

| Time from start of therapy | Mean $\log_{10}$ HIV RNA | | | | | Mean CD4 count/mm$^3$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Gr0 | Gr1 | Gr2 | $p_1$* | $p_2$** | Gr0 | Gr1 | Gr2 | $p_1$ | $p_2$ |
| Baseline | 4.63 | 4.27 | 4.58 | 0.11 | 0.06 | 697 | 540 | 621 | 0.10 | 0.05 |
| 6 months | 3.91 | 1.97 | 1.78 | <0.01 | 0.40 | 538 | 662 | 722 | 0.01 | 0.30 |
| 1 year | 4.24 | 2.13 | 1.73 | <0.01 | 0.26 | 567 | 657 | 721 | 0.11 | 0.14 |
| 2 years | 3.84 | 2.34 | 2.28 | 0.03 | 0.57 | 468 | 764 | 694 | 0.04 | 0.76 |
| 3 years | 4.77 | 1.01 | 1.70 | 0.10 | 0.09 | 380 | 938 | 693 | 0.27 | 0.82 |

## 38 - HIV Resistance and Transmission following Single-dose Nevirapine in a PMTCT Cohort

**N Martinson*[1,2,3], L Morris[1,2,3], G Gray[1,2], D Moodley[4], P Lupondwana[1,2], C Chezzi[1,2], S Cohen[1], C Pillay[1,2], A Puren[1], M Ntsala[1], J Sullivan[5], J Steyn[2], and J McIntyre[2]**

**[1]Natl. Inst. for Communicable Diseases, Johannesburg, South Africa; [2]Perinatal HIV Res. Unit, Johannesburg, South Africa; [3]Sch. of Med., Johns Hopkins Univ., Baltimore, MD, USA; [4]King Edward Hosp., Durban, South Africa; and [5]Univ. of Massachusetts Med. Sch., Worcester, USA**

Background: Nevirapine (NVP), given to mothers in labor and to neonates within 72 hours of delivery, is an effective, simple PMTCT regimen. Previous studies have shown that transient resistance develops in those exposed to this regimen. This study was designed to assess genotypic resistance induced by NVP (NVPR).

Methods: We enrolled 623 HIV-infected mothers at 2 tertiary hospitals in South Africa from 32 to 38 weeks' gestation. We report preliminary findings on baseline and follow-up visits scheduled at 6 weeks postpartum. High-level NVPR was defined as K103N, V106A/M, Y181C, YI88C, and G190A.

Results: The median CD4 and viral load of pregnant women was 393 x$10^6$/l (IQR 266 to 585) and 28 700 copies/mL (IQR 6560 to 100,000). No drug naïve women had resistance at baseline; 456 were followed at a median time of 7.0 weeks postpartum (IQR 6.3 to 10.3); all but 4 were clade C; 38.8% (95%CI: 34 to 44) of mothers and 42.4% (95%CI: 30 to 55) of their infants were found to have NVPR. Maternal resistance in the first (4 to 6 weeks postpartum), second (6 to 7 weeks), third (7 to 10 weeks), and fourth quartiles (10 to 36 weeks) of the follow-up visit was 43%, 44%, 44%, and 24%, respectively (test for trend p = 0.006). Maternal mutations included K103N (31%), Y181C (12%), and Y188C (8.1%); 21% had a single mutation, 13% had 2, and 5%, 3 or 4 mutations. Infants' mutations included Y181C (32%), K103N (12%) and Y188C (5%). The 10-week HIV MTCT rate was 8.6% (95%CI: 6.0 to 11.2). There was an association between postpartum NVPR and transmission (OR 2.9, 95%CI: 1.4 to 6.1) confounded by maternal viral load and CD4 count. Baseline CD4, log baseline viral load, the time from labor NVP dose to the postpartum blood draw and the total number of times a mother took NVP in her pregnancy were statistically significantly associated with development of resistance.

Conclusions: Maternal and infant resistance induced by NVP is high. Its effect on subsequent pregnancies and choice of HAART regimen remains to be explored.

ActualizaciónesOnline

## 39 - Low-frequency NNRTI-resistant Variants Contribute to Failure of Efavirenz-containing Regimens

**J Mellors*[1], S Palmer[2], D Nissley[2], M Kearney[2], E Halvas[1], C Bixby[1], L Demeter[3], S Eshleman[4], K Bennett[5], S Hart[6], F Vaida[5], M Wantman[5], J Coffin[2], and S Hammer for the ACTG 398 Study Group[7]**

**[1]Univ. of Pittsburgh, PA, USA; [2]Drug Resistance Prgm., NCI, NIH, DHHS, Frederick, MD, USA; [3]Univ. of Rochester, NY, USA; [4]Johns Hopkins Univ., Baltimore, MD, USA; [5]Harvard Sch. of Publ. Hlth., Boston, MA, USA; [6]Frontier Sci. and Technology Res. Fndn., Amherst, NY, USA; and [7]Columbia Univ., New York, NY, USA**

Background: The role of minor (low-frequency) drug-resistant variants in failure of antiretroviral therapy is not defined. In ACTG 398, 212 NNRTI-experienced and 269 NNRTI-naïve patients were randomized to efavirenz (EFV), abacavir, adefovir, and amprenavir plus a second PI or placebo. This allowed us to examine relations between NNRTI experience, NNRTI resistance, virologic response, and emergence of EFV resistance.

Methods: Baseline genotypes were obtained in 452/481 patients by a standard (ViroSeq v2.0). Minor NNRTI-resistant variants were sought with single genome RT-PCR and sequencing (SGS) and a Ty1/HIV-1 RT yeast system that detects EFV-resistant colonies. Phylogenetic analyses were performed with the neighbor joining method.

Results: Virologic failure was associated with NNRTI experience ($p < 0.001$), baseline NNRTI mutations ($p < 0.001$), and development of EFV resistance ($p < 0.001$). Standard genotype did not identify NNRTI mutations in baseline samples from 48 (22%) NNRTI-experienced patients. Virologic response in this group was no better than in the experienced group with baseline NNRTI mutations (n = 166), suggesting that standard genotype was insensitive for NNRTI-resistant variants. Baseline plasma from a random sample of 11 NNRTI-experienced and 12 NNRTI-naïve patients experiencing virologic failure despite negative standard genotypes for NNRTI mutations were assayed for NNRTI-resistant variants. Such variants were identified by SGS in 6/11 NNRTI-experienced patients with the following frequencies per positive patient: 181C and 190A (5/15 sequences); 181C (3/19); 181C (3/22); 108I (2/35); 103N (1/33); and 103N (1/34). By comparison, NNRTI-resistant variants were found in 2/12 NNRTI-naïve patients: 100I and 225L (1/33 sequences each) and 103N (1/41 sequences). The Ty1/HIV-1 RT assay detected EFV-resistant colonies in 8/10 NNRTI-experienced patients with the following frequencies: 7.2, 3.3, 2.8, 1.7, 1.7, 0.9, 0.8, and 0.6%. In NNRTI-naïve patients, resistant colonies were found in only 2/12 patients with frequencies of 0.6% and 0.4%. Phylogenetic analyses showed clustering of the baseline NNRTI-resistant variants identified by SGS with the genotype at virologic failure in 5/6 NNRTI-experienced patients. In the 2 NNRTI-naïve patients, the 103N variant clustered with the failure genotype but the 100I/225L variants did not.

Conclusions: Prior NNRTI expsoure can select minor NNRTI-resistant variants that are missed by standard genotyping and can contribute to failure of EFV-based regimens.

## 41LB - Exposure to Intrapartum Single-dose Nevirapine and Subsequent Maternal 6-Month Response to NNRTI-based Regimens

**G Jourdain*[1], N Ngo-Giang-Huong[1], P Tungyai[2], A Kummee[2], C Bowonwatanuwong[3], P Kantipong[3], P Lechanachai[4], S Hammer[5], M Lallemant[2], and Perinatal HIV Prevention Trial Group**

**[1]Harvard Sch. of Publ. Hlth., Boston, MA, USA; [2]PHPT-Inst. de Recherche pour le Développement, France and Thailand; [3]Ministry of Publ. Hlth., Bangkok, Thailand; [4]Chiang Mai Univ., Faculty of Associated Med. Sci., Thailand; and [5]Columbia Univ. Med. Ctr., New York, NY, USA**

Background: Single-dose nevirapine (SD-NVP) is efficacious in preventing HIV mother-to-child transmission (PMTCT) but resistance mutations to non-nucleoside reverse transcriptase inhibitors (NNRTI) are detectable in the postpartum period in a substantial proportion of mothers. Their clinical significance is unknown.

Methods: Immunocompromized women participating in PHPT2, a randomized trial in Thailand, which showed an 80% decrease in perinatal HIV with the addition of intrapartum NVP to zidovudine prophylaxis, were offered antiretroviral therapy. A 10-day postpartum sample was assessed for RT mutations (ViroSeq HIV-1 Genotyping System; WWW.IASUSA.ORG), first in a random sample of 90 women stratified on CD4 and virus load; and then in all women who subsequently received an NNRTI-based regimen and for whom viral load could be assayed at 3 and/or 6 (+ 1.5) months (Cobas Amplicor HIV-1 v1.5 Roche).

Results: NNRTI-resistance mutations were detectable in 18% of the random sample of women (K103N, G190A, or Y181C). At 3 months, 80% of the 66 women with at least one mutation, 87% of the 112 SD-NVP exposed women with no mutation and 88% of the 41 non exposed women had a viral load $\leq$400 copies/mL (viral load $\leq$50: 45%, 46%, and 54%). At 6 months, 68% of the 50 women with at least one mutation, 80% of the 92 exposed women without mutation and 85% of the 27 non exposed women had a viral load $\leq$400 (p for trend = 0.057) (viral load $\leq$50: 38%, 50%, 74%; p for trend = 0.0034). Of SD-NVP-exposed women without and with mutations who started therapy more than 6 months after delivery, 91% and 77%, had a viral load $\leq$400, vs 69% and 58% of those who started earlier (p = 0.006) (viral load $\leq$50: p = NS).

Conclusions: Mothers exposed to SD-NVP for PMTCT experienced a lower virological success rate of subsequent NNRTI-based therapy compared to non-exposed mothers. However, a clinically meaningful proportion of women still achieved virological success at 6 months even in the presence of mutations. Importantly, later initiation of therapy after NVP exposure was associated with an improved virological response. These results suggest that drug-resistance mutations that arise following SD-NVP exposure have an effect on the efficacy of subsequent NNRTI-based therapies. They also provide insight and demonstrate the necessity for further development of synergistic strategies which will maximize benefit of subsequent antiretroviral therapy for the mother while preserving the remarkable achievements of potent antiretroviral therapy for PMTCT.

## 51 - Poor Virologic Responses and Early Emergence of Resistance in Treatment Naive, HIV-infected Patients Receiving a Once Daily Triple Nucleoside Regimen of Didanosine, Lamivudine, and Tenofovir DF

**J Jemsek*, P Hutcherson, and E Harper**

**Jemsek Clin., Huntersville, NC, USA**

Background: The role of triple nucleoside analog reverse transcriptase inhibitor (NRTI) regimens remains uncertain for patients at various stages of HIV infection. We recently undertook a 24-week pilot study to evaluate the potency and safety of a once-daily regimen of didanosine EC (ddI) 250 mg, lamivudine (3TC) 300 mg, and tenofovir DF (TDF) 300 mg in treatment-naïve patients.

Methods: Patients were considered responders if a $\approx 2 \log_{10}$ reduction in plasma HIV-1 RNA from baseline was observed by week 12 of treatment. Genotyping was performed at baseline; genotyping and phenotyping (Phenosense GT) were performed at week 24 or time of study discontinuation.

Results: Of the 24 patients enrolled (20 males; 4 females; median age [range] of 39 [28 to 57] years), 1 withdrew consent and 1 was lost to follow up. Median (range) plasma $\log_{10}$ HIV 1 RNA and CD4 count at baseline were 4.91 (3.31 to 6.02) copies/mL and 133 (4 to 475) cells/mm$^3$; 38% had HIV 1 RNA $\approx$ 100,000 copies/mL, and 58% had CD4 < 200 cells/mm$^3$ at baseline. Of 22 evaluable patients, 2 completed the study while 20 patients (91%) discontinued treatment early (median [range] 16 [7 to 23] weeks) due to a suboptimal response. At week 12, the change from baseline in $\log_{10}$ HIV-1 RNA ranged from -2.66 to 0.73 with a median of -0.61 (n = 20, p = 0.003) copies/mL; 1 patient responded ($\approx 2 \log_{10}$ reduction in viral load) and 21 patients had a suboptimal response. Resistance testing (n = 20) showed M184I/V in all patients (100%) with 10 of these patients (50%) also having K65R. Of 19 patients who had phenotyping results available, all samples showed susceptibility to TDF (<1.4X WT), while 5 of 10 patients with K65R showed reduced susceptibility to ddI (>1.7X WT).

Conclusions: Use of a triple NRTI regimen of ddI + 3TC + TDF given QD resulted in a high frequency of suboptimal response with early emergence of resistance. While the primary cause is unclear, these findings are consistent with recent reports of other triple NRTI regimens showing high rates of suboptimal response and/or early failure and provide further evidence of the inferiority of such strategies.

