



HIV-Infektion

⇒ Opportunistische Infektionen

⇒ Antiretrovirale Therapie

⇒ Hepatitisvirus-Koinfektionen



Opportunistische Infektionen

Opportunistische Infektionen (OI)

Hintergrund

- Opportunistische Infektionen und Tumoren (Kaposi-Sarkom, Non-Hodgkin-Lymphom, Zerebrales Lymphom) sind die klinisch bedeutsamen Folgen der HIV-Infektion und bestimmen ganz wesentlich Befinden und Prognose des Patienten.
- Daher dürfen epidemiologische und klinische Veränderungen bezüglich der opportunistischen Infektionen nicht aus den Augen verloren werden.

OI in der US HIV Outpatient Study (HOPS)

- 7825 Patienten von 1994 bis 2006
- Berechnung der jährlichen Inzidenzraten (pro 1000 Personenjahre) mit Adjustierung für Geschlecht, Rasse und HIV-Risikogruppe

Kategorie	Inzidenzrate		Adjustierte Schätzungen der jährlichen Änderung der Inzidenzrate, % (95% CI)		
	1994	2006	1994-1997	1998-2001	2002-2006
AIDS assoziierte Malignome*	40,6	2,6	-37 (-44, -28)	-24 (-41, -1)	-19 (-34, -1)
Opportunistische Infektionen†	111,2	13,6	-27 (-36, -18)	-19 (-27, -10)	-9 (-20, 3)
CMV-Infektionen	46,2	2,9	-37 (-49, -21)	-27 (-47, 1)	19 (-12, 60)
<i>Pneumocystis</i>-Pneumonie	36,4	4,2	-30 (-41, -17)	-14 (-29, 4)	-12 (-26, 9)
<i>M. avium</i>-Komplex	33,9	1,3	-23 (-34, -10)	-23 (-37, -7)	-27 (-43, -6)
Kaposi-Sarkom	30,2	0,8	-39 (-47, -29)	-26 (-47, 3)	-10 (-33, 21)
Oropharyngealcandidose	18,7	5,6	-18 (-33, 1)	-24 (-34, -12)	-4 (-22, 17)
Tuberkulose	5,3	0,0	-30 (-48, -5)	7 (-24, 51)	-29 (-51, 3)
Non-Hodgkin-Lymphom	9,6	1,7	-37 (-50, -19)	-29 (-49, -1)	-26 (-46, 0)
HIV-Enzephalopathie	6,1	1,7	-13 (-35, 16)	0 (-33, 47)	-1 (-28, 34)

* KS, NHL und ZNS-Lymphome

† Alle AIDS-definierenden Infektionen außer rezidivierende bakterielle Pneumonie (da in Datenbank nicht zu identifizieren)

OI in der US HIV Outpatient Study (HOPS)

- Die CD4-Zellzahl bei der Diagnose stieg für Patienten mit KS, NHL und HIV-Enzephalopathie im Verlauf an – nicht jedoch für die anderen OI.
Z.B.: mediane CD4-Zellzahl bei KS-Diagnose in den drei untersuchten Zeiträumen: 38, 107, 143 / μ l ($p < 0,001$)

Schlussfolgerungen der Autoren

- Die Häufigkeit an OI hat sich von 1994 bis 2006 erheblich verringert.
- Die Rate der meisten OI hat sich jedoch in den letzten Jahren stabilisiert – nur für die opportunistischen Malignome und MAC ist noch eine weitere Abnahme zu sehen.
- Die Zunahme der Helferzellzahl bei Diagnose für Kaposi-Sarkom, NHL und HIV-Enzephalopathie könnte eine Wandlung des klinischen und epidemiologischen Bildes andeuten.

Kommentar

- Trotz der beeindruckenden Abnahme der OI sollte nicht vergessen werden, dass OI z.B. in der französischen ANRS-Kohorte weiterhin die häufigste Todesursache bei HIV-Patienten bleiben, vor Tumoren, leberassoziierter und kardiovaskulärer Sterblichkeit (Lewden C et al. JAIDS 2008; 48:590-8).

Opportunistische Infektionen

Ergänzende Studien

- Das Phänomen der ansteigenden Helferzellzahl bei Kaposi-Sarkomen (KS) wird von einer interessanten Beobachtung unterstützt (Ponte et al. H-2337):
 - ▶ Kaposi-Sarkome treten üblicherweise bei niedrigen Helferzellzahlen und hoher Viruslast auf. Unter ART bessern sich KS in der Regel.
 - ▶ Auf diesem Poster wurde über 10 Patienten (von 16 in der Klinik bekannten) berichtet, die ein kutanes KS entwickelt haben trotz hoher T-Helferzellzahl (alle $>330/\mu\text{l}$) und vollständig supprimierter Viruslast über mehr als zwei Jahre.
 - ▶ Unter fortgesetzter ART hatten alle einen benignen Verlauf ohne systemische Beteiligung. Teilweise waren Lokalthérapien notwendig.
- In zwei weiteren Abstracts wurden Analysen aus den Zulassungsstudien für den NNRTI Etravirine (DUET-Studie; H-1239) und den Integrasehemmer Raltegravir (BENCHMRK-Studie; H-1249) bezüglich der Häufigkeit von OI dargestellt.
 - ▶ In beiden Analysen konnte eine Reduktion an AIDS definierenden Erkrankungen und Todesfällen dokumentiert werden, was erneut bestätigt, dass die Suppression der HIV-RNA ein valider Marker auch für die klinischen Endpunkte ist.



Antiretrovirale Therapie (ART)

Wann mit der ART beginnen?

Hintergrund

- Der optimale Zeitpunkt für einen Therapiebeginn bei asymptomatischen HIV-Patienten ist nicht bekannt.
- Aktuelle Leitlinien empfehlen einen Therapiebeginn, wenn die CD4-Zellzahl unter 350/ μ l sinkt. Diese Empfehlungen gründen auf Beobachtungsstudien, nicht jedoch auf prospektiven Endpunktstudien.

Studiendesign

- Alle therapienaiven Patienten einer US-kanadischen Kohorte mit initialen CD4-Zellzahlen zwischen 351 und 500/ μ l wurden zwischen 1996 und 2006 beobachtet (n = 8374 mit 24994 Jahren *Follow-Up*).
- Mittels proportionaler Cox Risikoanalyse – gewichtet mittels *Inverse Probability Weights* – wurde das relative Risiko für Tod berechnet.
- Vergleich zwischen Patienten, die bei einer Helferzellzahl zwischen 351 und 500/ μ l mit der Therapie begannen, (n = 2473; 221 Todesfälle) und denen, die entweder gar nicht oder erst bei einem Abfall der Helferzellzahl unter 350/ μ l begannen (n = 5901; 446 Todesfälle)

Wann mit der ART beginnen ?

Ergebnisse

	Relatives Risiko	95%-Konfidenzintervall	p-Wert
Aufschub von ART, wenn CD4 zwischen 351-500/ μ l ist	1,7	1,4 – 2,1	<0,001
Weibliches Geschlecht	1,1	0,9 – 1,5	0,290
Höheres Alter (pro 10 Jahre)	1,6	1,5 – 1,8	<0,001
CD4-Zellzahl zu Baseline (pro 100 Zellen/ μ l)	0,9	0,7 – 1,0	0,083

- Das Risiko für Tod als Endpunkt war auch dann bei einem verzögerten Beginn der ART höher, wenn für Drogengebrauch oder Hepatitis C adjustiert wurde – zwei Risikofaktoren, die per se mit einer höheren Mortalität einhergingen

Kommentar

- Diese Studie liefert einen weiteren Hinweis, dass die Therapie vermutlich noch früher beginnen sollte als bisher empfohlen.

Vergleich von Atazanavir und Lopinavir bei therapienaiven Patienten (CASTLE)

Studiendesign

- Vergleichsstudie von zwei Standard-Proteasehemmern bei therapienaiven Patienten (1:1 randomisiert, offen)

Therapie

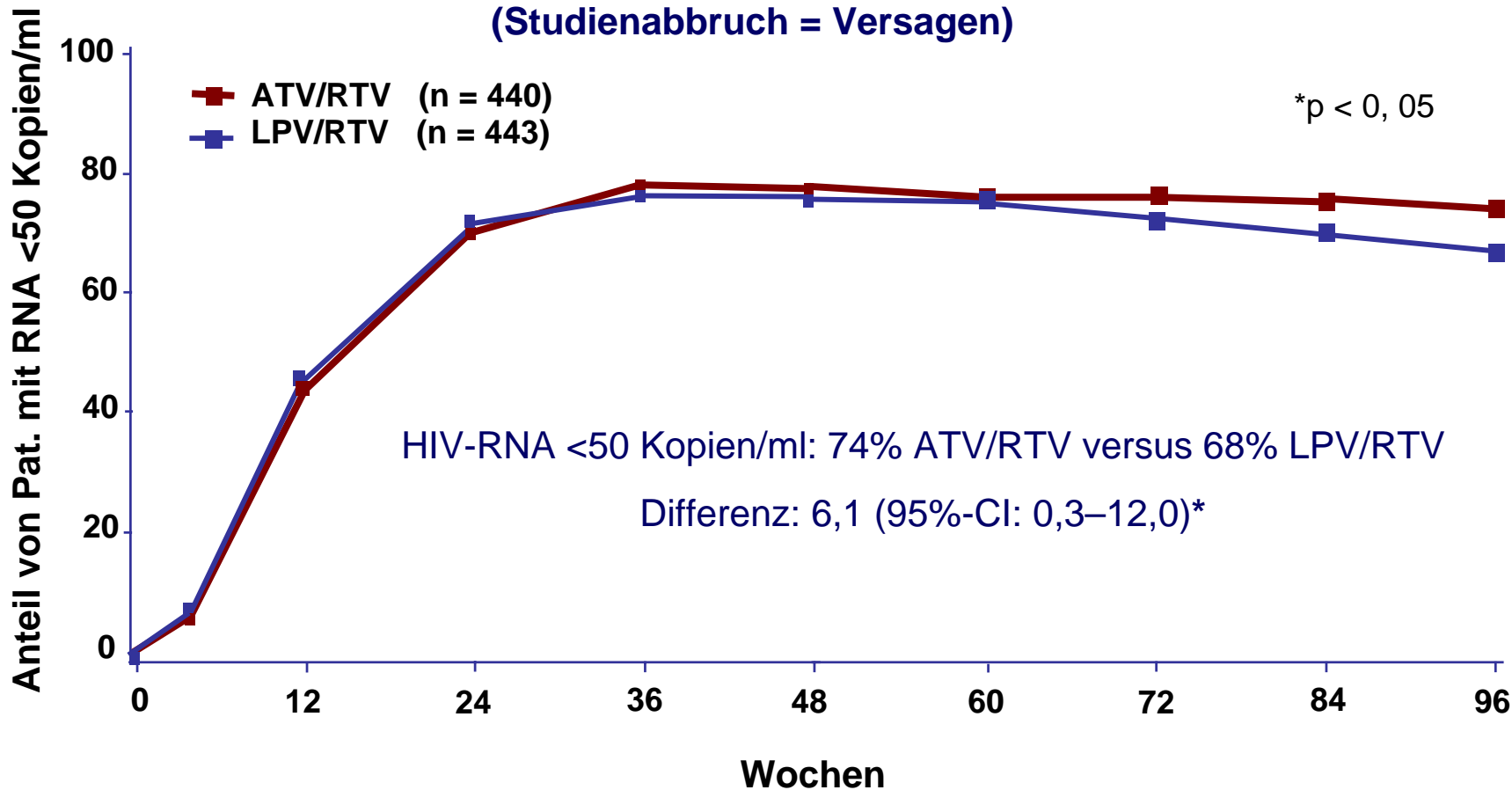
- Arm 1: Atazanavir 300 mg (ATV) geboostert mit Ritonavir (/r) + Tenofovir (TDF) 300 mg + Emtricitabine (FTC) 200 mg; alle 1x/d (n = 440)
- Arm 2: Lopinavir (LPV/r) 400/100 mg 2x/d + TDF 300 mg + FTC 200 mg 1x/d (n = 443)