## 52 - Low Genetic Barrier to Resistance Is a Possible Cause of Early Virologic Failures in Once-Daily Regimen of Abacavir, Lamivudine, and Tenofovir: The Tonus Study

**R Landman*[1], G Peytavin[1], D Descamps[1], F Brun Vezinet[1], H Benech[1,8], A Benalisherif[1,2], A Trylesinski[2,3], C Katlama[3,4], P M Girard[4,5], F Raffi[1], P Yeni[6], M Bentata[6], B Jarrousse[6,7], C Michelet[7,8], P Flandre[9], Tonus Study Group, and Tonus study group**

[1]Bichat Claude Bernard Hosp., Paris, France; [2]Gilead Sci., Paris, France; [3]Pitié-Salpêtrière Hosp., Paris, France; [4]Saint Antoine Hosp., Paris, France; [5]CHU Nantes, Hosp. Nantes, France; [6]Avicennes Hosp., Bobigny, France; [7]CHU Rennes, France; [8]CEA Lab., Orsay, France; and [9]Inserm U472. Villejuif, France

Background: High rates of early virological failure have been reported in naïve patients who received the triple nucleoside/nucleotide once daily regimen of abacavir (ABC), lamivudine (3TC), and tenofovir (TDF). Several explanations are being considered, including low genetic barrier to resistance and negative pharmacokinetic interactions (intracellular or plasma). We reported similar unexpected results of early virological failures.

Methods: Pilot study, HIV1+ patients, were included to receive ABC/3TC/TDF once daily for 12 months. Trough plasma concentrations (Cmin) at M1, CD4 cells count, and plasma viral load (pVL) at months 1, 3. and 6 were performed. Virological failure was defined as patients who never reached undetectable pVL below 400 copies/mL or a rebound above 0.7 $\log_{10}$ copies/mL after decrease. RT gene sequencing was performed at month 3 or 6. The trial was prematurely interrupted after an unplanned interim analysis.

Results: 38 antiretroviral naïve patients were included. At baseline median CD4 cells count was 221 cells/mm$^3$ (61 to 348) and median pVL was 4.9 $\log_{10}$ copies/mL (2.0 to 5.9): 30 and 8 patients with pVL above and below 4 $\log_{10}$ copies/mL, respectively. Virological failures were observed in 12/36 patients: 12/28 and 0/8 patients with baseline pVL above and below 4 $\log_{10}$ copies/mL, respectively ($p = 0.03$). Achievement of viral replication below 50 copies/mL was observed in 12/34 patients and 17/26 patients at month 3 and 6, respectively. At month 3, 5/26 (19%) and 7/8 (88%) of patients with baseline pVL above and below 4 $\log_{10}$ c/mL, respectively, were below 50 copies/mL ($p < 0.001$); similar results were found at month 6 (9/18 vs 8/8 ($p = 0.02$). In specimens available from 12 patients with virological failures between month 3 and month 6, 11/12 had both K65R and M184V mutations and 1 had the M184V mutation alone. At month 1, 32/37 patients had Cmin considered as adequate for all the 3 drugs and 5 had at least 1 Cmin below LOQ for TDF (5), ABC (3), and 3TC (3).

Conclusions: The association of adequate expected plasma Cmin of the 3 drugs, high proportion of early virological failures, and high rate of rapid selection of both K65R and M184V mutations in patients with pVL above 4 log copies/mL at baseline support the hypothesis of low genetic barrier to resistance as the major cause of failure of this triple nucleoside/nucleotide once daily regimen. From the preliminary results of the first series of 14 samples, major intracellular interaction between ABC, 3TC, and TDF is unlikely.

## 53 - COL40263: Resistance and Efficacy of Once-daily Trizivir and Tenofovir DF in Antiretroviral Naïve Subjects

**R Elion*[1], C Cohen[2], E DeJesus[3], R Redfield[4], J Gathe[5], R Hsu[6], L Yau[7], L Ross[7], B Ha[7], R Lanier[7], T Scott[7], and COL40263 study team**

[1]George Washington Sch. of Med., Washington DC, USA; [2]Community Res. Initiative of New England, Boston, MA, USA; [3]IDC Res. Initiative, Altamonte Springs, FL, USA; [4]Inst. of Human Virology, Baltimore, MD, USA; [5]Therapeutic Concepts, P.A., Houston, TX, USA; [6]St. Vincent's Hosp., New York, NY, USA; and [7]GlaxoSmithKline, Research Triangle Park, NC, USA

Background: This is a pilot, open-label, multicenter study evaluating the efficacy and safety of once-daily trizivir (TZV) + Tenofovir DF (TDF) in antiretroviral naïve subjects with entry HIV-1 RNA ≥30,000 copies/mL. A preliminary evaluation was performed to assess virologic response in this ongoing study due to the poor response previously reported with once-daily TDF + ABC/3TC in study ESS30009.

Methods: Analyses were performed on data from 88 subjects with at least 8 weeks of HIV-1 RNA data. Early virologic non-response (EVNR) was defined as: <2.0 log drop in VL and ≥50 copies/mL by week 8 or ≥1.0 log rebound from nadir at or before 8 weeks. Viral RT genotype and phenotype (Virco) were determined at baseline and longitudinally following protocol-defined virologic non-response (PVNR), i.e. confirmed HIV-1 RNA ≥400 copies/mL at 24 weeks or later, until the subject withdrew from the study.

Results: At baseline, median HIV-1 RNA and CD4+ cell count were 5.1 $\log_{10}$ copies/mL and 226 cells/mm$^3$, respectively. At week 24, the proportion of subjects with HIV-1 RNA <400 copies/mL and HIV-1 RNA <50 copies/mL was 78% (42/54) and 67% (36/54), respectively (observed analysis). Of 88 subjects, 10 (11%) met EVNR criteria, with most of these subjects (60%) having baseline HIV-1 RNA ≥100,000 copies/mL (High VL group). At the time of this evaluation, 8/54 subjects (15%) had met PVNR: 7 in the High VL group and 1 with baseline HIV-1 RNA <100,000 copies/mL. At baseline, 6/8 (75%) had wild-type virus and 2/8 (25%) had mutant virus (K103N and 215T/A reversion mutation). At withdrawal or at the last post-week 24 visit, 1/8 (13%) had K65R, 2/8 (25%) had wild-type virus, 2/8 (25%) had ≥1 TAMs without M184V, and 3/8 (37%) had ≥1 TAMs with M184V. To improve virologic response in subjects with HIV-1 RNA >50 copies/mL, the protocol is being amended to allow these subjects to optimize therapy.

Conclusions: The poor virologic response observed with TDF + ABC/3TC (ESS30009) was not observed with the once-daily TZV + TDF regimen, despite ZDV being dosed once-daily. In this study, virologic non-response appears to be associated with baseline HIV-1 RNA ≥100,000 copies/mL. This once-daily, PI- and NNRTI-sparing regimen shows promise in subjects with baseline HIV-1 RNA <100,000 copies/mL. The resistance pattern to date includes less K65R or M184V than would have been predicted by ESS30009, suggesting a potential role of ZDV in resistance modulation.

## 54 - K65R: A Multinucleoside Resistance Mutation of Increasing Prevalence Exhibits Bi-directional Phenotypic Antagonism with TAM

**U Parikh*[1], D Koontz[1], N Sluis-Cremer[1], J Hammond[2], L Bacheler[3], R Schinazi[4], and J Mellors[1]**

[1]Univ. of Pittsburgh, PA, USA; [2]Agouron Pharm., La Jolla, CA, USA; [3]VircoLab Inc., Durham, NC, USA; and [4]Emory Univ., Atlanta, GA, USA

Background: The 65R mutation in HIV-1 RT is selected in vitro by many D-nucleosides but has been paradoxically rare in vivo until recently. In the GS903 and ES30009 trials, 65R emerged in 24 to 54% of patients experiencing virologic failure on regimens containing tenofovir (without AZT). The reason for this change and the impact of 65R on susceptibility to approved and investigational NRTIs is uncertain. To gain further insight, we examined trends in the prevalence of 65R and its association with other NRTI mutations, determined the resistance profile of 65R alone and in combination with thymidine analog mutations (TAM), and analyzed the effect of 65R on the primer unblocking activity of RT.

Methods: We searched the Virco databases for the frequency of 65R and its association with other NRTI mutations. We examined the effect of 65R alone and with TAM on HIV-1 susceptibility to a large panel (n = 31) of D- , L-, and acyclic NRTI using a single cycle or multiple cycle replication assay. The primer unblocking activity of RT was assessed by measuring ATP-catalyzed removal of AZTMP from AZTMP-terminated primers.

Results: Of the >60,000 samples submitted to Virco for testing that contained any NRTI mutation, the frequency of 65R increased from 0.8% in 1998 to 3.8% in 2003. HIV-1 encoding 65R showed 2.5-fold to 10-fold reduced susceptibility to all D-, L- , and acyclic NRTI tested except those with a 3'azido moiety (AZT, AZA, AZG), which had wildtype sensitivity. In examining the frequency of other NRTI mutations that occurred with 65R, a strong negative relation was noted with 41L, 67N, 210W, and 215Y/F. This suggested that 65R is antagonistic to TAM. Indeed, the addition of 65R to 2 different clones (41L/210W/215Y or 67N/70R/215F/219Q) reduced AZT resistance >10-fold (>30-fold to ~3-fold) and reduced primer unblocking activity ~10-fold to wildtype levels. In addition, TAM altered the phenotypic effect of 65R, reducing resistance to ddC, ddI, d4T, abacavir, and tenofovir.

Conclusions: 65R is a multi-NRTI resistance mutation, reducing susceptibility to all D-, L-, and acyclic NRTI tested except those containing a 3'-azido moiety. 65R and TAM exhibit bidirectional phenotypic antagonism. Combining AZT with NRTIs that can select 65R is likely to prevent 65R from emerging.

## 58 - A 16-week Treatment Interruption Does Not Improve the Virologic Response to Multidrug Salvage Therapy in Treatment-experienced Patients: 48-week Results from ACTG A5086

**C Benson*[1], G Downey[2], D V Havlir[3], F Vaida[2], M Lederman[4], R Gulick[5], M Glesby[5], S Patel[6], M Wantman[2], C Bixby[6], C Pettinelli[7], A Rinehart[9], S Snyder[8], J Mellors[6], and the ACTG A5086 Study Team**

**[1]Univ. of Colorado Hlth. Sci. Ctr., Denver, USA; [2]Harvard Sch. of Publ. Hlth., Boston, MA, USA; [3]San Francisco Gen. Hosp., CA, USA; [4]Case Western Reserve Univ., Cleveland, OH, USA; [5]Weill Med. Coll. of Cornell Univ., New York, NY, USA; [6]Univ. of Pittsburgh, PA, USA; [7]NIAID, NIH, DHHS, Bethesda, MD, USA; [8]Social and Sci. Systems, Inc., Silver Spring, MD, USA; and [9]VircoLab Inc., Tibotec-Virco, Durham, NC, USA**

Background: Data are conflicting on the clinical and virologic response to antiretroviral therapy (ART) following structured treatment interruption (STI) in patients with multidrug resistant HIV-1.

Methods: A5086 was a phase 3, open-label, prospective, randomized, multicenter trial evaluating the efficacy of STI in heavily pretreated patients failing ART. Patients were randomized to a 16-week STI followed by salvage ART (STI) or immediate salvage ART (No STI); treatment was selected at entry using ART history and genotype plus virtual or actual phenotype. The primary comparison was the proportion of patients in each arm with HIV-1 RNA <400 copies/mL 48 weeks after randomization (Fisher's exact test). Phylogenetic analyses were performed by the neighbor joining method (PHYLIP).

Results: A total of 41 patients were randomized (enrollment was halted due to slow accrual and data from other studies); 39 completed 48 weeks (1 death at week 48; 1 off-study at week 12). Median entry CD4 count was 226 cells/˜L, median HIV-1 RNA was 38,000 copies/mL mean number of drugs in salvage ART was 4.4, and similar between arms. Of 39 evaluable patients (21 on STI and 18 on No STI) at week 48, 4 (19%) and 6 (33%), respectively, had HIV-1 RNA <400 copies/mL (p = 0.46), and 3 (14%) and 5 (28%), respectively, had HIV-1 RNA <50 copies/mL (p = 0.43). Median "CD4 was +10 for the STI arm versus +17.5 for the No STI arm; median "HIV-1 RNA was -0.65 log for the STI arm versus -1.15 log for the No STI arm. One patient in the STI arm developed a new or recurrent AIDS-defining event (lymphoma) at week 66 versus 0 patients in the No STI arm. Genotypes at end of STI showed reversion of baseline mutations in 5/18, partial reversion in 7/18, and little/no reversion in 6/18 patients (2/21 had no baseline resistance and 1/21 had no genotype). In patients with confirmed virologic failure despite reversion of mutations (n = 4), phylogenetic analyses showed that the virus population at failure clustered with the population at entry and not that at the end of STI. Reappearance of virus with 3 drug class resistance occurred without inclusion of all 3 classes in the salvage regimen.

Conclusions: A 16-week STI prior to starting best available salvage ART did not improve virologic response through week 48. STI led to partial or no reversion of mutations in most patients; in those with complete reversion, genetic analyses suggest that virologic failure resulted from reselection of variants present before STI that encode 3 class resistance mutation on the same genome.

## 98 - Pregnancy Outcome in ART-Treated HIV-Infected Women in Europe

**C Thorne*, M Newell, and European Collaborative Study**
**Inst. of Child Hlth., Univ. Coll. London, UK**

Background: Although highly successful in reducing the risk of mother-to-child transmission, the increasing use of HAART in HIV-infected women in pregnancy may be associated with adverse pregnancy outcomes.

Methods: In the European Collaborative Study, HIV-infected pregnant women and their infants are followed up prospectively in 9 European countries. Data from 1998 to 2002 were analyzed from this ongoing study, to describe pregnancy outcomes in the HAART era.