Einschlusskriterien

- Keine HIV-Vorthherapie; HIV-RNA >5000 Kopien/ml; keine CD4-Beschränkung

CASTLE-Studie: 96-Wochen-Ergebnisse HIV-RNA < 50 Kopien/ml

Intent to treat Analyse
(Studienabbruch = Versagen)



CASTLE-Studie: 96-Wochen-Ergebnisse

Eckdaten zu Resistenzen und Verträglichkeit

	ATV/r (n = 440)	LPV/r (n = 443)
Virologisches Versagen bis Woche 96, n (%)	28 (6)	29 (7)
Vorzeitiger Abbruch, n (%)	72 (16)	95 (21)
Major PI-Mutation, n	1	0
Minor PI-Mutation, n	1	1
Schwere unerwünschte Ereignisse, n (%)	63 (14)	50 (11)
Unerwünschte Ereignisse Grad 2-4, n (%)	133 (30)	140 (32)
Ikterus, n (%)	18 (4)	0
Übelkeit, n (%)	18 (4)	33 (8)
Diarrhoe, n (%)	11 (2)	54 (12)
Gesamt-Cholesterin >240 mg/dl, n (%)	47 (11)	108 (25)
Triglyzeride >750 mg/dl, n (%)	3 (<1)	18 (4)

CASTLE-Studie: 96 Wochen-Ergebnisse

Kommentar

- Atazanavir ist nach 96 Wochen in der ITT-Analyse leicht überlegen im Vergleich zu Lopinavir.
- Dieser Unterschied kommt hauptsächlich durch vermehrte Abbrüche im Lopinavir-Arm von Woche 48 bis Woche 96 zustande (2 im ATV-Arm, 8 im LPV-Arm). Die exakten Gründe bei diesen einzelnen Patienten lassen sich der Präsentation allerdings nicht entnehmen.
- Der Unterschied beruht jedoch nicht auf vermehrter Resistenzbildung. In beiden Armen wurden keine relevanten PI-Mutationen beobachtet.
- Erwartungsgemäß unterscheiden sich die Substanzen in ihrem Verträglichkeitsprofil: Mehr Patienten brachen im Atazanavir-Arm wegen Ikterus ab, während im Lopinavir-Arm vorwiegend Diarrhoe als Abbruchgrund genannt wurde. Das Lipidprofil von ATV ist ohne Zweifel günstiger als von LPV.
- Die Studie illustriert, dass sich die Wahl des Therapieregimes bei therapienaiven Patienten heutzutage hauptsächlich nach der zu erwartenden Verträglichkeit richten sollte.

Vergleich von Darunavir und Lopinavir bei therapienaiven Patienten (ARTEMIS)

Studiendesign

- Vergleichsstudie des „neuen“ Proteasehemmers Darunavir, der für die Behandlung bei vorbehandelten Patienten mit Resistenzen zugelassen ist, hier bei therapienaiven Patienten versus Standard-Proteasehemmer Lopinavir (1:1 randomisiert, offen)

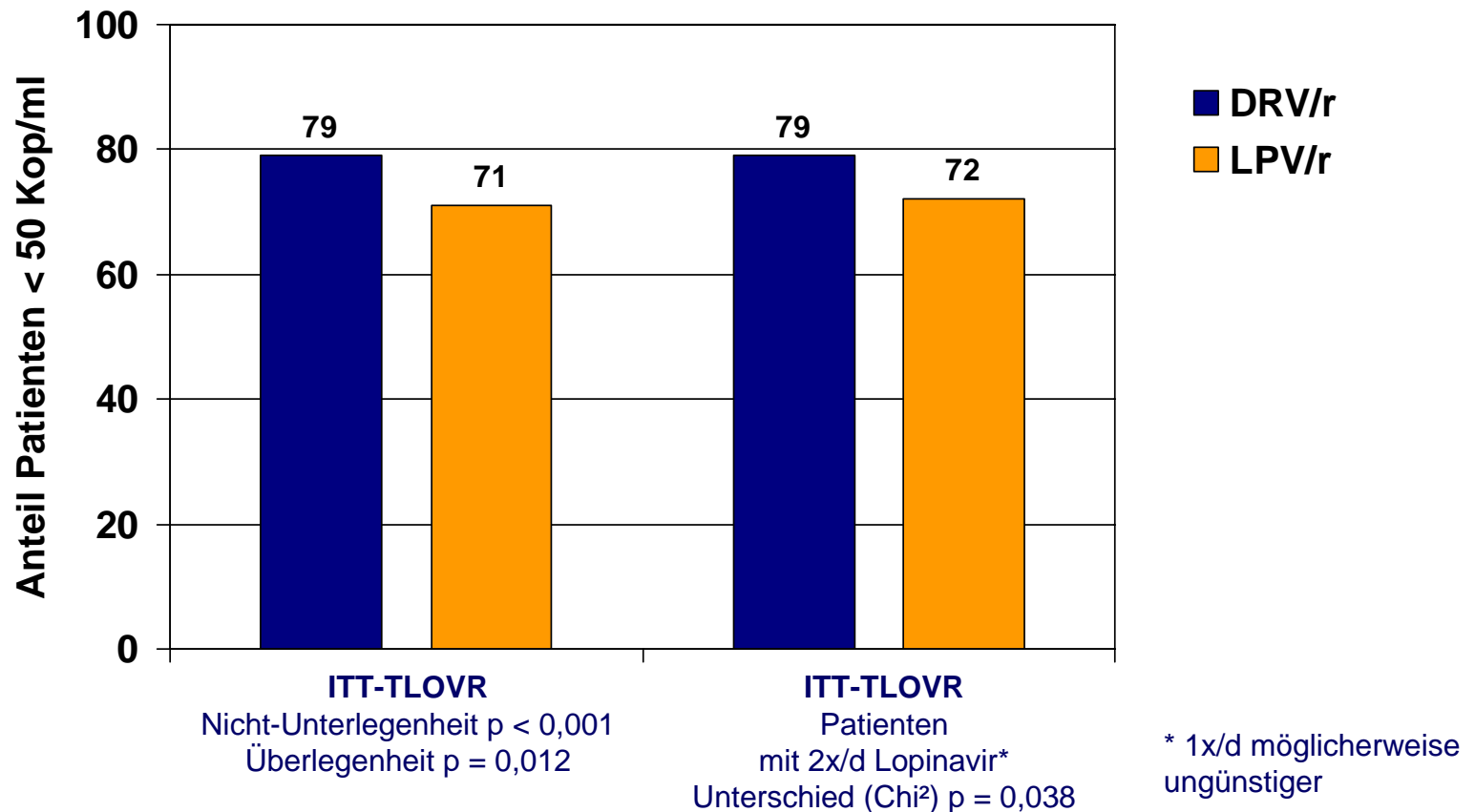
Therapie

- Arm 1: Darunavir 800 mg (DRV) geboostert mit Ritonavir (/r) + TDF 300 mg + FTC 200 mg; alle 1x/d (n = 343)
- Arm 2: Lopinavir (LPV)/r 800/200 mg Tagesdosis (teils 1x/d, teils 2x/d – je nach) + TDF 300 mg + FTC 200 mg 1x/d (n = 346)

Einschlusskriterien

- Keine HIV-Vortherapie; HIV-RNA >5000 Kopien/ml; keine CD4-Beschränkung

ARTEMIS-Studie: 96-Wochen-Ergebnisse HIV-RNA < 50 Kopien/ml



ITT = *Intention to treat*; TLOVR = *Time to loss of virologic response*

- Darunavir war in allen Subanalysen etwas besser als Lopinavir (Ausgangsviruslast > oder < 100.000 Kopien/ml; Helferzellzahl > oder < 200/μl)

ARTEMIS-Studie: 96-Wochen-Ergebnisse

Eckdaten zu Resistenzen und Verträglichkeit

	DRV/r (n = 343)	LPV/r (n = 346)
Differenz der CD4-Zellzahl versus Ausgangswert (/μl)	171	188
Virologisches Versagen bis Woche 96, n (%)	40 (12)	59 (17)*
Vorzeitiger Abbruch, n (%)	59 (17)	81 (23)
Unerwünschte Ereignisse Grad 2-4, n (%)	80 (23)	119 (34)
Diarrhoe, n (%)	14 (4)	38 (11)*
Übelkeit, n (%)	6 (2)	10 (3)
Hautausschlag, n (%)	9 (3)	5 (1)
Gesamt-Cholesterin >240 mg/dl, n (%)	60 (18)	95 (28)*
Triglyzeride >500 mg/dl, n (%)	15 (4)	46 (13)*

* Differenz signifikant.

ARTEMIS-Studie: 96-Wochen-Ergebnisse

Kommentar

- Darunavir ist nach 96 Wochen gegenüber dem Standardproteasehemmer Lopinavir überlegen.
- Dies ist ein wichtiger Unterschied zu mehreren anderen Vergleichsstudien, die primär die Nichtunterlegenheit gegenüber der Standardtherapie zeigen.
- Der Unterschied wird neben einer etwas besseren Verträglichkeit vor allem durch eine bessere virologische Wirksamkeit bedingt.
- Allerdings wurden auch in dieser Studie keine primären Proteasehemmer-Mutationen in beiden Armen beobachtet.
- Die hier getestete Dosierung ist in Deutschland nicht erhältlich.
- Darunavir ist noch nicht für die Behandlung von therapienaiven Patienten zugelassen, obwohl die Daten eine Erweiterung der Zulassung nahelegen.

Integrasehemmer Raltegravir bei therapienaiven Patienten (STARTMRK)

Hintergrund

- Der Integrasehemmer Raltegravir wurde für die Behandlung von Patienten mit virologischem Versagen einer ART entwickelt und zugelassen.
- Zur Eignung in anderen Situationen gibt es noch wenig Daten.

Studiendesign

- Raltegravir versus Efavirenz bei therapienaiven Patienten (doppelblind, 1:1 randomisiert)

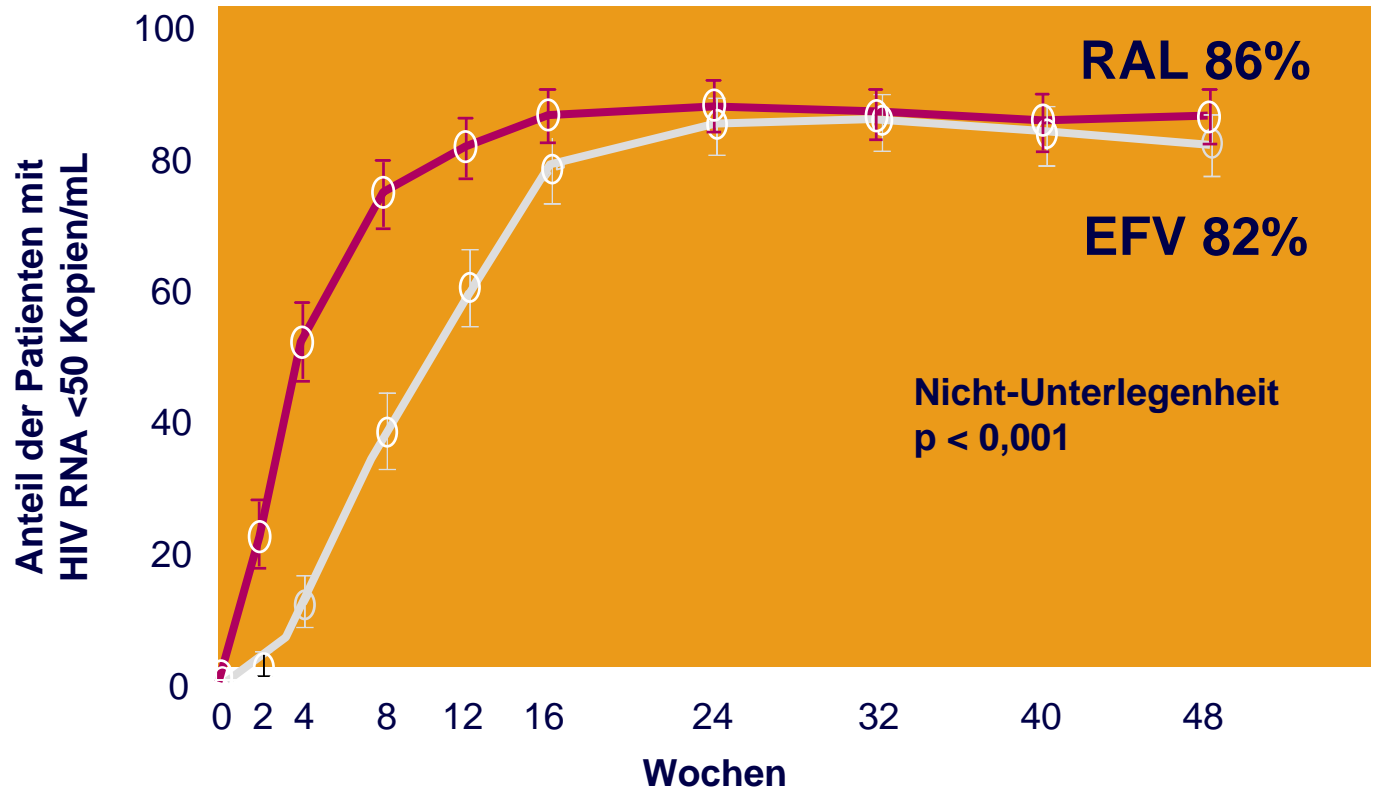
Therapie

- Raltegravir 400 mg (RAL) 2x/d + TDF 300 mg + FTC 200 mg 1x/d (n = 281)
- Efavirenz 600 mg (EFV) + TDF 300 mg + FTC 200 mg, alle 1x/d (n = 282)

Einschlusskriterien

- Keine HIV-Vorthherapie; HIV-RNA >5000 Kopien/ml; keine CD4-Beschränkung; alle Substanzen in der initialen Resistenztestung sensibel

STARTMRK: 48-Wochen-Ergebnisse



Anzahl der Patienten

Raltegravir 400 mg b.i.d.*	281	279	281	279	281	279	278	280	280
Efavirenz 600 mg q.h.s.*	282	282	282	282	281	282	280	281	281

* in Kombination mit TDF + FTC

Intent to treat Analyse

STARTMRK-Studie: 48-Wochen-Ergebnisse

Resistenzen und Verträglichkeit

	RAL (n = 281)	EFV (n = 282)
Differenz der CD4-Zellzahl vs. Ausgangswert (/µl)	189	163
Virologisches Versagen bis Woche 48, n (%)	27 (10)	39 (14)
Vorzeitiger Abbruch, n (%)	24 (9)	35 (12)
Bekannte RAL-Mutation, n	4	0
Bekannte EFV-Mutation, n	0	3
Therapieassoziierte UE – gesamt, n (%)	124 (44)*	217 (77)*
Therapieassoziierte UE – Grad 3/4, n (%)	45 (16)*	90 (32)*
Schwere UE, n (%)	28 (10)	27 (10)
Hautausschlag, n (%)	0	15 (5)
ZNS-UE, kumuliert bis Woche 8 (%)	10	18
Gesamt-Cholesterin >300 mg/dl, n (%)	0	7 (2)

UE = unerwünschtes Ereignis

* p < 0,001

STARTMRK: 48-Wochen-Ergebnisse

Schlussfolgerungen der Autoren

- Raltegravir war nach 48 Wochen versus Standardtherapie mit Efavirenz (jeweils in Kombination mit TDF+FTC) nicht unterlegen.
- Dabei war die Abnahme der Viruslast unter RAL schneller als unter EFV.
- Der Helferzellanstieg war größer.
- Die Verträglichkeit war besser.
 - ▶ Insgesamt weniger klinische medikamentenassoziierte Ereignisse
 - ▶ Weniger ZNS-Nebenwirkungen
- Raltegravir hatte minimalen Effekt auf die Serumlipide.

Kommentar

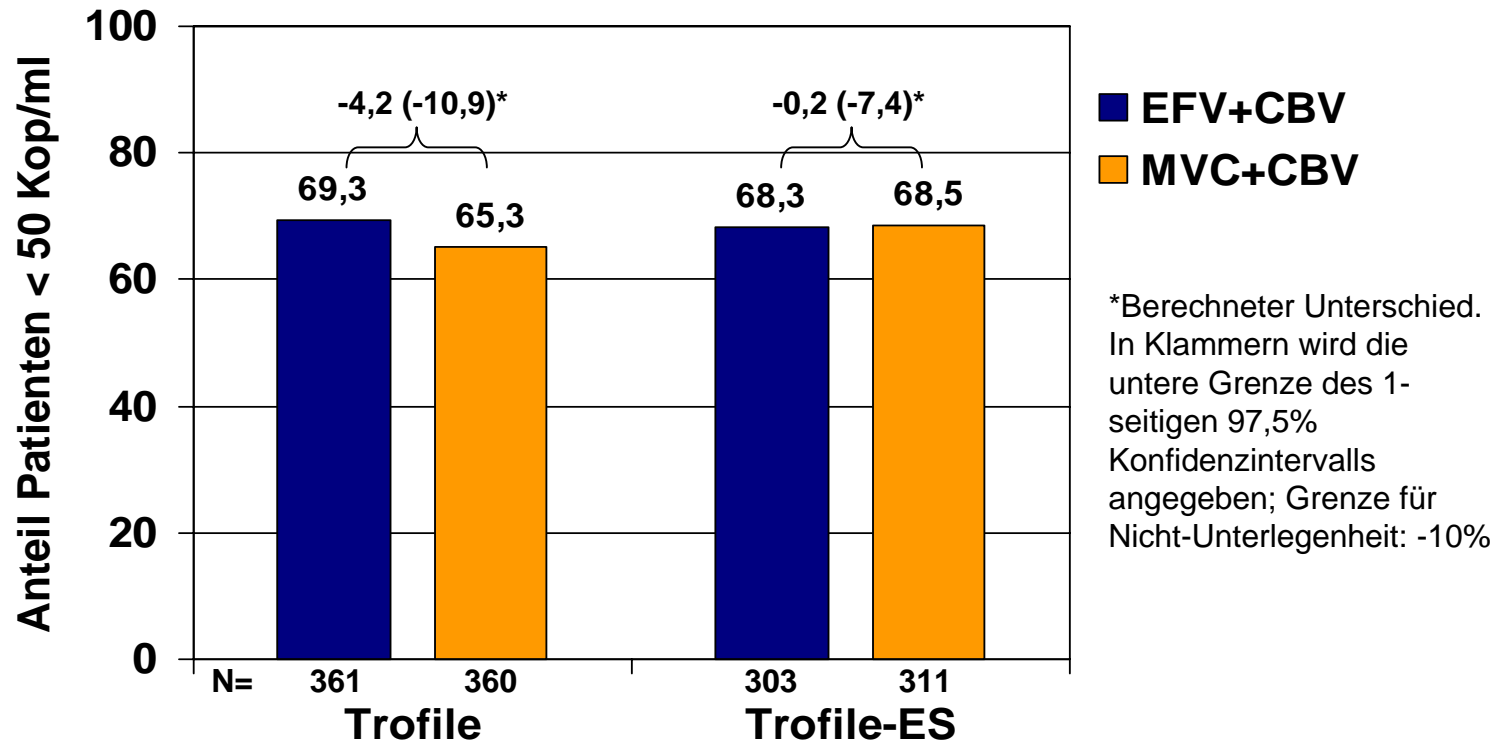
- Mit dieser Studie wird unterstrichen, dass Raltegravir auch als Option für therapienaive Patienten in Frage kommt.
- Es ist unklar, ob die schnellere Viruslastreduktion eine klinische Relevanz hat.
- Es werden die kumulativen ZNS-Toxizitäten bis Woche 8 angegeben. Die klinische Erfahrung lehrt jedoch, dass sich diese Toxizität im Verlauf der Therapie mit EFV fast immer zurückbildet und dann häufig kein klinisches Problem mehr darstellt.