Results: Most pregnant women acquired their infection through heterosexual contact (an increasing number were from sub-Saharan Africa) and 80% were asymptomatic (CDC class A). The mother-to-child transmission rate during this period was 3.04% (95% CI 2.06 - 4.32%), reflecting the fact that 88% (1252/1415) of women took antenatal ART, mostly HAART including a PI; a third of women received ART from before pregnancy. There has been a recent decline in the elective caesarean section rate, used as a PMTCT intervention, from 73% in 1999 to 58% (143/245) in 2002, with a corresponding rise in vaginal deliveries, from 12% in 1999 to 24% (59/245) in 2002. Simultaneous with the increase in HAART use was an increasing rate of prematurity (< 37 weeks). Among women having vaginal or emergency caesarean section deliveries, the prematurity rate increased from 26.8% in 1998 to 31.2% in 2002, compared with 14.0% in 1994 to 1997; in particular there were significant increases in the prevalence of severe prematurity (<34 weeks), rising from 3.3% to 16.0%, and of very low birth weight infants (<1500g), increasing from 0.5% to 6.0% between 1994-1997 and 1998-2002. The crude neonatal mortality rate was 13.4/1000 (19 neonatal deaths/1415 live births) in 1998 to 2002, compared with 6.3/1000 (6/947) in 1994-1997, already higher than in the general population. The median gestational age of the neonates who died was 28 weeks (range, 22 to 37 weeks) and median birthweight was 710 g (range, 500 to 2750 g). Neonatal death was primarily related to prematurity complications (16 cases); twins delivered at 25 weeks had evidence of GBS infection and 1 death due to severe asyphyxia. Twelve (63%) neonates were exposed to antenatal HAART, 2 to dual therapy, 2 to monotherapy and 3 to none.

Conclusions: Although HAART has substantially reduced rates of mother-to-child transmission in Europe, we present some worrying new findings from this ongoing cohort. These suggest the possibility of unexpected adverse effects associated with HAART and further investigation is needed.

## 99 - Mother-to-Child HIV Transmission Risk According to Antiretroviral Therapy, Mode of Delivery, and Viral Load in 2895 U.S. Women (PACTG 367)

**D Shapiro*[1], R Tuomala[2,3], H Pollack[4], S Burchett[3,5], J Read[6], M Cababasay[1], J McNamara[7], and G Ciupak[8]**

**[1]Harvard Sch. of Publ. Hlth., Boston, MA, USA; [2]Brigham and Women's Hosp., Boston, MA, USA; [3]Harvard Med. Sch., Boston, MA, USA; [4]New York Univ. Sch. of Med., NY, USA; [5]Children's Hosp.; [6]NICHD, NIH, DHHS, Bethesda, MD, USA; [7]NIAID, NIH, DHHS, Bethesda, MD, USA; and [8]Frontier Sci. and Technology Res. Fndn., Buffalo, NY, USA**

Background: Antiretroviral therapy (ART) during pregnancy and cesarean section before labor and membrane rupture (ECS) each reduce vertical HIV transmission, but their effects among women with low viral load are not well characterized.

Methods: Abstraction of medical records of HIV-infected pregnant women at 67 U.S. clinical sites (PACTG 367). Data on pregnancies resulting in singleton live birth(s) between January 1, 1998 and December 31, 2001 with known infant HIV status were analyzed using $c^2$, Fisher Exact, and trend tests, as well as logistic regression analyses.

Results: Of 2895 singleton births with known HIV infection status, 85 infants were HIV-infected (overall transmission rate: 2.9%; 95% CI 2.4 - 3.6%). From 1998 to 2001, overall transmission rate decreased (4.2% to 2.2%, p = 0.002), along with increases in multi-agent (≥2 antiretrovirals) ART use (75% to 90%, p <0.001) and ECS (12% to 33%, p <0.001). Transmission rate increased with higher plasma HIV RNA at last antenatal measurement (<1000: 0.7%; 1000 to 9999: 2.1%; ≥10,000: 5.9%; p <0.001). Transmission rate was lower with multi-agent than with single-agent ART (1.4% vs 5.1%, p <0.001) and did not differ significantly according to classification of agents used. Transmission rate with ECS did not differ significantly from that for vaginal delivery (2.2% vs. 3.5%). Transmission rate and univariate OR (95% CI) according to last antenatal HIV RNA were:

Last Antenatal HIV RNA, Copies/mL [n]

| Risk Factor | <$10^3$ [1726] | $10^3$-$10^4$ [567] | ≥$10^4$ [372] | No RNA in chart [228] |
|---|---|---|---|---|
| Multi-agent vs Single ART | 0.6% vs. 2.2% | 1.9 vs. 2.7% | 4.2 vs. 11.5% | 5.1 vs. 11.9% |
| | 0.3 (0.1-1.1) | 0.7 (0.2-3.2) | 0.3 (0.1-0.9)* | 0.4 (0.1-1.6) |
| ECS vs Vaginal Deliv. | 0.8% vs. 0.7% | 2.8 vs. 1.9% | 4.1 vs. 7.3% | 8.3 vs. 22.4% |
| | 1.2 (0.2-8.3) | 1.5 (0.4-5.0) | 0.5 (0.2-1.5) | 0.3 (0.1-0.9)* |

* = p <0.05

In a preliminary multivariate analysis of the subgroup of women with last RNA<1000, after controlling for RNA <400 vs ≥400, last $CD4^+$ cell count, duration of membrane rupture, and preterm birth, overall transmission rate differed significantly with multi- versus single-agent ART (adjusted OR 0.2, 95% CI 0.04 - 0.8) but not with ECS versus vaginal delivery (adjusted OR 0.7, 95% CI 0.03 - 4.6). Results were similar after excluding presumed in utero transmissions (infant $HIV^+$ ≤72 hours after birth).

Conclusions: Over time, multi-agent ART and ECS increased and transmission rate decreased. After controlling for other risk factors, transmission rate among women with plasma HIV RNA<1000 did not differ significantly according to delivery route but was significantly lower with multi- versus single-agent ART.

## 112 - Final Results of APRICOT: A Randomized, Partially Blinded, International Trial Evaluating Peginterferon-alfa-2a + Ribavirin vs Interferon-alfa-2a + Ribavirin in the Treatment of HCV in HIV/HCV Co-infection

**F J Torriani[1], J Rockstroh[2], M Rodriguez-Torres[3], E Lissen[4], J Gonzalez[5], A Lazzarin[6], G Carosi[7], J Sasadeusz[8], C Katlama[9], J Montaner[10], H Sette[11], F Duff[12], J DePamphilis[12], U M Schrenk[13], and D Dieterich*[14]**

**[1]Univ. of California, San Diego, USA; [2]Univ. of Bonn, Germany; [3]Fndn. de Investigación de Diego, Santurce, PR, USA; [4]Virgen del Rocío Univ. Hosp., Seville, Spain; [5]Hosp. La Paz, Madrid, Spain; [6]San Raffaele Vita-Salute Univ., Milan, Italy; [7]Univ. of Brescia, Italy; [8]Royal Melbourne Hosp., Australia; [9]Hosp. Pitié-Salpêtrière, Paris, France; [10]Univ. of British Columbia, Vancouver, Canada; [11]Inst. de Infectologia Emilio Ribas, Sao Paulo, Brazil; [12]Roche, Nutley, NJ, USA; [13]Roche, Basel, Switzerland; and [14]Mt Sinai Sch. of Med., New York, NY, USA**

**Background**: The AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT) was designed to evaluate the safety and efficacy of HCV therapies approved for patients with HCV mono-infection in patients with HIV/HCV co-infection.

**Methods**: We randomized 868 HIV/HCV co-infected subjects in 19 countries to 48 weeks of treatment with interferon-a-2a (IFN) 3-MIU 3 times a week plus 800 mg/day ribavirin (RBV), peginterferon-a-2a (40 kD) 180 mg weekly (PEGASYS) plus placebo, or PEGASYS 180 mg weekly plus 800 mg/day RBV. Eligible subjects were HCV RNA and HCV antibody positive, had compensated liver disease, a $CD4^+$ count e"100 cells/mL, and stable HIV disease, with or without antiretroviral therapy (ART). The primary endpoint, sustained virological response, was defined as HCV RNA <50 IU/mL at the end of 24 weeks of treatment-free follow-up (week 72), determined by the COBAS AMPLICOR HCV Test v 2.0. Sustained virological response rates were compared by Cochran-Mantel-Haenszel test stratified by geographical region, genotype and $CD4^+$ count using a closed testing procedure.

**Results:** A total of 860 subjects received study drugs. Final week-72 results are presented in the table:

| | IFN/RBV (A) (n = 282) | PEGASYS/placebo (B) (n = 288) | PEGASYS/RBV (C) (n = 289) |
|---|---|---|---|
| Baseline Characteristics | | | |
| Male (%) | 81 | 82 | 80 |
| Caucasian (%) | 78 | 79 | 80 |
| Age (years)[a] | 40±7.6 | 40±7.4 | 40±7.9 |
| HCV RNA ($10^6$ IU/mL)[a] | 3206±5934 | 6254±6429 | 6886±6451 |
| ALT (IU/L)[a] | 97±53 | 98±57 | 88±59 |
| HCV genotypes 1, 2, 3, 4, other (%) | 60, 5, 26, 8, <1 | 61, 6, 26, 7, 0 | 61, 4, 28, 6, 0 |
| HIV RNA (copies/mL)[b] | 50 | 50 | 50 |
| $CD4^+$ (cells/μL)[a] | 542±230 | 550±268 | 526±277 |
| Receiving ART (%) | 84 | 83 | 84 |
| Cirrhosis/bridging fibrosis (%) | 16 | 16 | 15 |
| Safety Outcome (%) | | | |
| Treatment discontinuations | | | |
| Overall | 111 (39) | 90 (31) | 72 (25) |
| Adverse effects or lab abnormalities | 44 (15) | 47 (16) | 42 (15) |
| Serious adverse effects (treatment-related[c]) | 15 (5) | 28 (10) | 24 (8) |
| Deaths (overall/treatment-related[c]) | 3/1 | 3/3 | 4/1 |
| Neutropenia (<0.5 x $10^9$/L) | 1 (<1) | 37 (13) | 31 (11) |
| HCV Virological Outcome (%) | | | |
| End-of-treatment | 41 (14) | 92 (32) | 145 (49) |
| Sustained virological response | | | |
| Overall | 33 (12) | 58 (20) | 116 (40) |
| | | $p = 0.0078$ vs A | $p = 0.0001$ vs A and B |
| HCV genotype 1 | 12/171 (7) | 24/175 (14) | 51/176 (29) |
| HCV genotypes 2&3 | 18/99 (18) | 32/90 (36) | 59/99 (60) |

[a]Mean±SD [b]Median [c]Considered possibly/probably related

Conclusions: The combination of PEGASYS + RBV produced significantly higher sustained virological response rates than conventional IFN + RBV in HCV/HIV co-infection (40% vs 12%, p <0.0001).

## 131 - Stop Study: After Discontinuation of Efavirenz, Plasma Concentrations May Persist for 2 Weeks or Longer

**S Taylor*[1], S Allen[2], S Fidler[3], D White[1], S Gibbons[4], J Fox[3], J Clarke[3], J Weber[3], P Cane[5], A Wade[2], E Smit[5], and D Back[4]**

**[1]Birmingham Heartlands Hosp. and Univ. of Birmingham, UK; [2]Coventry and Warwickshire Hosp., UK; [3]Imperial Coll. London & St. Marys Hosp., UK; [4]Univ. of Liverpool, UK; and [5]HPA, Birmingham Heartlands Hosp., UK**

**Background:** Current antiretroviral drugs differ in their relative plasma elimination half -lives (t1/2). The reported t1/2 of EFV is 40 to 55 hours; therefore EFV concentrations may persist at therapeutic levels for greaterlonger than 1 week following discontinuation. If drugs with a shorter half-lifet1/2 are stopped at the same time as EFV, patients will effectively be receiving monotherapy for a significant period of time. This may be important if there is ongoing viral replication, as nNRTI -resistant variants may be selected.

**Methods:** For 8 HIV-1+ patients who took part in an extended pharmacokinetics study, blood was drawn at baseline (day 0) and at days 4, 7, 14, and 21 after stopping EFV. Plasma samples were analyszed for EFV concentrations by HPLC and the half-life determined by regression analysis. Viral RNA +/- resistance testing was performed at each time point. A further 25 patients who stopped EFV after short -course antiretroviral therapy following seroconversion were assessed to obtain virological data on patients stopping EFV 5- to 7 days prior to other agents in the regimen. These patients had resistance testing prior tobefore commencement of treatment and an average of 4 weeks after stopping EFV.

**Results:** In the pharmacokinetics study the reasons for stopping EFV were virological failure (*n* = 4), toxicity (*n* = 1), stopping 1 of 2 NNRTI's (*n* = 2), and post seroconversion (*n* = 1). The median EFV concentration at day 0 (*n* = 8) was 3004 ng/mlL (range 894- to 8216); at day 7 was 310 ng/mlL (<40 -to 4478); at day 14 was 149 ng/mlL (<40- to 1845), and at day 21 was 62 ng/mlL (<40- to 637). The calculated t1/2half-life ranged from 36 to 100 hours. Of the 25 patients in the virological study only 1 had aexhibited resistance present 4 weeks after stopping treatment. However this was also present prior to EFV therapy. Using a protein -corrected EC95 value of 93 ng/mlL for wild type virus, 4/7 patients had EFV concentrations above this at day 7, 3/7 at day 14, and 2/7 at day 21.