Re-Analyse der MERIT-Studie zu Maraviroc bei therapienaiven Patienten

Hintergrund

- Der CCR5-Hemmer Maraviroc wirkt nur gegen CCR5-trope Viren. Daher muss vor der Anwendung getestet werden, ob das Virus CCR5-trop ist oder den Korezeptor CXCR4 nutzen kann.
- Als Standard gilt der Trofile-Test, ein phänotypischer Test, der weltweit nur von einem Labor angeboten wird (Monogram Biosciences, San Francisco).
- Seit 2008 gibt es einen verbesserten Test (TrofileES), der die (unerwünschten) CXCR4 nutzenden Stämme wesentlich sensitiver erkennen kann. Dadurch könnte Maraviroc möglicherweise noch gezielter eingesetzt werden.
- In der MERIT-Studie wurde Maraviroc im Vergleich zu Efavirenz in Kombination mit Combivir (= AZT+3TC) bei therapienaiven Patienten untersucht. Dabei wurde die Nichtunterlegenheit nach 48 Wochen knapp verfehlt.
- Möglicherweise wäre das Studienergebnis günstiger gewesen, wenn bereits der neue Test zur Verfügung gestanden hätte.

Re-Analyse der MERIT-Studie (= MERIT-ES)



- Etwa 15% der Patienten wurden mit dem neuen Test reklassifiziert (und damit aus der Analyse ausgeschlossen).
- Im Efavirenz-Arm gab es trotz der Ausschlüsse keine Änderungen.
- Im Maraviroc-Arm gab es weniger Abbrüche wegen Unwirksamkeit.
- Laut dieser retrospektiven Analyse wäre die Nichtunterlegenheit in MERIT bei Verwendung des neuen Test erreicht worden.

Re-Analyse der MERIT-Studie (MERIT-ES)

Kommentar

- Der Einsatz von Maraviroc ist vom Ergebnis der Tropismustestung abhängig.
- Seit Juni 2008 wird nur noch der neue Trofile-Test angeboten.
- In Europa haben mehrere Gruppen genotypische Tests für den Korezeptortropismus entwickelt, die mit dem phänotypischen Assay gut korrelieren (ggf. Rücksprache mit dem Labor, welcher Test sinnvoll und verlässlich ist).
- In Amerika finden genotypische Tropismustests bislang kaum Anwendung.

ART und Knochendichte

Hintergrund

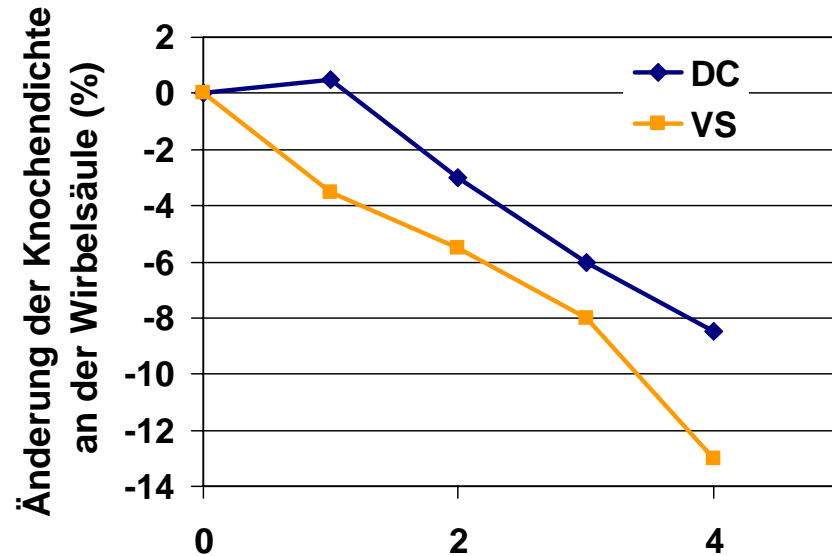
- HIV-Patienten haben eine geringere Knochendichte als die Allgemeinbevölkerung. Der genaue Einfluss von ART ist erst ansatzweise untersucht.
- Bei der SMART-Studie handelt es sich um eine große internationale, randomisierte Studie zu Therapieunterbrechungen. Es wurde ein Arm mit kontinuierlicher ART (*Viral Suppression* = VS) gegen einen Arm mit Therapieunterbrechungen (*Drug Conservation* = DC) verglichen.
- In einer Substudie wurde der Einfluss auf die Knochendichte untersucht. Dazu wurde die Knochendichte mit verschiedenen Methoden an Hüfte und Wirbelsäule gemessen.

Ergebnisse

- In der gesamten SMART-Studie wurden 10 Frakturen (Grad 4) im VS-Arm (n = 2753) und 2 Frakturen im DC-Arm (n = 2720) beobachtet. (*Hazard Ratio*: 4,9; 95%-CI: 1,1-22,5; p = 0,04)
- Im Verlauf der Substudie konnten bei 214 Patienten Knochendichtemessungen durchgeführt werden.

ART und Knochendichte

- Es bestand keine klare Assoziation der Knochendichte mit einem einzelnen Medikament.
- Die Abnahme der Knochendichte im DC-Arm nach dem ersten Jahr wird mit dem zunehmenden Wiederaufnahme der ART erklärt, da sich rasch ein Nachteil von Therapiepausen gezeigt hatte und Pausen nicht mehr empfohlen wurden.



	Jahre				
N =	0	1	2	3	4
DC	116	113	88	53	11
VS	98	97	79	48	15

Kommentar

- Die Studie zeigt, dass möglicherweise bislang zu wenig auf andere Aspekte von möglichen Langzeitnebenwirkungen der ART geachtet wird, z.B. ZNS-Veränderungen, Organveränderungen und eben die Knochendichte.

Tenofovir und Schwangerschaft

- Sämtliche antiretroviralen Medikamente sind für die Anwendung in der Schwangerschaft nicht empfohlen.
- Die Erfahrungen gründen sich daher fast ausschließlich auf Beobachtungen bei schwangeren HIV-Patientinnen.
- Besonders große Unsicherheit herrscht in Bezug auf Tenofovir, eines der aktuell am häufigsten verwendeten HIV-Medikamente, weil hier im Tierexperiment Störungen der Knochenbildung beobachtet wurden.
- In der *Antiretroviral Pregnancy Registry* (APR) wurde bislang nur für Didanosin ein erhöhtes Fehlbildungsrisiko beschrieben, nicht jedoch für Tenofovir, Abacavir, Efavirenz, Indinavir, Lopinavir, Nelfinavir, Nevirapin, Ritonavir und Stavudin.

Kommentar

- Aktive Mitarbeit ist gefragt: Schwangerschaften können unter www.apregistry.com registriert werden.

Neue antiretrovirale Substanzen

Name	Gruppe/ Wirkweise	Derzeit Phase	Hersteller	Kommentar	Abstract
Beviramat	Cleavage-Site- Inhibitor	II	Panacos	Erster Vertreter einer neuen Substanzgruppe Vielfersprechende Verträglichkeit Wirkt nicht bei bestimmten Polymorphismen im gag-Protein	➔ H-891
Elvucitabin	Nukleosidischer RT-Inhibitor	IIb	Achillion	10- bis 100-fach höhere Potenz als Lamivudin gegen HIV und HBV Lange Halbwertszeit	➔ H-892
GRL02031	Proteaseinhibitor	Prä- klinisch	Kumamoto Universität Japan	Nicht-peptidischer Proteaseinhibitor Bindet zweifach – daher weniger Resistenzbildung erhofft	➔ H-1267
MK-2048 MK-0536	Integraseinhibitor	Prä- klinisch	Merck	Integraseinhibitor der „2. Generation“ – wird entwickelt für Patienten nach Vorbehandlung mit Raltegravir	➔ H-1232
PRO 140	CCR5- Antikörper	II	Progenics	Wirkt nur bei CCR5-tropem Virus;nur i.v.	➔ H-1269a
RDEA806	Nicht- nukleosidischer RT-Inhibitor	IIa	Vanguard	Entwickelt für Efavirenz-Resistenz Gute Verträglichkeit; verstärkt die renale Harnsäureausscheidung (aber keine Interaktion mit Tenofovir)	➔ H-893
SPI256	Proteaseinhibitor	I	Sequoia	Lässt sich mit Ritonavir boostern	➔ H-1265
TRI-1144	Fusionsinhibitor	I	Trimeris	Lokalreaktionen, aber milde	➔ H-1268

Neue antiretrovirale Substanzen

Kommentar

- Nach der Zulassung mehrerer neuer Medikamente – davon zwei aus neuen Substanzklassen (CCR5-Antagonist und Integraseinhibitor) – im Laufe der vergangenen eineinhalb Jahre herrscht bei vielen HIV-Behandlern den Eindruck, für Patienten, bei denen auch diese Medikamente versagen, bestünden keine weiteren Optionen mehr.
- Diesem Eindruck wurde ein wenig entgegengewirkt: Weiterhin werden zahlreiche Substanzen entwickelt, davon auch einige mit ganz neuen Wirkprinzipien (z.B. *Cleavage Site Inhibitor*).
- Allerdings befinden sich die meisten noch in recht frühen Stadien der klinischen Entwicklung.



Hepatitisvirus-Koinfektion

Hepatitis-B-Koinfektion in Stichworten

HBV-Testung

- Es wird zu wenig auf Hepatitis-B-Virus (HBV) getestet !
- In der amerikanischen HOPS-Kohorte wurden von 7050 aktiven Teilnehmern nur 61,2% (4315) auf HBV getestet. Von diesen hatten 369 (8,6%) eine chronische Hepatitis B.
- Die Prävalenz der HBV-Koinfektion hat sich in den vergangenen zehn Jahren nicht verändert (V-1622).

HBV-Impfung

- Die Hepatitis-B-Impfung ist unter ART erfolgreicher. Dies gilt auch für Patienten, deren Helferzellzahlen über 350/ μ l liegen.
- Dennoch lag die Rate der Patienten mit Impfansprechen insgesamt nur bei 44% (H-2314).

Hepatitis-C-Koinfektion in Stichworten

- Die HCV-Seroprävalenz in Spanien nimmt signifikant ab, da Drogengebrauch als Übertragungsweg seltener wird.
- Die Prävalenz betrug 2006 „nur“ noch 16,2% (V-1629).
- Es spielt keine Rolle, welches der beiden pegylierten Interferone zur Behandlung verwendet wird (V-1631).
- Lediglich 15-30% der koinfizierten Patienten erhalten eine Therapie, auch wenn keine Kontraindikationen vorliegen (V-1634, V-1637).
- Bei Patienten mit CD4 >350/μl war der Einsatz einer ART mit einer geringeren nekroinflammatorischen Aktivität in der Leberbiopsie assoziiert.
- Dies deutet auf einen günstigen Effekt der ART hin, der die mögliche Hepatotoxizität überwiegt (H-2319).