**Conclusions:** Based on virological data it would appear reasonable to stop EFV 7 days prior to stopping other shorter -acting drugs in the regimen. It may also be possible to consider exchanging EFV for a drug with a shorter t1/2half-life prior tobefore stopping all drugs. However, based on this extended pharmacokinetics data, it may be more prudent to increase the stop window to 2 weeks in order to minimisze the potential for selecting for nNRTI resistance. These findings will have implications for conserving future therapeutic options and also stopping other agents with long plasma or intracellular half -lives.

## 395 - Structured Treatment Interruptions in Primary HIV Infection: Final Results of the Multicenter Prospective PRIMSTOP Pilot Trial

**B Hoen*[1], I Fournier[2], I Charreau[2], C Lacabaratz[3], M Burgard[4], C Arvieux[5], E Bouvet[6], F Pariente[2], J P Aboulker[2], A Venet[3], C Rouzioux[4], F Raffi[7], and the Primstop study group**

**[1]Univ. Hosp., Besançon, France; [2]INSERM SC10, Villejuif, France; [3]Univ. Paris Sud, Le Kremlin-Bicêtre, France; [4]Univ. Hosp. Necker, Paris, France; [5]Univ. Hosp., Rennes, France; [6]Univ. Hosp. Bichat, Paris, France; and [7]Univ. Hosp., Nantes, France**

**Background**: PRIMSTOP (ANRS 100), a multicenter, prospective trial, evaluated the ability of structured treatment interruptions to induce anti-HIV immune response and to control HIV replication following HAART discontinuation in patients with primary HIV infection.

**Methods:** Patients with early acute symptomatic primary HIV infection were given 34-weeks of continuous therapy combining didanosine, stavudine, nelfinavir, and hydroxyurea. At week 34, patients with plasma viral load <50 copies/mL entered the structured treatment interruption phase that consisted of 3 consecutive periods of 2 (week 34 to 36), 4 (week 48 to 52), and 8 (week 64 to 72) weeks off HAART, each separated by 12 weeks on HAART. HAART was permanently stopped at week 84 and patients were followed up until week 108. The primary and secondary efficacy endpoints were the proportions of subjects with plasma viral load < 50 and < 1000 copies/mL, respectively, at week 108.

**Results**: Of the 29 patients enrolled, 3 were lost to follow-up (at week 20, week 34, week 74) and 26 completed the trial and are analyzed hereafter. Baseline characteristics were as follows: 21 male/5 female; median age 32 years; median plasma viral load 5.25 $\log_{10}$ copies/mL; and median CD4 515 cells/mm$^3$. In all, 22 patients underwent all 3 structured treatment interruptions and had no major violations to the protocol. All 26 patients remained off therapy at week 108. No patient died or developed an AIDS-defining event. Hydroxyurea was stopped in 52% of the patients, because of grade 3 neuropathy in 2 of them. At week 108, only 1 patient had plasma viral load < 50 copies/mL, while 7/26 (27%) had plasma viral load < 1000 copies/mL, and median plasma viral load was 4.0 $\log_{10}$ copies/mL (IQR: 2.84; 4.45). Only sex was significantly associated with a plasma viral load < 1000 copies/mL at week 108: 4 of 5 women vs 3 of 21 men ($p$ = 0.01). No other parameter, either at baseline (age, number of positive Western blot bands, CD4/CD8 counts, plasma viral load, cell-associated HIV-DNA, anti-HIV CD4 and CD8 response) or at week 84 (hydroxyurea exposure, cell-associated HIV-DNA, anti-HIV CD4 and CD8 response) predicted virological success (plasma viral load < 1000 copies/mL) at week 108. A major PI resistance mutation (90M) developed in 3 patients.

**Conclusions:** This trial failed to confirm that a significant proportion of primary HIV infection patients can maintain suppression of viremia after a sequence of HAART/structured treatment interruptions followed by HAART discontinuation, even while HAART was initiated very early after primary HIV infection and included didanosine and hydroxyurea. In addition, this strategy was associated with the selection of protease gene-resistance mutations in 3/26 patients. Of note however, 6 months after HAART discontinuation, no patient had resumed HAART.

## 547 - Efficacy and Safety of Atazanavir with Ritonavir or Saquinavir vs Lopinavir/Ritonavir in Patients Who Have Experienced Virologic Failure on Multiple HAART Regimens: 48-Week Results from BMS A1424-045

**E DeJesus[1], B Grinsztejn[2], C Rodriguez[3], L Nieto-Cisneros[4], J Coco[5], A Lazzarin[6], K Lichtenstein[7], M Johnson*[8], A Rightmire[9], S Sankoh[10], and R Wilber[10]**

**[1]IDC Res. Initiative, Altamonte Springs, Florida, USA; [2]Inst. de Pesquisa Clin. Evandro Chagas-Fiocruz, Rio de Janeiro, Brazil; [3]Hosp. Argerich, Buenos Aires, Argentina; [4]Hosp. Gabriel Mancera, IMSS Mexico, D.F., Mexico; [5]Pendleton Memorial Methodist Hosp., New Orleans, LA, USA; [6]S. Raffaele Hosp., Milan, Italy; [7]Univ. of Colorado Hlth. Sci. Ctr., Denver, USA; [8]Royal Free Hosp., London, UK; [9]Bristol-Myers Squibb Co., Hopewell, NJ, USA; and [10]Bristol-Myers Squibb Co., Wallingford, CT, USA**

**Background:** Atazanavir (ATV) is a potent azapeptide PI with a pharmacokinetic profile allowing for once-daily dosing. ATV trough levels are boosted 5- to 8-fold by ritonavir (RTV) co-administration. The objectives of the study are to compare the efficacy and safety of ATV/RTV and ATV/saquinavir (SQV) to lopinavir (LPV)/RTV as part of combination antiretroviral therapy in highly treatment-experienced HIV-infected patients.

**Methods:** Ongoing, prospective, multinational, open-label, 3-arm study in patients who have failed 2 or more HAART regimens containing at least 1 PI, NNRTI, and NRTI, randomized (1:1:1) to ATV/RTV 300/100 mg daily, ATV/SQV 400/1200 mg daily, or LPV/RTV 400/100 mg twice daily, each combined with tenofovir 300 mg daily and 1 NRTI. Parameters assessed include HIV RNA, CD4 cell count, and safety (including lipids).

**Results:** The following table shows the 48-week results of 358 patients randomized and 347 treated. Median prior PI treatment was 2.5 years.

| | ATV/RTVn = 120 | ATV/SQVn = 115 | LPV/RTVn = 123 |
|---|---|---|---|
| **Baseline Characteristics** | | | |
| AIDS (%) | 28 | 29 | 30 |
| Median HIV RNA ($\log_{10}$ c/mL) | 4.44 | 4.44 | 4.47 |
| Median CD4 (cells/mm$^3$) | 318 | 294 | 289 |
| **Efficacy End Points PrimaryMean change, baseline to Week 48 (SE)** | | | |
| HIV RNA ($\log_{10}$ c/mL) | -1.93 (0.12) | -1.55 (0.14) | -1.87 (0.13) |
| CD4 (cells/mm$^3$) | 110 (22.9) | 72 (19.7) | 121 (20.1) |

Time-Averaged Difference* Baseline to Week 48 (97.5% CI)

## 550 - Virologic Failure in Antiretroviral Therapy Naive Patients Is Only Determined by Extreme Low Values of CD4$^+$ Cells or High Values of HIV-1 RNA Concentration, Not by Choice of Treatment with Nevirapine or Efavirenz

**F van Leth*[1], S Andrews[2], B Grinsztjen[3], E Wilkins[4], M Lazanas[5], J Lange[1,6], J Montaner[7], and for the 2NN study group**

**[1]Intl. Antiviral Therapy Evaluation Ctr., Amsterdam, The Netherlands; [2]Brooklyn Med. Ctr., Cape Town, South Africa; [3]Ctr. de Pesquisa Hosp. Evandro Chagas, Rio de Janeiro, Brazil; [4]North Manchester Gen. Hosp., UK; [5]Gen. Hosp. 'Korgialenio-Benakio-Hellenic Red Cross', Athens, Greece; [6]Academic Med. Ctr., Univ. of Amsterdam, The Netherlands; and [7]St. Paul's Hosp., Vancouver, Canada**

Background: The 2NN study was the first large randomized trial to compare efficacy and safety of the two most widely used non-nucleoside reverse transcriptase inhibitors, nevirapine (NVP) and efavirenz (EFV). The present study looks in-depth at the influence of the number of CD4$^+$ cells and the plasma HIV-1 RNA concentration (plasma viral load) at baseline on the risk of virologic failure.

Methods: We enrolled 1216 therapy-naive patients who were randomized to NVP (once or twice daily), EFV, or NVP+EFV, in combination with stavudine and lamivudine. Broad strata of CD4 and plasma viral load were derived after collapsing multiple smaller strata, based on statistical inference or clinical relevance. CD4 strata: <25, 25-200, and >200 cells/mm$^3$, plasma viral load strata: <100,000 and e"100,000 copies/mL. Subsequently, CD4 and plasma viral load strata were combined to define 6 combination strata. The relationship between initial stratum and virologic failure was assessed by Cox regression analysis. The association between virologic failure and study arm in each combination stratum was assessed by Kaplan Meier analysis. Virologic failure was defined as never a plasma viral load <400 c/mL, or a rebound to 2 consecutive plasma viral load >400 c/mL. NVP arms were combined because of similar efficacy in the main study. A 400 copy plasma viral load cut-off was chosen for comparisons with earlier studies. Patients were censored when discontinuing the study or study medication.

Results: Patients with a CD4 count <25 (n = 140) had a significant higher risk of failure (HR: 1.5; p = 0.04) compared to patients with a CD4 count >200 cells/mL (n = 592), while those with a CD4 count between 25-200 (n=484) had not (HR: 1.02; p = 0.92). Patients with a baseline plasma viral load e"100,000 copies/mL (n = 398) had a significantly higher risk of failure compared with those with a lower plasma viral load (n = 818) (HR: 1.5; p = 0.004).

| CD4 | Plasma Viral Load | NVP | | EFV | | p-value |
|---|---|---|---|---|---|---|
| | | n | prop. fail | n | prop. fail | NVP vs EFV |
| <25 | ≥100,000 | 48 | 0.33 | 31 | 0.26 | 0.58 |
| | <100,000 | 25 | 0.20 | 16 | 0.19 | 0.96 |
| 25-200 | ≥100,000 | 104 | 0.32 | 79 | 0.22 | 0.06 |
| | <100,000 | 135 | 0.16 | 81 | 0.16 | 0.86 |
| >200 | ≥100,000 | 39 | 0.16 | 27 | 0.23 | 0.56 |
| | <100,000 | 256 | 0.19 | 166 | 0.17 | 0.47 |

In each CD4 stratum, patients with a plasma viral load e"100.000 copies/mL had a higher risk of virologic failure (except in CD4 stratum >200 for NVP). In none of the combined CD4 and plasma viral load strata was there a significant difference in virologic failure between NVP and EFV. The same was true for the arm that combined NVP and EFV.

Conclusions: Only baseline CD4 count <25 cells/mm$^3$ was associated with a significantly higher risk of virologic failure, as was a baseline plasma viral load e"100,000 copies/mL. Risk of failure was not statistically different between NVP- and EFV-treated patients at any of the strata evaluated here.

## 554 - Time to Triple Drug Class Failure after Initiation of HAART

**A Mocroft*[1], B Ledergerber[2], J P Viard[3], S Staszewski[4], M Murphy[5], A Chiesi[6], A Horban[7], A B Hansen[8], A N Phillips[1], J D Lundgren[9], and the EuroSIDA study group**

**[1]Royal Free and Univ. Coll. Med. Sch., London, UK; [2]Univ. Hosp. Zurich, Switzerland; [3]Hosp. Necker-Enfants Malades, Paris, France; [4]JW Goethe Univ. Hosp., Frankfurt, Germany; [5]St. Bartholemews Hosp., London, UK; [6]Inst. Superiore di Sanita, Rome, Italy; [7]Ctr. Diagnostyki i Terapii AIDS, Warsaw, Poland; [8]Rigshospitalet, Copenhagen, Denmark; and [9]Hvidovre Hosp., Copenhagen, Denmark**

Background: After exposure to the three main classes of antiretrovirals treatment options in patients with HIV may be limited due to difficulties in maintaining undetectable levels of viraemia, decreasing CD4 counts and clinical disease progression. We sought to describe the incidence of and time to virologic triple drug class failure (failure) and the factors related to it after starting HAART.

Methods: 3538 patients from the pan-European observational study, EuroSIDA, were followed from the date of starting HAART (baseline) until failure. Rates of failure were described using incidence rates. Cox proportional hazards models were used to describe factors related to failure in both treatment-naïve and treatment-experienced patients.

Results: A total of 469 patients (13.3%) failed 3 drug classes; of these, 400/2430 (16.5%) were treatment-experienced and 69/1108 (6.2%) were treatment-naïve. At 6 years after baseline, 24.1% of treatment-experienced patients were estimated to have failed (95%CI: 21.6 to 26.6) compared to 11.9% of treatment-naïve patients (95%CI: 8.6 to 15.2) while the prevalence of failure among patients under follow-up at/after 2002 was 16.1% in treatment-experienced patients and 5.5% in treatment-naïve. Among treatment-naïve patients, there was an increase in the incidence of failure with increasing time from baseline from 1.2 per 100 person-years follow-up (95%CI: 0.7 to 1.7) in the first 2 years to 4.7 per 100 person-years follow-up (95%CI: 2.1 to 8.9) at or after 5 years from baseline (33% per year increase (95%CI: 12 to 58%, p = 0.030), similar to the rate seen in treatment-experienced patients treated for the same period of time (5.4 per 100 person-years follow-up, 95%CI: 3.5 to 7.3). Patients who were treatment-naïve with higher CD4 count and lower viral load at baseline were at a decreased risk of failure, but there was no clear cut-off value at which the risk started to increase. In addition, treatment-experienced patients who also started 2 new nucleosides at baseline had almost a 50% reduced risk of failure (95%CI: 0.34 to 0.77, p = 0.0012), while each additional 12 months exposure to nucleosides before baseline was associated with a 6% increased risk of failure (95%CI: 2 to 11%, p = 0.0016).

Conclusions: We found a low rate of triple drug class failure among patients starting HAART, particularly among treatment-naïve patients; this rate increased with time from starting HAART in treatment-naïve patients. Low CD4 counts and high viral loads at baseline were associated with an increased risk of triple drug class failure in treatment-naïve patients. The longer term consequences of triple class virologic failure on the durability of HAART and how best to manage this situation deserves further focus.

## 570 - Once-daily vs Twice-daily Lopinavir/ritonavir in Antiretroviral-naive Patients: 48-Week Results

**J Gathe*[1], D Podzamczer[2], M Johnson[3], R Schwartz[4], V Yeh[5], N Travers[6], K Luff[6], R Tressler[6], and S Brun[6]**

**[1]Therapeutic Concepts, P.A., Houston, TX, USA; [2]Hosp. de Bellvitge, Barcelona, Spain; [3]Royal Free Hosp., London, UK; [4]Private Practice, Fort Myers, FL, USA; [5]AIDS Healthcare Fndn., Los Angeles, CA, USA; and [6]Abbott Labs., Abbott Park, IL, USA**

**Background:** In a pilot study, the safety, tolerability, and antiviral activity of a once-daily lopinavir/ritonavir (LPV/r)-based regimen appeared comparable to that of a twice-daily LPV/r-based regimen.

**Methods:** Study 418, the first trial of an entirely once-daily LPV/r-based regimen, is a prospective, randomized, open-label clinical trial of LPV/r 800/200 mg once daily (n = 115) vs LPV/r 400/100 mg twice daily (n = 75), each dosed with once-daily emtricitabine (FTC) and tenofovir DF (TDF) in antiretroviral-naive patients.

**Results:** Median baseline viral load and CD4 count were 4.8 $\log_{10}$ copies/mL and 216 cells/mm$^3$, respectively. Prior to week 48, 17% (once daily) and 20% (twice daily) patients discontinued, primarily due to adverse events (11% once daily, 5% twice daily) or loss to follow-up or non-adherence (2% once daily, 11% twice daily). Virologic responses through 40 to 48 weeks were comparable between arms (see the table below). The 95% CI for the difference in week 40 intent-to-treat NC = F response proportion (once daily minus twice daily) was (-8%, 20%). Genotypic resistance testing was conducted on all samples with HIV RNA >500 copies/mL from week 12 to 24. Results from 14 patients (8 once daily, 6 twice daily) indicated no new primary or active site protease inhibitor mutations. No patient demonstrated tenofovir resistance (K65R mutation in reverse transcriptase) and 3 patients (2 once daily, 1 twice daily) demonstrated FTC resistance (M184V/I mutation). Mean increases in CD4 count from baseline to week 40 were 162 (once daily) and 166 (twice daily) cells/mm$^3$.

| Week | Proportion with HIV RNA <50 copies/mL | Once Daily | Twice Daily |
|---|---|---|---|
| 40 | ITT noncompleter = failure (final data) | 67% | 61% |
| 40 | Observed data (final data) | 84% | 80% |
| 48 | Observed data (preliminary data based on to date) 84 patients reaching week 48 | 88% | 85% |

Adverse event and laboratory data to date: diarrhea (13% once daily, 5% twice daily, p = 0.14) and nausea (10% once daily, 8% twice daily) were the most common moderate or severe, study drug-related adverse effects, and 79% and 77% of patients had maximum total cholesterol or triglycerides values of grade 0 to 1 (<240 mg/dL and <400 mg/dL, respectively). Preliminary week 48 data indicate no significant changes from baseline in LDL:HDL or Total:HDL cholesterol ratios. Complete week 48 efficacy, safety, and resistance data will be presented.

**Conclusions:** Through 40 to 48 weeks, a once daily regimen of TDF+FTC+LPV/r resulted in similar virologic responses in antiretroviral-naive patients compared to the same regimen with LPV/r dosed twice daily. Both regimens were well tolerated, and no protease inhibitor or tenofovir resistance has been observed to date.

## 607 - Atazanavir Enhances Saquinavir Hard Gel Concentrations in a Ritonavir-Boosted Once Daily Regimen.

**M Boffito*[1], M Kurowski[2], G Kruse[2], A Hill[3], M Nelson[1], G Moyle[1], A Benzie[1], C Higgs[1], C Fletcher[1], I Hitchcock[4], B Gazzard[1], and A Pozniak[1]**

**[1]Chelsea and Westminster Hosp., London, UK; [2]Therapia GmbH, Berlin, Germany; [3]Roche, Welwyn, UK; and [4]Bristol-Myers Squibb Co., London, UK**

**Background**: Atazanavir (ATV) and ritonavir (RTV) have both shown boosting effects on saquinavir (SQV); it is unknown whether the boosting mechanisms are overlapping or independent. Multiple PI combinations might increase PI efficacy and overcome PI resistance. The aim of this study was to investigate the pharmacokinetics of SQV/RTV/ATV 1600/100/300 mg once daily.

**Methods**: To 20 HIV$^+$ patients (2 females; mean age 41 years; median CD4 442 cells/mm$^3$) we administered SQV/RTV 1600/100 mg once daily with a 20-g fat meal. On day 2, ATV 300 mg once daily was added to the regimen for 30 days. Safety analysis was performed at screening, D1, 11, 31, and follow-up. One day before and 11 days after addition of ATV, blood was drawn pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose for pharmacokinetics analysis. Geometric mean ratios and 95%CI were used to compare SQV pharmacokinetics parameters measured without and with ATV. SQV/RTV/ATV concentrations were measured by HPLC-MS/MS.

**Results**: No significant changes in ALT, AST, glucose, total cholesterol and triglycerides were observed, whereas total and indirect bilirubin increased by 5 times after 10 days of ATV therapy (median, range: 36, 11-139, and 32, 9-128 mmol/L, respectively). Four patients developed scleral icterus and 2 jaundice. SQV and ATV pharmacokinetics data are summarized in the table below. A statistically significant increase in SQV $C_{trough}$ (geometric mean ratios, 95%CI: 2.12, 1.72 to 3.50), $C_{max}$ (1.42, 1.24 to 1.94) and AUC (1.60, 1.35 to 2.43) was observed. ATV concentrations were in accordance with the ATV concentrations observed in pts with ATV/RTV.

SQV and ATV Pharmacokinetic data.

| Parameter | SQV (+RTV) | SQV (+ATV/RTV) | ATV (+SQV/RTV) |
|---|---|---|---|
| | Geom mean (95% CI) | Geom mean (95% CI) | Geom mean (95% CI) |
| $C_{trough}$ (ng/mL) | 87 (71.9-138.8) | 184 (140.3-311.3) | 767 (577.2-1426.8) |
| $C_{max}$ (ng/mL) | 2756 (2218.9-4551.2) | 3923 (3334-5349.9) | 4982 (4432.3-6235.4) |
| $AUC_{0-24}$ (ng.h/mL) | 18270 (14951-30057) | 29445 (24986-40048) | 51036 (44369-64591) |

$C_{trough}$=trough concentration; $C_{max}$=maximum concentration; AUC=area under concentration-time curve.

**Conclusions**: Addition of ATV to SQV/RTV increased SQV AUC, $C_{max}$ and $C_{trough}$ by 60%, 42% and 112% respectively (p <0.05). RTV and ATV may have independent mechanisms of boosting SQV and other CYP3A4 substrates.

ActualizaciónesEN ESPAÑOL

## 615 - A Comparison of the Pharmacokinetics of Ritonavir Boosted Generic (Inhibisam) versus Brand Indinavir

**C Zala*[1], C S Alexander[2], C Ochoa [1], S Guillemi[2], L S Ting[2], J J Asselin[2], P Cahn[1], and J S G Montaner[2]**

**[1]Fndn. Huesped, Buenos Aires, Argentina and [2]British Columbia Ctr. for Excellence in HIV/AIDS, Vancouver, Canada**

Background: Generic antiretrovirals are increasingly used in resource-limited settings, often in the absence of independent pharmacokinetic, safety or efficacy testing. In this cross-over study, detailed 12-hour steady-state exposures to indinavir (IDV) obtained from a generic formulation (Inhibisam) widely used in Argentina were compared to brand IDV (Crixivan) to determine whether the 2 formulations afforded similar exposures.

Methods: Steady-state pharmacokinetic profiles were obtained for 10 patients receiving a 2-daily regimen consisting of 2 NRTI plus IDV/ritonavir (RTV) (800/100 mg). Five patients were initially prescribed generic IDV while 5 were receiving Crixivan. Blood samples were taken immediately prior to the morning dose of IDV/RTV and then at 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. Patients were then switched to receive the alternative formulation of IDV and the pharmacokinetic were reassessed in the same way. Plasma IDV concentrations were determined by a validated assay utilizing high performance liquid chromatography coupled with tandem mass spectrometry. Pharmacokinetic parameters ($C_{trough}$ [12 hour post dose], $C_{max}$, $AUC^{0-12}$) were compared by parametric and non-parametric methods.

Results: On 10 patients, 20 evaluations were conducted. All had completed >24 weeks of successful combination therapy (plasma viral load <50 copies/mL). The IDV $C_{trough}$, $C_{max}$ and $AUC^{0-12}$ were not significantly different for the two sources of IDV (see table below). Plasma HIV RNA remained <50 copies/mL at the time of the second pharmacokinetic assessment for all patients.

| Pharmacokinetic parameter (Mean) | Inhibisam | Crixivan | p-value (paired t-test) |
|---|---|---|---|
| Ctrough (ng/mL) | 1,383 | 1,007 | 0.07 |
| Cmax (ng/mL) | 7,534 | 7,896 | 0.78 |
| $AUC^{0-12}$ (ng"h/mL) | 50,630 | 42,635 | 0.31 |

## 656 - Pathways to Atazanavir Resistance in Treatment-experienced Patients and Impact of Residue 50 Substitutions

**R Colonno*[1], N Parkin[1,2], C McLaren[1], D Seekins[3], S Hodder[3], S Schnittman[1], and T Kelleher[1]**

**[1]Bristol-Myers Squibb Pharm. Res. Labs., Wallingford, CT, USA; [2]ViroLogic Inc., South San Francisco, CA, USA; and [3]Bristol-Myers Squibb Virology, Plainsboro, NJ, USA**

Background: The I50L substitution is the signature resistance mutation for atazanavir (ATV) and results in ATV-specific resistance and increased susceptibility to other protease inhibitors (PI) in treatmentreatment-naïve patients. In this evaluation, ATV resistance pathways in treatment-experienced patients are examined along with a retrospective analysis of substitutions at residue 50.

Methods: Phenotypic (ViroLogic Inc.) and/or genotypic (ViroLogic Inc. and LabCorp Inc.) evaluations were performed on baseline and on-treatment isolates from nearly 700 treatment-experienced patients treated with either ATV or lopinavir/ritonavir (LPV/r) regimens in clinical studies AI424-009, -043, and -045. Additionally, phenotypic patterns associated with I50L or I50V (1 of several APV signature mutations) were analyzed using the Virologic database.

Results: ATV resistance was observed in 102 clinical isolates (21%) from ATV treatment-experienced patients. Unlike treatment-naive patients, I50L was detected in only 29% (vs. 100%) of treatment-experienced patients treated with ATV (n = 13) or ATV/r (n = 5). None of 40 ATV/SQV-treated patient isolates contained an I50L. I50L-containing viruses displayed ATV resistance and either unchanged or increased susceptibility to LPV, NFV, RTV, and SQV. Equivalent susceptibility increases were not observed for ATV- and LPV/r-resistant isolates lacking I50L. Five other PI mutations frequently accompanied emergence of I50L: A71V (in 50% of I50L viruses), G73S (31%), K45R (26%), E34X (19%), and L33F (17%). Continued ATV treatment in patients with virus containing I50L showed maintenance of the unique resistance phenotype and no significant accumulation of additional PI substitutions. Viruses in the ViroLogic database containing I50L (n = 18) had a median ATV FC of 9.0, but <1 for other PI; no sample had an FC over the biological cutoff for any PI other than ATV. In contrast, the presence of I50V was associated with a median ATV FC of 1.1, and median FC of 20.2 and 8.4 for APV and LPV, respectively (no other primary PI mutations were allowed; n = 29); 41% of I50V isolates had a FC above the 10-fold cutoff for LPV/r.

Conclusions: The I50L pathway to ATV resistance is an important and unique pathway in both treatment-naive and treatment-experienced patients, and confers increased phenotypic susceptibility to multiple PI in both treatment-naive and treatment-experienced patients. In contrast, APV-related PI substitutions may reduce phenotypic susceptibility to subsequent PI therapy, including LPV/r. Early use of atazanavir may preserve future treatment options.