➔ Perez V-1629

➔ Butt V-1634

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⬆️ Übersicht



Abstracts

H-456

Use of Tenofovir Disoproxil Fumarate (TDF) in Pregnancy: Findings from the Antiretroviral Pregnancy Registry (APR)

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Background: The beneficial role of antiretrovirals (ARVs) in the prevention of mother-to-child transmission (PMTCT) of HIV was first demonstrated 14 years ago in ACTG Study 076 using zidovudine (ZDV) monotherapy. Studies of TDF have demonstrated a benefit in PMTCT in animal models and in pregnant women.

Methods: The APR is a prospective registry to detect major teratogenic effects involving ARVs administered to pregnant women through voluntary reporting from health care providers. The APR, which enrolls ~900 pregnant women with exposure to ARVs in the US each year (~14% of live births to HIV+ women) reports data since its inception January 1, 1989. Sufficient numbers of 1st trimester exposures to 11 ARVs including ZDV and TDF have been monitored to detect at least a 1.5- and 2-fold increase in overall birth defects respectively.

Results: Through July 31 2007 in 8483 prospective cases reported to the APR, no overall increase in congenital anomalies in infants following any first or 2nd/3rd trimester ARV exposure has been seen compared to the general population. Prevalence of anomalies with any ARV exposure in the first trimester was 2.8/100 live births (95% CI: 2.2-3.5) [74/2673]; with 2nd/3rd trimester exposure 2.6/100 live births (2.1-3.1) [109/4220]. Prevalence of anomalies with first trimester exposure to TDF was 1.6% (0.6-3.4) [6/380]; with 2nd/3rd trimester exposure 1.5% (0.4-3.9) [4/263]. No specific pattern of anomalies was reported. Prevalence of anomalies with first trimester exposure to ZDV was 2.9% (2.2-3.8) [53/1816]; with 2nd/3rd trimester exposure 2.7% (2.2-3.2) [121/4491]. These rates are comparable to those from the CDC population-based birth defects surveillance system (2.7/100 live births).

Conclusion: To date no increase in prevalence of or any specific pattern of congenital anomalies has been seen with use of TDF in 643 live births through prospective voluntary reporting to the APR. Additional studies of women receiving TDF during pregnancy and for PMTCT are warranted.

H-891

A Phase 2 Safety and Efficacy Study of Bevirimat (BVM) in Heavily Treatment Experienced HIV+ Patients Identifies the Target Phase 3 Study Profile

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Background: BVM is a novel HIV-1 maturation inhibitor targeting the Gag capsid SP-1 cleavage site. A prior 10 day study showed a 1 log viral load reduction (VLR) in patients given BVM 200mg QD. A separate retrospective analysis showed that patients without key baseline Gag polymorphisms at Q369, V370 or T371 were more likely to respond to BVM.

Methods: In a Phase 2 double-blind, randomized dose escalation study, 59 treatment-experienced patients with ≥ 1 primary resistance mutation received 2 weeks of BVM or placebo as functional monotherapy on top of a failing (VL >2000 copies/mL) background regimen. Patients initially received a 400mg BVM tablet dose, or placebo; in the modified study, patients received a 250, 300, 350 or 400mg BVM liquid dose, or placebo.

Results: Of 44 patients given the assigned BVM dose, the mean VL change was -0.6 log copies/mL (+0.05 log for 13 patients given placebo); 12/13 (92%) patients with BVM trough levels ≥ 20 ug/mL and without the key Gag polymorphisms had a VLR ≥ 0.5 log; 10/13 (77%) had a VLR >1.0 log (group mean VLR: -1.26 log). 32/46 (70%) BVM treated patients and 10/13 (77%) placebo treated patients had ≥ 1 adverse event (AE). For BVM and placebo treated patients respectively, the most common AEs were diarrhea (22%; 39%), nausea (20%; 31%) and headache (20%; 23%); all were Grade 1. For BVM and placebo treated patients respectively, the most common lab changes were: glucose (13%; 8%), total cholesterol (11%, 15%) and triglycerides (9%, 15%); nearly all were Grade 2.

Conclusion: Through 2 weeks BVM and placebo were similarly well tolerated, and responder patients with BVM troughs ≥ 20 ug/mL had a high magnitude VLR of 1.26 log. Planned Phase 3 studies will employ these criteria to confirm the utility of BVM in treatment-experienced patients.

H-892

Elvucitabine Phase II 48 Week Interim Results Show Safety and Efficacy Profiles Similar to Lamivudine in Treatment Naive HIV-1 Infected Patients with a Unique Pharmacokinetic Profile

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Background: Elvucitabine (ACH123,446)(ELV) is a cytosine NRTI analog with potent in-vitro activity against wild type HIV-1 virus

Methods: A Phase II, prospective, randomized, blinded, comparison of ELV 10 mg versus lamivudine (LAM) 300 mg both administered daily in combination with efavirenz 600 mg and tenofovir DF 300 mg in HIV-1-infected, treatment-naïve subjects.

Results: 77 subjects were randomized with 76 subjects receiving at least one dose of study medication. Seventy-four subjects (37 per treatment group) had both baseline and post-baseline HIV-1 RNA measurements. Fifty-five subjects completed 48 weeks of treatment. The reasons for not completing 48 weeks were: physician decision (n=5), voluntary withdrawal (n=5), adverse event (n=4), lost to follow-up (n=4), sponsor decision (n=3), and death (n=1). Baseline characteristics were similar between treatment groups. The proportion of subjects at week 48 with HIV-1 levels of less than 50 copies/mL in the ITT patient population was : 65% in the ELV and 78% in the LAM treatment group (95% CI for the difference = -0.34, 0.07)(as-treated patient population was 96% for ELV and 97% for LAM). At week 48, the ELV treatment group experienced a mean (SD) change in percent CD4 of +9.9 (6.3) versus +9.1 (7.2) with LAM. The incidence, frequency, type, and severity of adverse events were similar between treatment groups.

Conclusions: ELV administered in combination with tenofovir and efavirenz demonstrates substantial anti-viral activity.

H-893

RDEA806, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, Shows Positive Outcome in Treatment of Näive HIV Patients

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Background: RDEA806 is a novel NNRTI in development for the treatment of HIV infection. Preclinical testing has shown RDEA806 has a better resistance profile than other NNRTIs, and was safe and well tolerated with single or multiple doses in phase 1 trials. A phase 2a study was conducted to evaluate the pharmacokinetics (PK) of RDEA806 and its relationship with pharmacodynamic (PD) response (viral load reduction) after RDEA806 monotherapy in naïve HIV patients. In addition, secondary PD evaluation included the effect of RDEA806 on uric acid and b-hydroxycortisol/cortisol ratio.

Methods: A Phase 2a, randomized, double-blind, placebo-controlled, proof-of-concept trial was conducted in two cohorts of 12 naïve HIV patients each (9 active and 3 placebo); patients either received RDEA806 400 mg twice daily (BID), or 600 mg once daily (QD), for 7 days and a single morning dose on Day 8 for PK determination. Blood and urine samples were collected to assess viral load, b-hydroxycortisol/cortisol ratio, uric acid, and RDEA806 plasma levels.

Results: RDEA806 was readily absorbed with a mean T_{max} of 2.1 hr in both cohorts. Mean C_{trough} at steady state were 407 and 112 nM for the BID and QD groups, respectively, and were well above the anti-HIV EC_{50wt} (3 nM) and $EC_{50K103N}$ (2.3 nM). There was no correlation between the 1.5 - 2.0 log viral load reduction and AUC or C_{max} , although a trend was seen with C_{trough} . Significant dose-related reduction in uric acid levels was observed. b-hydroxycortisol/cortisol ratio was not significantly changed, indicating a lack of CYP450 3A4 induction.

Conclusions: RDEA806 exhibits favorable PK parameters with positive outcomes for both viral load and serum uric acid reduction. Studies with additional cohorts to evaluate higher once daily doses with an enteric coated tablet formulation are underway.

H-896a

STARTMRK, A Phase III Study of the Safety & Efficacy of Raltegravir (RAL)-Based vs Efavirenz (EFV)-Based Combination Therapy in Treatment-Naïve HIV-Infected Patients

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Background: We compared RAL-based to EFV-based regimens in treatment-naïve patients.

Methods: Patients with HIV RNA levels >5000 c/mL & no resistance to EFV, tenofovir (TDF) or emtricitabine (FTC) were eligible for a blinded randomized study of RAL (400 mg bid) vs EFV (600 mg qhs), each with TDF/FTC. The primary efficacy endpoint was the proportion of patients with RNA levels <50 c/mL at Wk 48.

Results: Of 281 RAL-treated & 282 EFV-treated patients, 53% had RNA levels >10⁵ c/mL & 47% had CD4 counts <200 cells/mm³ at entry. At Wk 48 counting non-completers as failures, 86.1% vs 81.9% achieved RNA levels <50 c/mL in the RAL & EFV groups, respectively [D (95% CI) = 4.2% (-1.9, 10.3), non-inferiority p<0.001]. Time to virologic response was shorter for RAL vs EFV recipients (p<0.001). Mean CD4 count change from baseline to Wk 48 was 189 vs 163 cells/mm³ in the RAL & EFV groups, respectively [D (95% CI) = 26 (4, 47)]. Clinical adverse events (CAEs) (90% vs 96%; p=0.002) and drug-related CAEs (44% vs 77%; p<0.001) occurred less often in RAL vs EFV recipients. By Wk 8, 31 central nervous system (CNS) symptom had occurred in more EFV than RAL recipients (p<0.001). At Wk 48, changes from baseline cholesterol (C), LDL-C, & triglycerides were lower in RAL vs EFV recipients (each p<0.001); modest increases in HDL-C seen in both groups were higher in the EFV group (p<0.001). Cancer occurred in 1 RAL & 9 EFV recipients, & was deemed drug-related in 2 EFV cases.

Conclusions: In treatment-naïve patients given 48 wks of therapy, RAL/TDF/FTC had non-inferior antiretroviral activity compared to EFV/TDF/FTC & was associated with greater increases in CD4 counts & fewer CNS symptoms.

H-896b

Initiating Rather than Deferring Haart at a CD4+ Count Between 351-500 Cells/mm³ is Associated with Improved Survival

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Background: The optimal time to initiate highly active antiretroviral therapy (HAART) for asymptomatic HIV-infected individuals is uncertain. Clinical trial data are lacking, but guidelines recommend HAART for patients with a CD4+ count of <350 cells/mm³ based on observational data. However, previous studies have been limited by insufficient sample size, follow-up, and methods to examine HAART initiation among patients with higher CD4+ cell counts.

Methods: In a U.S. and Canadian collaboration, we examined all participants with a CD4+ count of 351-500 cells/mm³ between 1996-2006 who were free of clinical AIDS and were antiretroviral naïve. We compared the relative hazard (RH) of death for patients who initiated HAART with a CD4+ count between 351-500 cells/mm³ with those who deferred treatment using inverse-probability weighted Cox proportional hazards analyses.