## 666 - Comparison of the Dynamics of Resistance-associated Mutations to NRTI, NNRTI, and PI after Cessation of Antiretroviral Combination Therapy

**M Wirden*, B Amellal, C Delaugerre, A G Marcelin, N Ktorza, H Ait-Mohand, L Schneider, C Katlama, and V Calvez**

**Pitié-Salpêtrière Hosp., Paris, France**

**Background**: Structured treatment interruptions have been proposed as a strategy to induce reversion of resistance to wild type amino acid residues. However, the expected shift is not systematically observed and the dynamics of reversion seems to be different among patients and among resistance mutations. To know whether an antiretroviral-class could recover a favorable genetic background faster than another class, we compared the dynamics of between the three following class-mutation group: protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and nucleoside inhibitors (NRTI).

**Methods:** This prospective study was conducted in 19 HIV-1 patients who were enrolled in a prospective Structured treatment interruption study. The genotypes included at week 0, 8, 14, 20, and 26 in the monitoring of this structured treatment interruption study allowed a comparison of the dynamics of disappearance for the 3 class-mutation groups. For each group, we took into account the time of genotype harboring a shift of all baseline resistance mutations to wild type amino acid residues. The dynamics of reversion were compared using the non-parametric Logrank (Mantel-Cox) test.

**Results:** At baseline, median HIV-1 RNA level was 5.06 log copies/mL (range 4.51 to 5.69) and median CD4 cell count was 61.5 cells /$mm^3$ (range 4 to 361). The genotypic HIV-1 drug resistance testing harbored a median of 7 (5 to 8) resistance-associated mutations to NRTI, 2 (0 to 4) resistance mutations to NNRTI, and 4 (3 to 5) major resistance mutations to PI. We have observed a significant difference between the dynamics of the 3 class-mutation groups ($p < 0.05$). The kinetics of shift to wild type amino-acid residues was faster for the PI, intermediate for the NNRTI and slower for the NRTI (see the figure below). Another result is the difficulty in obtaining a reversion for some NRTIs mutations (M41L, T215Y/F, K219Q/E/N).

**Conclusions:** In this study we have observed that the order of resistance mutation disappearance is PI, NNRTI, and NRTI. Thus, in subsequent regimen, it would be interesting to use multiple PI whose the resistance mutations disappeared significantly faster than those associated to NRTI. However, further studies involving other resistance profiles can be useful to confirm these results.

## 674 - Reduced Sensitivity to Antiretrovirals Is Associated with an Increased Risk of Death among Persons Initiating HAART

**RS Hogg*, C S Alexander, B Yip, T Mo, J Woodward, W Dong, B Wynhoven, L Ting, M V O'Shaughnessy, J S G Montaner, P R Harrigan, and HOMER Cohort**

**British Columbia Ctr. for Excellence in HIV/AIDS, Vancouver, Canada**

Background: Antiretroviral therapy is not curative and any ongoing viral replication can increase the risk of selecting for virus populations that are resistant to treatment. The objective of this study is to determine the effect of reduced sensitivity to antiretrovirals in the first year on survival in subsequent years.

Methods: This analysis is based upon HIV-positive individuals aged 18 years and older who initiated triple combination therapy between August 1996 and July 2000 and who have been followed for at least 1 year. The first 12 months was used to measure intermittent use of therapy and the emergence of resistance to antiretrovirals (3TC, other NRTI, NNRTI, and PI). Age, CD4 cell count, plasma HIV-1 RNA levels, prior AIDS diagnosis, history of injection drug use, and physician's experience were measured at the end of year 1. Cox-proportional hazard regression analysis was used to model the simultaneous effect of prognostic variables

on survival from the first year onwards.

Results: A total of 851 participants aged 18 years and over initiated triple combination therapy between August 1996 and July 2000 and had at least 1 year of follow-up. As of March 31, 2002, a total of 93 deaths were identified in the study population with an all cause mortality rate of 10.9%. HIV-drug resistance to any class was observed in 148 (17%) persons in the first year. Of these participants, 3 (<1%) exhibited resistance to all 3 classes, 41 (5%) to 2 classes, and 104 (12%) to 1 class. A total of 94 (11%) exhibited resistant to 3TC, 45 (5%) to other nucleosides, 49 (6%) to NNRTI, and 28 (3%) to PI. After adjusting for all prognostic factors found to be significant in the univariate analysis, persons who exhibited reduced sensitivity to NNRTI in the first year were 2.96 times (95% CI: 1.52, 5.75; p = 0.001) more likely to die than those who did not. In a separate analysis restricted to persons taking NNRTI-based regimens only, persons with reduced sensitivity to NNRTI and 3TC in the first year were 4.57 times (95%CI: 1.02, 20.61) more likely to die than those who did not.

Conclusions: These preliminary results indicate that although the emergence of resistance remains relatively low after the first year on therapy, persons who exhibited reduced sensitivity to one or more antiretrovirals during this period are at greater risk of death

## 689 - HIV Drug Resistance in a Large Clinical Cohort—Effect of Initial Triple Therapy Regimen on Time Course of Selection of Resistance Mutations

**P R Harrigan*, W Dong, J Asselin, C Alexander, T Mo, B Wynhoven, Z Brumme, R Hogg, and J S G Montaner**

**British Columbia Ctr. for Excellence in HIV/AIDS, Vancouver, Canada**

Background: Few longitudinal resistance studies are performed outside clinical trials. We wished to quantify the rate and patterns of antiretroviral resistance as a function of initial therapy in a large population-based drug-naïve cohort starting triple combination therapy.

Methods: In British Columbia, Canada, antiretrovirals are distributed centrally at no cost to eligible HIV-infected individuals. Our analyses were based on a retrospective cohort of >1200 therapy naïve HIV-positive adults starting triple therapy between August 1996 and September 2000 (the Homer cohort). Genotypic HIV protease and RT resistance analyses (n >3000 assays) were attempted on all samples with a viral load >1000 copies/mL as long as 30 months after starting therapy. Four resistance categories (3TC, any other nRTI, any NNRTI, or any PI) were assigned based upon the IAS-USA table. Samples with HIV-1 RNA <1000 copies were assumed not resistant. Data were analysed on an intent-to-treat basis.

Results: Resistance data were available from 1091 individuals. The most commonly used initial regimens were D4T/3TC/IND (n = 321); AZT/3TC/IND (n = 254); D4T/3TC/NEV (n = 136); D4T/3TC/NFV (n = 65); AZT/3TC/SQV (n = 47), and D4T/ddI/NEV (n = 45). 3TC resistance occurred with a ~3-fold hazard ratio compared with the other 3 categories in PI-containing regimens, but in NNRTI-based regimens NNRTI resistance was more common than 3TC resistance. Patients were assigned therapy non-randomly, so direct comparisons cannot be made between regimens. Nonetheless, resistance development after starting AZT/3TC/SQV (primarily unboosted Invirase) was startlingly high. For example, by 30 months, 68%, 34%, and 19% of individuals starting initial AZT/3TC/SQV had developed resistance to 1, 2, or 3 resistance categories, respectively (see left figure). This compares to 20%, 7%, and 2% for those starting AZT/3TC/IND (right figure). We have also described the rate of selection of each individual mutation with each therapy. For example, 10% of patients starting D4T/3TC/NEV had developed an M184V, K103N, and Y181C by 12 and 11 and 11 months, respectively.

Conclusions: These data represent one of the first systematic efforts to describe the emergence of drug resistance and time-course of the selection of specific mutations in a clinical setting. They should also serve as a benchmark for comparison of more recently introduced therapies.

## 693 - B/F Intersubtype Recombinants of HIV-1 in Argentina: Effect on Genotypic Patterns Associated with Antiretroviral Drug Resistance

**A Petroni*[1], G Deluchi[1], P Zanotto[2], and J Benetucci[1]**

**[1]Lab. de Retrovirus y Virus Asociados, FUNDAI, Buenos Aires, Argentina and [2]LEMB - Inst. of Biomed. Sci., Univ. of São Paulo, Brazil**

Background: The clinical implications of HIV-1 diversity remain unclear. The genetic variability of viral strains might affect the development of resistance to antiretroviral drugs. In Argentina, about the half of the circulating strains are B/F recombinant viruses (RecBF). The aim of this work was to study the impact of such genetic background on the occurrence of resistance-associated mutations.

Methods: Plasma samples were collected from 316 HIV-1 Argentinean patients from Buenos Aires city and Buenos Aires province (87%), and the rest of the country (13%). Subjects were treated with antiretroviral drugs and attended the FUNDAI Laboratory between June 1999 and February 2002 due to treatment failure. Viral RNA from plasma samples was analyzed with the HIV Genotyping System (Applied Biosystems), using an ABI 310 DNA Sequencer (pol gene sequences comprised the protease and the first 320 codons of the reverse transcriptase [RT]). Phylogenetic analysis was implemented with ClustalX and recombinant sequences were confirmed with the Simplot software. Fisher's exact test, $c^2$, Kruskal-Wallis, and Student's t-test were used for statistical analysis.

Results: The subtype distribution resulted in 164 (51.9%) sequences from subtype B; 151 (47.8%) RecBF, and a single (0.3%) subtype F sequence. Intersubtype breakpoint mapping of RecBF revealed a prevalent structure (5'F/B/F/B3') showing 3 breakpoints also found in CRF12_BF previously reported in Argentina; other 2 common structures showing minor differences with the former, and a high diversity of mosaics (48%, 22%, and 30% of RecBF, respectively). Although there was a variety of administered antiretroviral regimens, there were non-significant differences in treatment history between patients carrying either RecBF or subtype B viruses. However, significant differences between RecBF and subtype B were found in the frequencies of several RAMs, both in protease (K20R/M, I54V/L, V82A/F/T were prevalent in RecBF, while M46L/I, A71V/T, G73S/C, I84V, L90M, in subtype B), and in reverse transcriptase (M41L, K43E/Q/N, E44D/A, V118I, and L210W were prevalent in subtype B). Interestingly, V82A/F/T was highly associated with K20R/M and I54V/L, in RecBF (74% vs 19% in subtype B, p <0.001), but with A71V/T, M46L/I, or I54V/L, in subtype B (64% vs 11% in RecBF, p <0.001).

Conclusions: The genetic background of RecBF may affect the genetic routes to resistance by influencing the emergence of resistance-associated genotypic profiles.

## 716 - Toxicity and Efficacy of 3TC/EFV Associated with Stavudine or Abacavir in Antiretroviral-naive Patients: 48-week Results of a Randomized Open and Multicenter Trial (ABCDE Study)

**D Podzamczer*[1], E Ferrer[1], P Sanchez[1], J M Gatell[2], M Crespo[3], M Lonca[2], J Sanz[4], J Niubo[1], S Veloso[5], J M Llibre[6], P Barrufet[7], A Salas[8], E Merino[9], J Martinez-Lacasa[10], L del Rio[11], and ABCDE Study Team**

**[1]Hosp. Univ. de Bellvitge. L'Hospitalet, Barcelona, Spain; [2]Hosp. Clin., Barcelona, Spain; [3]Hosp. Vall d'Hebron. Barcelona.; [4]Hosp. Principe de Asturias. Alcala de Henares. Madrid; [5]Hosp. Joan XIII. Tarragona; [6]Hosp. Sant Jaume de Calella. Calella; [7]Hosp. de Mataro. Mataro; [8]Hosp. Son Dureta. Palma de Mallorca; [9]Hosp. Gen. de Alicante; [10]Hosp. Mutua de Terrassa. Terrassa; and [11]CETIR, Barcelona, Spain**

Background: Few randomized comparisons of the incidence of lipodistrophy between PI-sparing regimens including or not stavudine (d4T) have been performed to date.

Methods: We included in a randomized study 237 eligible patients to compare 3TC/EFV plus d4T or abacavir (ABC), both twice daily. Lipodystrophy and mitochondrial toxicity was assessed by physician and patient observation, anthropometry, blood lactate, and DEXA scans and mtDNA/nDNA in a subgroup of patients. Virological success was defined as the proportion of patients with HIV-1 RNA < 50 copies/mL at 48 weeks by ITT (NC = F) and OT analyses.

Results: No differences in baseline characteristics were observed between arms. Most patients were white men, 29% former drug users, and 21% had prior AIDS. Mean CD4 was 214/uL and mean HIV-1 RNA 5.2 log. After 48 weeks, a mean weight increase of more than 3 kg was observed in both arms (p <0.001). However, a moderate to severe subjective lipoatrophic feature apparent for both physicians and patients identified in at least one localization was observed in 20% of d4T patients and 2.7% in ABC patients (p = 0.001), with a significant greater frequency of fat loss in face (15% vs 1.3%, p = 0.002), arms (12% vs 1.3, p = 0.011) and buttocks (11% vs 1.3%, p = 0.02). Clinical observations correlated with changes in anthropometric measures. DEXA scans were performed at baseline and at 48 weeks in 78 patients who continued with the initial allocated regimen, showing a greater fat loss in d4T vs ABC arm: overall (-1152 g vs +1749 g, p = 0.015), in arms (-177 g vs +136 g, p = 0.013) and in legs (-1,234 g vs +519 g, p <0.001). Fasting total cholesterol and triglycerides levels significantly increased in both arms (p <0.001). Blood lactate levels significantly increased in d4T patients (p <0.001 from baseline, and p = 0.039 comparing with ABC). mtDNA/nDNA results in a subgroup of patients are pending. Frequency of drug discontinuation due to adverse events was similar in both arms (14% vs 15%). No differences were found in viral load <50 copies/mL by ITT (63.9% and 64.3%) and by OT (76.8% and 82.2%). Mean CD4 count increase was similar with a gain of more than 200 cells/uL in both arms.

Conclusions: After 48 weeks, d4T showed a higher rate of lipoatrophy than ABC, both combined with 3TC/EFV. No differences in virological and immunological responses were found.

## 717 - Lipid Abnormalities and Body Habitus in a Double-blind, Randomized, Controlled Trial Comparing Emtricitabine to Stavudine in HIV+ ART-naive Patients

**W Powderly*[1], P Cahn[2], F Raffi[3], M Saag[4], A Shaw[5], J Hinkle[5], E Mondou[5], J B Quinn[5], and F Rousseau on behalf of the FTC-301A Study Team[5]**

**[1]Washington Univ. Sch. of Med., St. Louis, MO, USA; [2]Fndn. Huesped, Buenos Aires, Argentina; [3]CHU Nantes, France; [4]Univ. of Alabama at Birmingham, USA; and [5]Gilead Sci., Inc., Durham, NC, USA**

Background: Lipid abnormalities and body fat redistribution are common in HIV-infected patients receiving antiretroviral (ARV) therapy, and assessment of the effect of new ARV drugs on these safety issues is essential.

Methods: Prospective, double-blind, randomized, controlled trial comparing 200 mg emtricitabine (FTC) once daily to standard doses of stavudine (d4T) twice daily within a background of ddI-EC plus efavirenz given once daily in 571 ARV-naïve, HIV-infected patients (mean age 36 years, 85% male). The mean change from baseline at week 72 in body weight (BW), body mass index (BMI), abdominal girth (AG), waist circumference (WC), hip circumference (HC), waste/hip ratio % (WHR), chest circumference (CC), fasting triglycerides (TRI), HDL cholesterol (HDL), total cholesterol (CHOL), LDL cholesterol (LDL), and glucose (GLUC) was compared using a stratum-adjusted 95% confidence interval for the difference between treatment arms.

Results: The significant superiority of FTC over d4T, both on efficacy and safety criteria, as long as week 60, has already been reported for the comparative phase of this clinical trial. The mean change from baseline at week 72 for the parameters described above are as follows:

| | BW (kg) | BMI (kg/m²) | AG (cm) | WC (cm) | HC (cm) | WHR (%) | CC (cm) | TRI (mg/dL) | HDL (mg/dL) | LDL (mg/dL) | CHOL (mg/dL) | Gluc (mg/dL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FTC | +1.2 | +0.4 | +0.9 | +0.3 | +0.6 | 0 | +0.8 | +27.7 | +13.5 | +17.4 | +37.2 | +4.3 |
| d4T | -1.7 | -0.6 | -0.8 | -1.0 | -1.7 | +0.9 | -1.1 | +93.8 | +8.8 | +15.3 | +43.8 | +2.7 |
| Δ FTC - d4T | +3.0 | +1.0 | +2.1 | +2.0 | +2.3 | -1.3 | +1.7 | -66.6 | +5.1 | +1.6 | -7.3 | +0.6 |
| p | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | NS | <0.05 | <0.05 | <0.05 | NS | NS | NS |

All differences that were statistically significant were in favor of the FTC treatment arm.

Conclusions: As part of a triple combination regimen with ddI plus efavirenz when compared with d4T, FTC was associated with a significantly more favorable lipid and body habitus profile over 72 weeks of follow-up.

## 720 - Lipid Profiles of Patients Enrolled in the MaxCmin 2 Trial: A Randomized, Open-label Multi-center Comparative Trial Evaluating the Safety and Efficacy of Lopinavir/Ritonavir (400/100 mg Twice Daily) vs Saquinavir/Ritonavir SQV/r (1000/100 mg Twice Daily)

**S L Walmsley*[1], J Benetucci[2], A Brutus[3], N Clumek[4], U B Dragsted[5], B Gazzard[6], N Obel[7], P Vernazza[8], Z Fox[5], J D Lundgren[5], and on behalf of the MaxCmin 2 Trial Group**

**[1]Univ. of Toronto, Canada; [2]FUNDAI, Buenos Aires, Argentina; [3]Brookdale Univ. Hosp., Brooklyn, NY, USA; [4]Ctr. Hosp. Univ. Sainte-Pierre, Brussels, Belgium; [5]Hvidovre Univ. Hosp., Copenhagen, Denmark; [6]Chelsea and Westminster Healthcare Trust, London, UK; [7]Odense Univ. Hosp., Denmark; and [8]Kantonsspital, St Gallen, Switzerland**

**Background**: Limited comparative data are available on the lipid profiles of patients receiving ritonavir-boosted protease inhibitors.

**Methods**: In this planned ITT analysis of lipid changes from the MaxCmin 2 trial, fasting triglycerides (TG), total cholesterol (TC), and LDL cholesterol (LDL) were measured at baseline and at weeks 4 and 48. Use of lipid lowering agents was recorded. Median values and changes were calculated.

**Results**: A total of 324 patients initiated the assigned treatment, 163 randomized to LPV/r and 161 to SQV/r. Median values increased for all lipids in both arms over the first 4 weeks and persisted through 48 weeks; all median values remained in the normal ranges (TC <6.2 mmol/L, TG <2.3 mmol/L, LDL <3.2 mmol/L). There was no difference in TC but a statistically significant difference in median TG at week 4 and 48; 2.3 and 2.2 mmol/L for LPV/r, and 1.8 and 1.7 mmol/L for SQV/r, p = 0.002, p = 0.0015, respectively. The median percentage increase (IQR) in TC from baseline to week 48 was 6.7% (-4.5, +35%) for LPV/r, and 13.6%(-6.5, +33%) for SQV/r, p = 0.52, LPV/r vs SQV/r. Median percentage increases (IQR) in TG were 28.6% (-13.4, +90.5%) for LPV/r, and -5.9% (-31.9, +55.6%) for SQV/r, p <0.001. As LDL cannot be calculated for many patients. if TG >4.5 mmol/L, it is not possible to compare median values for changes in LDL given many missing data points, which were more frequent in the LPV/r group given the greater increases in TG. The values were calculated for patients. in whom both the TG and LDL values are available but may underestimate the changes in each arm and not accurately reflect the difference between arms. The median LDL at week 4 and week 48, were 2.7 and 2.8 mmol/L for LPV/r, and 3.1 and 3.1 mmol/L for SQV/r, p = 0.02, p = 0.07, respectively. The median percentage increase (IQR) from baseline to week 48 was 0% (IQR -17, +28.9%) for LPV/r, and 14.4% (-8.7,+46.7%,) for SQV/r, p = 0.07. Lipid lowering agents were used in 5 patients at baseline and initiated in 5 patients in each arm over 48 weeks. The presence of clinical lipodystrophy at baseline increased the likelihood of abnormal TC and TG at baseline and follow-up by 8- to 12-fold, but adjustment for this factor did not alter the associations with treatment arm described above.

**Conclusions:** Patientss randomized to LPV/r had a 29% median increase in TG levels over the study, whereas median TG levels did not increase in the SQV/r arm. As high TG levels affect the determination of LDL cholesterol, the latter cannot be reliably compared between arms. TC increased slightly in both arms without evidence of differences between arms.

## 762 - Retrospective Comparison of 3 Antiretroviral Treatment Options in Patients with HIV Infection and Tuberculosis Receiving Rifampin

**L Lourtau[1], J Toibaro[1], O Garcia Messina[2], A Duran[1], C Saenz[1], C Gonzalez[1], and M Losso*[1]**

**[1]Hosp. Gen. de Agudos JM Ramos Mejía, Buenos Aires, Argentina and [2]Hosp. of Agudos Parmenio Piñero, Buenos Aires, Argentina**

Background: Concomitant antituberculous and ARV treatment in patients with TB improves global and disease-free survival. The vast majority of TB patients world-wide are treated with rifampin (RFM)-based regimens. There is an urgent need of information regarding use of ARV regimens in TB patients. Our objective was to describe early clinical, virologic, and immunologic outcome of 3 different ARV regimens in patients with TB and HIV infection.

Methods: We conducted a retrospective analysis of data from patients followed in 2 ambulatory HIV clinics in Buenos Aires. The following data from patients treated with combinations of at least 3 ARV drugs were collected (demographics, clinical status, HCV/HBV co-infection, TB localization, timeline between TB and HIV diagnosis, treatment for TB). Virological and immunological data were analyzed in those patients with at least 24 weeks of follow-up. Statistical analysis were done by one group variance test, Neuman and Bonferoni tests and unpaired t-test using StatView 5.0.

Results: Demographic and baseline characteristics are shown in the table below. The NNRTI group included 7 patients with EFV and 5 with NVP. Simultaneous HIV and TB diagnosis were done in 20 patients. TB localization (n) were disseminated (20), lymph node (8), pleural (13), and pulmonary (13). HCV and HBV co-infections were present in 16 and 4 patients. There were no statistical differences in CD4 cell increments between groups at 24 weeks. All regimens produced significant decrease in HIVRNA levels. Comparison between the three strategies showed a more pronounced effect between 2 NRTI plus SQV/r and 3 NRTI (mean reduction 3.7 log vs 2.0 log respectively. p = 0.0008)

| | 3 NRTI | 2 NRTI+NNRTI | 2NRTI+SQV/r |
|---|---|---|---|
| N | 18 | 12 | 14 |
| Median Age (yrs) | 42 | 36.1 | 39 |
| Gender M/F | 16/2 | 9/3 | 13/1 |
| Death (n) | 1 | 1 | 2 |
| Grade III-IV adverse events (n) | 1 | 3 | 3 |
| Mean BL Viral load ($log_{10}$ cps/ml) | 5.31 | 4.4 | 5.4 |
| Mean BL CD4 cell count (cells/ml) | 94 | 117 | 131 |
| Mean Viral Load Decrease at week24 | -2.03 | -2.53 | -3.73 |
| Mean CD4 cell increase at week 24 | +100 | +92 | +53.5 |

Conclusions: These preliminary results in a small subset of patients suggested that all the treatment modalities were well tolerated and safe. HAART including SQV/r or NNRTI appears to provide more benefit over HIVRNA levels. Further evaluation of long term safety and efficacy is required.

## 817 - The Impact of the Hepatitis C virus on CD4 Response Post Initiation of HAART among Patients Enrolled in Clinical Trials

**C Zala*, P Patterson, C Ochoa, A Krolewiecki, R Quercia, A Federico, H Perez, and P Cahn**

**Fndn. Huesped, Buenos Aires, Argentina**

**Background**: Population-based studies suggest that HCV infection blunts CD4 T-cell responses following initiation of HAART. We explored this effect in antiretroviral therapy naïve individuals enrolled in controlled clinical trials of HAART.

**Methods**: We searched a database of patients consecutively enrolled in phase 3 clinical trials of HAART (PI, NNRTI, and triple NRTI) at a single Institution between 1998 and 2003. Data on HCV serology, HIV RNA, and CD4 T-cells count were retrieved from subjects who completed at least 10 laboratory visits and had achieved and sustained plasma HIV RNA below 400 copies/mL at 48 weeks follow-up. Effects of HCV co-infection on absolute CD4 T-cells count over time were evaluated by comparison of median changes from baseline to week 24 and week 48 and by Kaplan Meier curves among HCV antibody positive and HCV antibody negative individuals.

**Results**: Of the 229 ART-naïve individuals, who initiated triple combination therapy, 213 achieved plasma HIV RNA below 400 copies/mL at 48 weeks of HAART; 33 (15%) were HCV seropositive and 180 (85%) were HCV seronegative. No significant differences were found in baseline CD4 T cells at initiation of HAART between groups. Mean time to increase 75 CD4 T cells from baseline was 19.9 weeks (CI 95%: 17.4 to 22.4) and 26.1 weeks (19.8 to 32.3) in the HCV seronegative and HCV seropositive individuals respectively (long rank test = 4.23; p = 0.03). Differences remained after adjusting by CD4 and HIV RNA at baseline. There were significant differences in median increase of CD4 T cells count from baseline to week 24 and 48 in HCV seropositives and HCV seronegatives.

| | Baseline | Week 24 | Week 48 |
|---|---|---|---|
| $HCV^+$ n = 33 median (IQR) | 230(114-348) | 295(189.5-434) | 300(181.5-520) |
| $HCV^-$ n = 180 median (IQR) | 269(164-397) | 398(260-546) | 440.5(292-608) |
| p | 0.121 | 0.020 | 0.036 |

**Conclusions**: In this selected group of HIV-infected individuals, CD4 T- cell responses at 48 weeks of a successful first HAART regimen, were significantly smaller and delayed among HIV/HCV-co-infected individuals. Intensive monitoring of plasma HIV RNA and CD4 T-cells counts in the context of controlled clinical trials of HAART reproduces prior observations from population-based HIV treatment cohorts.

## 895 - Effect of Interventions to Reduce HIV-1 Vertical Transmission in a Cohort of Buenos Aires

**M Losso*, S Ivalo, F Masciottra, A Hackim, L Adissi, R Zlatkes, J Toibaro, L Lourtau, and A Duran**

**Hosp. Ramos Mejia, Buenos Aires, Argentina**

Background: Since the results of PACTG 076 documented the reduction in HIV-1 perinatal transmission, many advances have been made in the treatment and monitoring of infected pregnant women. Objectives were to describe epidemiological and clinical features of HIV-infected pregnant women on follow-up at one multidisciplinary HIV perinatal clinic.