Results: Of 5,926 patients who had a CD4+ count between 351-500 cells/mm³, 1,921 (32%) initiated HAART and the remaining 4,005 (68%) deferred treatment. Among patients who initiated HAART, 206 died during 6,949 person-years of follow-up (3.0 deaths per 100 person-years). Among those who deferred treatment, 387 died during 12,155 person-years of follow-up (3.2 deaths per 100 person-years). In adjusted analyses stratified by cohort and calendar-year, patients with a CD4+ count between 351-500 cells/mm³ who deferred treatment had a significantly higher risk of mortality compared with those who initiated HAART (RH 1.74, 95% CI 1.4-2.1; p<0.001).

Conclusions: We found 74% higher risk of death for patients who deferred treatment rather than initiating HAART at a CD4+ count between 351-500 cells/mm³. Results from this large North American cohort collaboration support initiation of HAART at a CD4+ count of 351-500 cells/mm³, an earlier stage of HIV disease than currently recommended.

H-1232

Cross Resistance Between HIV-1 Integrase Strand Transfer Inhibitors (InSTIs) Raltegravir, Elvitegravir and Second Generation InSTIs

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Background: Raltegravir (RAL) is the first approved agent in a new HIV-1 therapeutic class, the integrase strand transfer inhibitors. Other drugs in this class are in development including elvitegravir (EVG). As with all antiretrovirals, InSTIs can select for mutations that confer cross resistant to other drugs in the class. To understand the potential for cross resistance among InSTIs, we examined the susceptibility of a panel of RAL-resistant viruses to EVG and second generation InSTIs, focusing on mutants identified from the RAL clinical trials.

Methods: Virologic failure to RAL was generally associated with one of three signature mutations in integrase (N155H, Q148H/K/R, or Y143C/H/R), usually in combination with additional secondary mutations. These mutations were introduced into a wild-type proviral DNA clone and the resultant viruses were evaluated for drug susceptibility in a single cycle infectivity assay.

Results: The single mutations N155H, Q148H/K/R or Y143R all conferred resistance to RAL which was further increased by the presence of relevant secondary mutations. Most RAL-resistant viruses displayed greater resistance to EVG. In contrast, the second generation inhibitors MK-0536 and MK-2048 displayed less cross resistance, but in general the degree of resistance to those compounds was much lower than to either RAL or EVG.

Conclusions: Mutations identified in patients who developed RAL resistance in clinical trials conferred significant cross-resistance to EVG. Though clinical cutoffs for neither RAL nor EVG have been established, this observation suggests sequencing these two InSTIs is unlikely to be successful. By contrast, such viruses remained sensitive to second generation inhibitors developed to be active against clinical RAL-resistant variants, providing proof of principle for developing InSTIs capable of addressing RAL- or EVG-resistance in vivo.

H-1232a

Reanalysis of the MERIT Study with the Enhanced Trofile Assay

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Background: A study of maraviroc (MVC) vs efavirenz (EFV), both with Combivir (CBV) (MERIT), in ARV-naive patients with only R5 HIV-1 failed to show noninferiority of MVC for <50 copies/mL at Week 48 (ITT). Nearly half of MVC virologic failures occurred with CXCR4-using HIV possibly present but undetected at screening. Improved detection of low CXCR4-using virus may have better identified patients unlikely to respond to MVC.

Methods: Screening samples from MERIT patients enrolled on the basis of an R5 Trofile (Monogram) result were retested with the recently introduced enhanced Trofile assay with greater sensitivity for CXCR4 use. Key Week 48 endpoints were reanalyzed after excluding those who rescreened with non-R5 virus.

Results: 107 of 721 patients (14.8%) across both treatment arms were excluded for dual/mixed tropism using the new test. Baseline characteristics were similar for the original and revised populations.

Conclusions: A retrospective analysis of MERIT screening samples with the enhanced Trofile assay identified ~15% of patients with non-R5 HIV. Excluding these improved the efficacy of MVC relative to EFV compared with results using the original assay. The lower one-sided 97.5% confidence bound of the 48 week treatment difference between MVC and EFV for both < 400 and < 50 copies/mL was greater than -10% in this retrospective analysis.

Tabelle siehe nächste Folie

H-1232a (Forts.)

Week 48 [†]	Enhanced Trofile reanalysis			Original analysis (Standard Trofile)		
	MVC BID + CBV (N=311) ^{††}	EFV + CBV (N=303) ^{††}	Difference* (lower bound of 1-sided 97.5% CI)	MVC BID + CBV (N=360)	EFV + CBV (N=361)	Difference* (lower bound of 1-sided 97.5% CI) [#]
Number excluded for a dual/mixed screening result by enhanced Trofile	49	58	N/A	-	-	-
HIV RNA <400 copies/mL, %	73.3	72.3	0.6 (-6.4)	70.6	73.1	-3.0 (-9.5)
HIV RNA <50 copies/mL, %	68.5	68.3	-0.2 (-7.4)	65.3	69.3	-4.2 (-10.9)
Mean change from baseline in CD4+ T-cell count, cells/mL (LOCF)	174	144	30 (10-51 [‡])	170	143	26 (7-46 [‡])
Discontinuations, %:						
Lack of efficacy	9.3	4.0	N/A	11.9	4.2	N/A
Adverse events (all cause)	4.2	14.2	N/A	4.2	13.6	N/A
Other	10.9	7.6	N/A	10.8	7.5	N/A

[†]Includes all patients with an R5 screening result by enhanced Trofile assay who received at least one dose of MVC BID or EFV; missing values classified as failures/non-responders except where indicated; ^{††}After exclusions listed; *Adjusted for randomization strata; [‡]95% CI. [#]Noninferiority defined by lower bound of 1-sided 97.5% CI > -10%. Since the primary analysis is based on the original Trofile assay, the confidence intervals presented in this table for the enhanced assay are for descriptive purposes only.

H-1239

Reduction in AIDS Defining Events/Death (ADE/D) with Etravirine (ETR) Compared to Placebo (PL): Pooled DUET 48 Week Results

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Background: The clinical benefit of newer regimens for treatment experienced patients is unknown.

Methods: ADE were adjudicated by an independent panel (confirmed or probable) from 2 placebo controlled studies of ETR + darunavir + NRTI(s) +/- enfuvirtide (ENF). Pre-specified analyses were done using all patients and stratified by de novo or not de novo (including recycled ENF or not used) ENF use.

Results: 1203 patients had a baseline median CD4 of 105, log₁₀ HIV RNA of 4.8 and 59% had CDC C classification. Overall, 59 (9.8%) of PL and 35 (5.8%) of ETR patients had an ADE/D (P = 0.041). 22 ADE/D occurred in the first 30 days (16 in PL). Time to ADE/D was significantly shorter for PL than ETR (figure). The most common ADEs were Candida esophagitis (10), PCP (9), HSV (8), MAC, (7) CMV retinitis (6) and KS (6). Death was the first event in 8/20 PL and 8/12 ETR patients.

In the sub-group on de novo ENF (n=312), events were similar. However, in those not on de novo ENF (n=891), PL had more events than ETR (10.1% vs 5.4%; P = 0.0086).

Conclusions: In addition to virologic and immunologic benefits, use of ETR was associated with a significant longer time to ADE/D compared to placebo in treatment-experienced patients.

H-1249

AIDS Defining Conditions (ADCs) in the BENCHMRK -1 and -2 trials: 48 Week Analysis

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Background: Two phase III trials (BENCHMRK-1 and -2) of the integrase inhibitor raltegravir (RAL) (400 mg bid) vs placebo (PBO), plus optimized background therapy (OBT), in highly treatment experienced patients failing other antiretroviral therapies were analyzed through 48 weeks of double-blind treatment; primary endpoint was HIV RNA. Although not designed to detect significant differences in development of ADCs, a meta-analysis was done to evaluate their occurrence.

Methods: All new or recurrent clinical ADCs (excluding CD4 < 200/uL) identified by investigators or study personnel were reviewed by an independent adjudicator not involved in the trials and blinded to treatment assignment, for determination whether the event met prespecified criteria for a confirmed ADC. Confirmed ADCs included definitive and presumptive diagnoses, according to established conventions. Results are shown as incidence rate per 100 patient-years (PYR) at risk.

Results: At entry, patients had advanced disease; 293/462 (63%) and 165/237 (70%) of the RAL and PBO groups had a previous clinical ADC and median CD4 counts were 119 and 123 cells/uL, respectively. At wk 48, 62% and 33% of patients in the RAL vs PBO groups achieved HIV RNA <50 copies/mL. 17/462 pts treated with RAL had at least 1 confirmed ADC compared with 11/237 treated with PBO. The incidence rates per 100 PYR were 3.7 for RAL and 6.2 for PBO. The RR (95% CI) was 0.6 (0.3, 1.4). The most common ADC in both groups was esophageal candidiasis. The median (IQR) time to onset of the ADC was 64 (50-122) and 105 (19-118) days for RAL and PBO groups, respectively.

Conclusions: The incidence rate of confirmed ADCs was numerically lower for RAL compared with PBO at Week 48, though not statistically significant.

H-1250c

ARTEMIS: Efficacy and Safety of Darunavir/ritonavir (DRV/r) 800/100 mg Once-daily vs Lopinavir/ritonavir (LPV/r) in Treatment-naïve, HIV-1-infected Patients at 96 Wks

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Background: DRV/r efficacy & safety are compared with LPV/r in treatment-naïve patients (pts) in ARTEMIS; Wk 96 results are shown.

Methods: Pts (HIV-1 RNA [VL] ³5000 cpm, stratified by baseline [BL] VL & CD4) received DRV/r 800/100 mg qd or LPV/r 800/200 mg total daily dose, + TDF & FTC. Primary endpoint: non-inferiority of DRV/r to LPV/r (D $\frac{3}{4}$ 12%) in confirmed VL <50 cpm, ITT-TLOVR. DRV/r superiority (D 0%) was assessed if it was non-inferior.

Results: 689 pts randomized & treated; mean BL VL: 4.85 log₁₀ cpm; median CD4: 225 cells/mm³. Significantly more DRV/r than LPV/r pts had VL <50 cpm, confirming DRV/r non-inferiority (p<0.001) and superiority (Table). DRV/r response rates were statistically superior to LPV/r in pts with high BL VL & low BL CD4, demonstrating higher potency of DRV/r. Fewer DRV/r than LPV/r pts (4% vs 9%) discontinued treatment due to adverse events. Fewer DRV/r than LPV/r pts (4% vs 11%, p=0.0006) had grade 2-4 treatment-related diarrhea. Grade 2-4 treatment-related rash occurred infrequently (3% DRV/r vs 1% LPV/r, p=0.273). DRV/r pts had smaller mean increases in triglycerides & total cholesterol (0.1 & 0.6 mmol/L) than LPV/r pts (0.8 & 0.9 mmol/L, p<0.0001 for both); levels remained below NCEP cut-offs.

Conclusions: At 96 wks, DRV/r 800/100mg qd proved non-inferior and statistically superior to LPV/r in treatment-naïve pts. DRV/r was associated with lower rates of diarrhea and smaller mean increases in triglycerides & total cholesterol.

VL <50 cpm (ITT-TLOVR), n (%)	DRV/r	LPV/r	DRV/r-LPV/r [95% CI]	P value of superiority
All pts	271/343 (79)	245/346 (71)	8 [2; 15]	0.012
BL VL <100,000 cpm	182/226 (81)	170/226 (75)	5 [-2; 13]	0.174
BL VL ³ 100,000 cpm	89/117 (76)	75/120 (63)	14 [2; 25]	0.023
BL CD4 <200 cells/mm ³	111/141 (79)	96/148 (65)	14 [4; 24]	0.009
BL CD4 ³ 200 cells/mm ³	160/202 (79)	149/198 (75)	4 [-4; 12]	0.345

H-1250d

CASTLE: Atazanavir-Ritonavir vs Lopinavir-Ritonavir in Antiretroviral-Naïve HIV-1 Infected Patients: 96 Week Efficacy & Safety

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Background: ATV/r has similar efficacy to LPV/r with more favorable lipid & GI profiles in treatment-naive HIV-infected patients after 48 weeks of therapy. Efficacy & safety through Week (Wk) 96 are presented.

Methods: Randomized, open-label, prospective study of once-daily ATV/r vs twice-daily LPV/r, both with fixed dose tenofovir/emtricitabine in 883 patients. Analyses at Wk 96: % with HIV RNA <50c/mL, emergence of resistance, adverse events (AEs), D CD4 cell count & fasting lipids.

Results: Overall 19% of subjects discontinued before Wk 96 (16% ATV/r, 21% LPV/r). Virologic failure was low in both arms (7%). Grade 2-4 related hyperbilirubinemia was greater on ATV/r ; grade 2-4 related diarrhea & nausea were greater on LPV/r. Mean percent D in fasting TGs & TC from baseline were significantly lower on ATV/r vs LPV/r.

Conclusions: Non-inferiority of ATV/r vs LPV/r was confirmed at Wk 96. In the ITT analysis, ATV/r had higher response rates. This difference in response was driven by discontinuations among subjects on LPV/r. ATV/r continues to demonstrate a better lipid profile and fewer GI AEs vs LPV/r.

Efficacy Results at Wk 96 - As-Randomized Subjects	ATV/r N = 440	LPV/r N=443	Difference Estimate (95% CI; p-value) ATV/r - LPV/r
HIV RNA < 50 c/mL, n/N (%) CVR NC=F (ITT)	327/440 (74)	302/443 (68)	6.1 (0.3, 12.0; p<0.05)
Qualifying HIV RNA >= 100,000 c/mL	165/223 (74)	149/225 (66)	
Baseline CD4 < 50 cells/mm ³	45/58 (78)	28/48 (58)	
VR-OC (OT)	326/365 (89)	302/345 (88)	1.6 (-3.1, 6.2, p=NS)
CD4, mean change from baseline, cells/mm ³	268	290	-21.2 (-43.3, 0.9; p=NS)

H-1265

A First in Human Study Evaluating the Safety, Tolerability and Pharmacokinetics (PK) of SPI-256, a Novel HIV Protease Inhibitor (PI), Administered Alone and in Combination with Ritonavir (RTV) in Healthy Adult Subjects

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Background: There is an ongoing need for potent and broad-spectrum HIV PI in primary treatment settings and to treat multi-drug resistant (mdr) HIV strains. SPI-256 is a novel HIV PI, designed to inhibit the development of resistance by focusing on conserved segments of the protease enzyme; the average IC₅₀ against a panel of mdr HIV is 3.9 nM.

Methods: In this single-, escalating-dose FTIH study, 59 healthy volunteers, who took either single doses of SPI-256 in Phase 1 (N=38), or a single dose of SPI-256 co-dosed on the third day of RTV dosing in Phase 2 (N=29), were enrolled; 16 subjects participated in both phases. One cohort evaluated exposures after a high fat meal (N=8). Primary endpoints were subject safety and PK data.

Results: There were few adverse events (AEs). There was a single SAE in a subject who was never exposed to SPI-256. Safety labs (hematology, chemistry, urinalysis) were largely unremarkable. Three (7.9%) subjects reported a total of 8 AEs in Ph.1, and 2 (5.4%) subjects each reported 1 AE in Ph. 2, which were considered possibly or definitely related to study medication. Tachycardia (orthostatic in all but 1 report) was the single most frequently reported AE, with 13 reports in Ph. 1 and 12 reports in Ph. 2, and was equally noted in subjects on placebo, SPI-256/RTV, and RTV alone.

Median SPI-256 t_{max} after a single oral dose (fasted), with and without co-dosed RTV was 1 to 4 hr, and was prolonged slightly (6 hr) when administered alone with food. Mean t_{1/2} ranged from approximately 6 to 14 hr and was unaffected by food or RTV. RTV increased SPI-256 exposure dramatically; food also increased SPI-256 exposure.

Conclusions: SPI-256 is a promising new HIV PI with desirable safety and PK profiles. RTV markedly enhances SPI-256 exposure, suggesting that SPI-256 may be amenable to boosting with novel CYP3A inhibitors (PK enhancers).

H-1267

Bimodal Binding to HIV-1 Protease of GRL-02031 (G31), a Novel Protease Inhibitor (PI) Containing a Cyclopentanyltetrahydrofuran (Cp-THF)

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Background: We generated a novel non-peptidic PI, G31, by incorporating a stereochemically defined fused Cp-THF and determined its activity against various laboratory, clinical, and mutant infectious clonal HIV-1 strains and examined the binding mode of G31 with protease.

Methods: Anti-HIV-1 activity of various PIs against HIV-1 was determined with p24 assay using MT-4 cells. The interactions of G31 with HIV-1 protease were determined with refined simulation and molecular docking based on published crystallographic data of HIV-1 protease complexed with PIs.

Results: G31 was potent against various wild-type and multi-drug-resistant HIV-1 variants of differing clades with EC_{50} values of 0.014 - 0.042 mM. In detailed analyses using HIV-1_{NL4-3}-based molecular infectious clones containing a single primary mutation including D30N, G48V, I50V, and L90M or combined mutations, we found no significant changes in EC_{50} values, although G31 was slightly less active against HIV-1 variants containing consecutive amino acid substitutions: M46I/I47V or I84V/I85V (~3x difference in EC_{50}). Structural modeling analyses demonstrated a distinct bimodal binding to HIV-1 protease of G31. The alternate binding modes should provide advantages to the PI in maintaining its antiviral potency when HIV-1 has polymorphism and/or develops amino acid substitutions under drug pressure.

Conclusions: The present data warrant that G31 with a unique bimodal protein binding profile be further developed as a potential therapeutic agent for treatment of infection with multi-drug-resistant HIV-1.

H-1268

TRI-1144: A Placebo-Controlled, Single-Dose Escalation Study of the Fusion Inhibitor TRI-1144 in Healthy Volunteers

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Background: Enfuvirtide (ENF, Fuzeon[®]), the first approved HIV entry inhibitor and an important therapeutic for treatment-experienced patients, is administered as a 90 mg/1mL SC injection BID. Challenges with reconstitution, administration and injection site reactions (ISR) have limited ENF use. Comparatively, TRI-1144 has demonstrated similar to improved potency and a higher genetic barrier to resistance *in vitro* and markedly improved physical and pharmacokinetic (PK) properties in *cyno* monkeys. Reported herein are initial PK, safety, and ISR data from the first human trial of TRI-1144.

Methods: This was a blinded, placebo-controlled single-dose, escalation study. Healthy subjects were randomized to receive TRI-1144 (125 mg/mL) or placebo (saline). Serial plasma samples for PK analyses, plus AE and ISR were collected through 7 days post-dose.

Results: 24 subjects were enrolled and dosed at 25 mg (N=3), 50 mg (N=6), 125 mg (N=6), 250 mg (N=3) or saline (N=6); all completed the study. PK was linear over the dose range. Mean values for C_{max} ranged from 1.4 to 16.3 mg/mL, C_{24h} from 0.67 to 12.4 mg/mL, AUC from 34.2 to 489.3 (h.mg/mL) and $t_{1/2}$ from 13.4 to 19.7 h. T_{max} (median) was dose independent at ~11 h.

Safety: 8/24 subjects experienced 10 AE's; 7 mild (4 considered possibly related) and 3 moderate but unrelated to drug/placebo.

Tolerability: 17/24 subjects experienced a Grade 1 or greater ISR; the most frequently noted ISR signs/symptoms were erythema, pain/discomfort and induration with most resolved by 96 h post-dose. No nodules/cysts were noted and no ISR was observed in the 25mg group.

Conclusions: TRI-1144 was well-tolerated by all subjects in this Phase I study and no ISR were noted at 25mg. Given the *in vitro* profile of TRI-1144, PK analyses suggest that a 25 to 50 mg daily dose of TRI-1144 could achieve therapeutic plasma levels (~1 mg/mL). Thus, TRI-1144 appears to be an excellent FI candidate from this initial assessment and may offer advantages over ENF use in the clinic.

H-1269a

Antiviral Activity and Tolerability of 5 mg/kg and 10 mg/kg Doses of PRO 140, a Humanized Monoclonal Antibody to CCR5

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Background: PRO 140 potently inhibits CCR5-tropic (R5) HIV *in vitro*. In a prior study, single 5mg/kg IV doses reduced HIV RNA by 1.83 log₁₀ in subjects with early-stage disease and R5 virus only. The present study compared 5mg/kg and 10mg/kg IV doses for antiviral activity and tolerability.

Methods: Entry criteria included HIV RNA >5,000 copies/mL, R5 virus only, CD4 >300/mL, and no antiretroviral therapy for 12 weeks. Subjects were randomized to receive placebo, 5mg/kg PRO 140 or 10mg/kg PRO 140. They were followed for 58 days post-treatment. An interim analysis was performed on data from the first 15 subjects.

Results: Interim enrollment was equally distributed across the treatment groups. Baseline HIV RNA and CD4 averaged 35,480 cps/mL and 403/mL, respectively. Mean maximum log₁₀ reductions in HIV RNA were 0.48 (range 0.15-0.73) for placebo, 1.90 (range 1.44-2.17, p<0.0001) for 5mg/kg PRO 140 and 2.17 (range 2.09-2.26, p<0.0001) for 10mg/kg PRO 140. At Day 12, mean log₁₀ changes in HIV RNA were +0.06, -1.88 (p<0.0001), and -2.01 (p<0.0001) for placebo, 5mg/kg and 10mg/kg, respectively. The mean viral load reduction was >1.5 log₁₀ through Day 22 at 10mg/kg. PRO 140 was generally well tolerated. Trial enrollment has completed, and updated data will be presented.