Methods: To compare HIV transmission rates according to antiretroviral therapy (ARV) and mode of delivery, we reviewed the charts of 363 infected pregnant women in follow-up at our unit from April 1994 to August 2003. Data on the relationship between time on pregnancy and the diagnosis of HIV infection, ARV treatment, type of delivery and newborn HIV infection status were collected

Results: Complete data were obtained from 349 patients. Mean age was 26.8 years . Previous AIDS defining events were found in 12.6% of cases . Mean viral load and $CD4^+$ cell count were 3.61 $log_{10}$ copies/mL and 415 cells/$mm^3$.Risk factor for HIV infection was sexual exposure in 67% of cases. The proportion of patients with diagnosis of HIV during pregnancy decreased from 60% (1994-2000) to 27% (2001-2003) and since 1997 more than 75% received any ARV treatment. For the analysis of the transmission rate aborts (8), fetal deaths (6), and unknown or pending newborn HIV status cases (42) were excluded. Type of delivery was vaginal in 168 (59%), caesarean in 117 (41%), 88 electives (EC) and 29 non-electives (NEC); 241 patients received ARV and 52 no therapy (n = 293). Type of treatment was 32% complete ACTG 076 (94/293), 8.19% incomplete ACTG 076 (24/293), 42% combined therapy (123/293; 51 2NRTI, 35 + 1 NNRTI, 37 + 1 PI), and 17.7% no treatment (52/293). Of 293 newborns, 28 were infected (global transmission rate: 9.55%). Transmission rates according to type of delivery were vaginal 9.52% (16/168), EC 6.81% (6/88), and NEC 17.24% (5/12). Relationship between transmission rate and ARV therapy was: 4.24% complete ACTG 076 (4/94), 20.83% incomplete ACTG 076 (5/24), 36.5% no treatment (19/52), and 0% combined therapy (1 vs 4, p <0.016; 2 vs 4, p < 0.0039; any group vs 3, p <0.0001).

Conclusions: The proportion of patients with known HIV status who become pregnant is increasing. Prophylaxis with ZDV decrease rate of HIV transmission even though it is incomplete. Combined antiretroviral therapy improves efficacy of monotherapy to reduce perinatal HIV transmission, irrespective of type of delivery

## 940 - Toxicity Related to Antiretroviral Therapy in a Cohort of HIV Pregnant Women of Buenos Aires

**A Duran*, F Masciottra, J Toibaro, L Lourtau, S Ivalo, and M Losso**

**Hosp. Ramos Mejia, Buenos Aires, Argentina**

Background: Combined ARV has been shown to improve zidovudine (ZDV) monotherapy to reduce perinatal transmission rate of HIV-1 infection. Few data concerning adverse events during pregnancy are available. Objectives were to evaluate toxicity related to ARV in a cohort of HIV infected pregnant women, and to describe the prevalence of birth defects in this cohort.

Methods: We conducted a retrospective analysis of patients followed at our HIV clinic. The charts of 349 pregnant women were reviewed. Data related with adverse effects and congenital abnormalities were collected. WHO Toxicity Tables were used to evaluate adverse events severity. Two groups were defined: monotherapy (complete or incomplete ACTG 076 protocol), and combined therapy (2 NRTI alone or combined with NNRTI or PI).

Results: Mean age was 26.8 years. Mean viral load and $CD4^+$ cell count at baseline were 3.61 log (1.6 to 5.7) and 415 cells/cc (27 to 1485), respectively; 271 patients received any ARV,138 monotherapy with ZDV, and 133 combined therapy (54 :2 NRTI, 41: 2 NRTI + 1 NNRTI, and 38: 2 NRTI + 1 PI). No cases of HIV transmission were detected in the combined therapy group. 187 episodes of adverse events were found in 88 women who received at least one ARV agent: 140 grade I (74.86%), 38 grade II (20.32%), and 9 grade III-IV (4.8%). Distribution of adverse events by group of treatment was: ZDV alone = 10.16% (19/187), 2NRTI = 35.3% (66/187), 2NRTI + NNRTI = 24.6% (46/187) and 2 NRTI + PI = 29.9% (56/187). More prevalent adverse events were anemia: 38.5% (72/187), hypercholesterolemia: 17.64% (33/187), hypertrigliceridaemia 10.7% (20/187), increase of ALP: 10.7% (20/187), or ALT/AST: 6.95% (13/187) levels and gastrointestinal upset: 5.34% (10/187). Less frequent toxicity include: thrombocytopenia, neutropenia, rash, hyperglycemia and high levels of amylase and CK. Eight cases of congenital abnormalities were detected (8/349 = 2.3%),6 in the monotherapy group: renal agenesis (1), imperforate anus (2), gastroschisis (1),harelip (2), myelomeningocele (1) and miocardiopathy (1).

Conclusions: In this cohort combined therapy has improved efficacy of ZDV monotherapy to reduce HIV-1 vertical transmission. No increase in toxicity was observed attributable to ARV, in this retrospective analysis. Prevalence of congenital abnormalities at birth was not different to that expected in the general population. Further follow-up of this pediatric cohort is required to define long term toxicities.

# Desafíos en HIV pediátrico. El develamiento de la información

**Jonathan Kogan, Silvia Warth***

## Resumen

*Con el advenimiento de nuevos y eficaces tratamientos antiretrovirales para el niño con infeccion por HIV/sida, nos enfrentamos a nuevas perspectivas y desafios, entre ellos y de manera fundamental el develamiento.Proceso que consideramos prioritario para una mejor calidad de vida , por los beneficios que reporta al niño al conocer su serologia*

## Introducción.

En los últimos años en la Argentina, la transmisión vertical ha sido sustancialmente modificada a partir del protocolo ACTG 076, (Zidovudina) y de otras medicaciones antirretrovirales. Estos avances permitieron situar la problemática del HIV/sida en una nueva categoría, la cronicidad.

Estos cambios nos abren nuevas perspectivas y plantean otros desafíos en relación a como es vivir con HIV.

El interés de éste artículo es desarrollar una cuestión fundamental en el HIV pediátrico, el develamiento de la información.

## El develamiento.

El diccionario define el término develar como el acto de quitar o descorrer el velo que cubre a alguien,que vela lo oculto, lo secreto.

Dejar al descubierto el diagnóstico de HIV/sida es una tarea nada sencilla.Develar una enfermedad crónica siempre es difícil, ya que compromete la identidad, más aún cuando se trata de niños. Entre los profesionales no hay consenso de cómo y cuándo, sí de la necesidad de que el niño conozca su diagnóstico. La práctica reconoce que una comunicación abierta entre los adultos y el niño acerca de lo que le sucede resulta beneficiosa, ya que posibilita el desarrollo de herramientas para enfrentar de una mejor manera, su enfermedad.

*Unidad de Infectología Hospital Fernández / Área de Salud Mental Fundación Huésped. Angel Peluffo 3932. (C1202ABB) Ciudad de Buenos Aires. Swarth@icatel.net. Jmkogan@infovia.com.ar*

El HIV/sida a diferencia de otras enfermedades, presenta características que le son propias. Hablamos de una enfermedad multi -generacional, los padres enfrentándose a la infección de su hijo, se encuentran también con la suya; generando sentimientos de culpa, castigo y responsabilidad por la transmisión del virus.

La pregunta acerca del develamiento, revela algo que circula en todo el grupo familiar y lo afecta de manera compleja.

Pensamos el develamiento como un proceso. Como la construcción de una historia que supone conocimientos previos en el niño. Proceso que le permite conectar, comprender, dar sentido, responder interrogantes y formular otros nuevos. Nombrar lo que hasta entonces permaneció como innombrable.

Este proceso implica tanto a los padres, familiares, cuidadores, como al equipo de salud que atiende al niño.

## Temores con relación a la apertura de la información.

Muchas veces son los padres quienes no aceptan informar a su hijo acerca de su diagnóstico, pensando que así lo preservan del dolor. Algunas de las motivaciones más frecuentes son:

- Temor a perder el control de la información y que ésta circule de forma indiscriminada.
- Tener que dar cuenta de la enfermedad de los padres y de su origen (con los sentimientos de culpa que esto implica)
- La idea de que aún es muy pequeño para recibir la información y es necesario protegerlo de la misma.
- Temor a la respuesta social. Que lo traten como a un niño diferente o que viva experiencias de discriminación.
- Que el niño se deprima o pierda el deseo de vivir.
- Que la noticia pueda acelerar la evolución de la enfermedad.

El diagnóstico de la seropositividad del niño compromete,involucra y presenta un desafio a todo el grupo familiar. Produce un impacto emocional que desorganiza y altera, instalando una sombra de miedo respecto al futuro. La manera en que cada familia (y los adultos en especial) pueda procesar esta situación facilita o dificulta el camino que deberá recorrer, en relacion al develamiento de la información del diagnostico hacia el niño.

**Alguno de los aspectos que se ponen en juego son:**

- Culpabilidad: Hay un aspecto de dolor y culpa que no es fácilmente elaborable por los padres (a veces sabotean sus propios tratamientos para no estar mejor que sus hijos).
- Vergüenza: mantienen una mirada inflexible sobre ellos mismos.No pueden poner en cuestionamiento sus propios prejuicios respecto de las personas infectadas.
- Negacion: Si no se habla del tema, entonces no existe.
- Desamparo: Para algunas familias, el diagnostico es vivido como un ataque o una agresión mas en la vida.

La consideración de estos puntos es importante a fin de poder establecer una estrategia de trabajo con los padres, familiares, adultos a cargo o instituciones conjuntamente con el equipo interdisciplinario de salud, buscando la forma mas pertinente del manejo de la información.

Entendemos el develamiento como un proceso, como un canal abierto que posibilite un trabajo de elaboración que solo se da en el tiempo. No es un simple acto.Para asistir a los adultos, el equipo de salud debe trabajar en primera instancia sobre los obstáculos que dificultan o impiden el develamiento de la información y por otra parte poner el acento sobre las ventajas de compartir el diagnostico con el niño.Algunas ventajas serian:

- Mayor confianza en el equipo de salud.
- Mayor comunicación familiar.
- El niño puede hacerse cargo de su enfermedad, de la importancia de tomar la medicación y el cuidado de su salud, facilitando la adherencia.
- Mejor preparación para el ingreso a su sexualidad.

Sobre la base de nuestra experiencia en el proceso de develamiento quisiéramos puntualizar algunas consideraciones:

- Decidir cuando y como decir al niño es un gran desafío en la atención del paciente pediatrico con HIV/sida.
- El develamiento debe ser evaluado en forma individual, caso por caso, tomando en cuenta su capacidad cognitiva, su etapa evolutiva, su historia, su estadío clínico y las circunstancias sociales y familiares.
- Los profesionales debemos ayudar a los adultos a cargo, a determinar conjuntamente la mejor forma de develamiento.
- El niño cuenta con un saber acerca de lo que le pasa, es preciso escucharlo conociendo sus fantasías y temores.
- La información debe ser gradual, acorde con su etapa de desarrollo y su situación particular. La

información debe ser dosificada, atendiendo lo que el niño quiera y pueda escuchar en cada momento.

- El trabajo con los aspectos de resistencia hacia los adultos, sus preocupaciones, sus temores a la discriminación, preguntas acerca de la escolaridad, aspectos legales, y la posibilidad de imaginar un futuro para el niño.

## A modo de conclusión

Un eficiente proceso de develamiento facilita la aceptación de la enfermedad, permitiendo una mayor comunicación familiar, estimulando la adherencia a los tratamientos y fundamentalmente, promoviendo una mejor calidad de vida para los niños y los adultos.

Es por eso que sostenemos que, un acercamiento sistemático interdisciplinario al develamiento del diagnostico al niño, construye una firme y permanente alianza entre los chicos, los adultos a cargo y el equipo de salud.

## Bibliografía consultada

*Chirilia O, Petrea S, Cotoanta V, Voicu I. The opportunity of disclosure and the process of telling to HIV children and adolescents. XIV International Aids Conference 2002.*

*Fassler D, Mc.Queen K. Que es un virus. New York: Watt Books; 1990.*

*Lee MB, Rotherman Borus MJ. Parents disclosure of HIV to their children. AIDS 2002; 16: 2201-2207.*

*Lewis SY. Living beyond the odds. FXB Worldwide 1997; 3.*

*Lipon M. Telling discussion of HIV and death with children and adolescents. Pediatric Aids and HIV infection, fetus to adolescent 1996; 7 (4): 239-242.*

*Melvin D. Informing older HIV infected children about their diagnosis. HIV and AIDS Current Trends 2001; 4 (7).*

*Menting A. Issues in pediatric aids treatment. Harvard Aids Review, Children and AIDS 2000.*

*National Pediatric and Family HIV Resource Center. Su hijo, su familia y el HIV. NJ, USA; 1999.*

*Newel ML. HIV-infected children surviving 10 years often free of severe symptoms. J. Acquir Inmune Defic. Syndr. 2002; 29: 396-401.*

*Tasker M. Jimmy and the eggs virus. USA, Maternal and child Health Bureau Program, Health Resources and Services Administration, Department of Health and Human Services: 1999.*

*Oleske JM. The many needs of the HIV-infected child. Hospital Practice 1994: 81-85.*

*Oleske JM. Review of recent Guidelines for antiretroviral treatment of HIV infected children. Topics in HIV Medicine 2003: 180-184.*

*Wiener LS, Best A, Pzzo PA. Be a friend. ILL, USA: Albert Whitman and company; 1994.*

*Working group on antiretroviral therapy and medical management of HIV infected children. Guidelines for the use of antiretroviral agents in pediatric HIV infection 2003.*

## Summary

With the arrival of new and more effective antiretroviral treatment regarding HIV/AIDS infected children, we face new perspectives and challenges, among them and mainly the disclosure process.We consider as a main priority this procedure in order to get a better life quality due to benefits obtained as a result of the knowledge by the child of his serology status.