Conclusions: The data confirm the antiviral activity reported previously for 5mg/kg PRO 140. A 10mg/kg dose increased the duration of antiviral effect. The findings indicate the potential for infrequent IV dosing. SC dosing regimens are also being evaluated.

H-2312a

Continuous Antiretroviral Therapy (ART) Decreases Bone Mineral Density: Results from the SMART Study

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Background: HIV-infected adults have lower bone mineral density (BMD) than the general population and may experience more fractures. We evaluated the role of ART.

Methods: In the SMART trial, HIV+ patients with CD4 counts > 350 cells/mm³ were randomized to continuous ART (Viral Suppression [VS] group) or CD4-guided intermittent ART (Drug Conservation [DC] group). In 214 patients, hip and spine BMD were measured annually by dual-energy x-ray absorptiometry (DXA) and trabecular BMD of the spine by quantitative computed tomography (qCT). We compared treatment groups for change in BMD using longitudinal models and, in the main SMART study, for incidence of passively reported fractures using Cox regression. In the VS cohort, we evaluated associations of BMD decline with cumulative ART use.

Results: Patients (98 randomized to the VS and 116 to the DC group; median 44 years, 19% female, 73% on ART, 12% with osteoporosis, median t-scores -0.5 [femur], -0.9 [spine qCT], and -0.7 [spine DXA]) were followed for a mean of 2.4 years. In the VS group, patients received ART for 93% of follow-up time, compared with 37% in the DC group. BMD declined by 0.9% per year (femur), 2.9% (spine qCT) and 0.4% (spine DXA) in the VS group, and significantly less in the DC group. Estimated DC minus VS group differences in mean BMD change from baseline through follow-up were 1.4% (95% CI 0.5 to 2.3; p=0.002) at the femur, 2.9% (95% CI 0.7 to 5.1, p=0.01) for spine qCT, and 1.2% (95% CI 0.02 to 2.3, p=0.05) for spine DXA. No consistent drug-specific association with BMD decline was found. In the main study (n=5472, mean 2.8 years of follow-up), 10 patients in the VS and 2 in the DC group reported fractures as grade 4 adverse events (hazard ratio 4.9 [95% CI 1.1 to 22.5]; p=0.04).

Conclusions: Continuous ART is associated with decline in BMD and possibly more fractures relative to intermittent, CD4-guided ART. Intermittent ART is not recommended due to increased risk of AIDS and death observed in the SMART study.

H-2314

Highly Active Antiretroviral Therapy Improves Hepatitis B Vaccine Response Regardless of CD4 Count

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Background: The impact of HAART on response to hepatitis B (HB) vaccine in HIV-infected individuals has not been reported. We analyzed factors associated with developing a protective vaccine response in the Tri-Service AIDS Clinical Consortium HIV Natural History Study.

Methods: Patients without prior vaccination who received ³1 dose of HB vaccine after HIV infection were included. HBsAb results 3-9 months after last vaccination were used to classify vaccinees as nonresponders (HBsAb <10 IU/L) or responders (HBsAb ³10 IU/L). Multivariate logistic regression was used to assess factors at first vaccination associated with subsequent vaccine response. Odds ratios are given with 95% confidence intervals.

Results: Of 626 persons, 217 (35%) were vaccine responders. In multivariate analyses being male was associated with a reduced odds of developing a response (0.54, 0.31-0.96) while receipt of ³3 doses compared to ²2 doses was associated with increased odds of response (2.07, 1.39-3.08). Compared to those on HAART with CD4 count ³350, those on HAART with CD4 count <350 had equivalent odds of developing a response (0.60, 0.26-1.41), while those not on HAART at vaccination had significantly reduced odds of developing a vaccine response irrespective of CD4 category (0.25, 0.12-0.51 for those with CD4 count <350; 0.53, 0.30-0.91 for those with CD4 count ³350).

Conclusions: Receipt of HAART at the time of initial HB immunization significantly increased the probability of developing a protective HB vaccine response in patients with HIV, even those with CD4 counts ³350, providing additional evidence of benefits from HAART in those with higher CD4 counts.

H-2319

HAART is Associated with a Lower Level of Hepatic Necroinflammatory Activity in HIV-HCV Coinfected Patients with CD4 > 350 at the Time of Liver Biopsy

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Background: It has been suggested that HAART should be initiated earlier in HIV-HCV coinfecting patients but there are very few data to support this recommendation. The objective of our study was to evaluate factors (including use of HAART) associated with liver damage in HIV/HCV coinfecting patients with > 350 CD4.

Methods: HIV-HCV coinfecting patients who underwent liver biopsies and had a CD4 cell count ≥ 350 cells/mm³ at the time of liver biopsy were included. Exclusion criteria included positive hepatitis B surface antigen and prior anti-HCV therapy. All liver biopsies were evaluated by a single pathologist. Necroinflammatory activity (NA) and fibrosis was scored by the Scheuer System. Steatosis was scored according to the % hepatocytes affected. Logistic regression analysis was used to assess determinants of NA ≥ 3 . Since this is a cross-sectional study we selected NA as the main variable because using or not using HAART probably has a less time-dependent impact on NA than in fibrosis progression.

Results: 119 coinfecting patients were included. (Table 1). Values are expressed as the median (IQR) for continuous variables and as N (%) for categorical variables.

Conclusions: Use of HAART at the time of liver biopsy was associated with lower levels of NA. NA was strongly associated with higher fibrosis scores. These results suggest that HAART might decrease hepatitis C activity in HIV/HCV coinfecting patients with > 350 CD4.

Tabelle siehe nächst Folie

H-2319 (Forts.)

Characteristic	NA \geq 3 (n=30)	NA < 3 (n=89)	Univariate analysis p value	Multivariate analysis OR (95%CI) p value
Age (yr)	37 (34-40)	38 (35-41)	NS	
Male Sex	24 (80)	69 (77.5)	NS	
Alcohol Abuse*	12 (40)	17 (19.1)	0.021	NS
ALT (U/L)	137 (56-203)	92 (51-113)	0.022	1.01 (1-1.02) 0.052 0.16
Receiving HAART at the time of biopsy	20 (66.7)	73 (82)	0.078	(0.03-0.78) 0.024
Duration of HAART in days	1504.5 (1268-1972)	1421 (1127-1908)	NS	
Nadir CD4 (cells/ mL)	152 (81-331)	218 (117-345)	NS	
CD4 (cells/mL)	593 (447-645)	615 (464-684)	NS	
HIV RNA <400 copies/mL	16 (53.3)	55 (61.8)	NS	
HCV RNA >800.000 copies/mL	17 (56.7)	41 (46.1)	NS	
HCV Genotype 1 or 4	21 (70)	64 (71.9)	NS	
Fibrosis score \geq 3	23 (76.7)	4 (4.5)	<0.001	131.9 (24.8-700.8) <0.001
Steatosis	25 (83.3)	52 (58.4)	0.014	NS

Note: NS, not significant. *Current HAART was not associated with alcohol abuse.

H-2330

Rates of AIDS-Defining Opportunistic Conditions (ADOCs) and CD4 Cell Counts at ADOC Diagnosis in the U.S. HIV Outpatient Study (HOPS), 1994-2006

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Background: Highly active antiretroviral therapy (HAART) and antimicrobial prophylaxis have reduced the rates of ADOCs among HIV-infected persons, but it is not clear if these rates have continued to decline or have stabilized in recent years.

Methods: We calculated annual incidence rates of ADOCs per 1000 person-years (py) among HOPS patients at 10 U.S. clinics. Start of observation (baseline) was 1/1/1994 or first HOPS visit thereafter. End of observation was the earliest of: date of ADOC diagnosis, date of last HOPS contact, or 12/31/2006. Using Poisson regression models, and adjusting for sex, race, and HIV risk category, we estimated annual percent changes in ADOCs rates within 3 periods: 1994-1997, 1998-2001, and 2002-2006.

Results: Among 7825 patients analyzed (median age at baseline 38 years, median CD4 at baseline 295 cells/mm³, 81% male, 57% white, and 58% men who had sex with men), rates of ADOCs fell precipitously during 1994-1997 (Table) with continued declines through 2006 for *Mycobacterium avium* complex (MAC) and the combined category of OI malignancies. The CD4 at ADOC diagnosis increased over time for Kaposi's sarcoma ([KS], median CD4 of 38, 107, 143 cells/mm³, respectively over the 3 periods, p<0.001), but did not change significantly for other ADOCs in the Table.

Conclusions: The rates of most ADOCs have stabilized during 2002-2006. The increases in median CD4 at diagnosis of KS may signal a shift in the epidemiology of this cancer in the HAART era.

Table. Observed incidence rates per 1000 py and adjusted annual changes in the rates of first occurrence of each AIDS-defining opportunistic illness among HOPS patients, 1994-2006

Category	Incidence rate		Adjusted estimates of annual percent change in incidence rate during period (95% CI)		
	1994	2006	1994-1997	1998-2001	2002-2006
OI cancers†	40.6	2.6	-37 (-44, -28)	-24 (-41, -1)	-19 (-34, -1)
OI infections‡	111.2	13.6	-27 (-36, -18)	-19 (-27, -10)	-9 (-20, 3)
CMV disease	46.2	2.9	-37 (-49, -21)	-27 (-47, 1)	19 (-12, 60)
PCP	36.4	4.2	-30 (-41, -17)	-14 (-29, 4)	-12 (-26, 9)
MAC	33.9	1.3	-23 (-34, -10)	-23 (-37, -7)	-27 (-43, -6)
KS	30.2	0.8	-39 (-47, -29)	-26 (-47, 3)	-10 (-33, 21)
Esophageal candidiasis	18.7	5.6	-18 (-33, 1)	-24 (-34, -12)	-4 (-22, 17)

*CI: Confidence Interval; CMV, cytomegalovirus; PCP, *Pneumocystis jirovecii* pneumonia. † Includes KS, non-Hodgkin's lymphoma and CNS lymphoma. ‡ Includes all AIDS-defining opportunistic infections, except recurrent pneumonia (because unable to distinguish viral from bacterial pneumonia in the database) and salmonella septicemia (because only one case).

H-2337

The Longitudinal Characterization of an Emerging Pattern of HIV-associated Kaposi's Sarcoma

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Background: HIV-associated Kaposi's Sarcoma (KS) typically presents in patients with low CD4 count and high HIV viral load and regresses when antiretroviral therapy (ART) is maximized.

Methods: Cohort of fourteen homosexual males with HIV and persistent KS despite at least two years of sustained CD4 count above 300 cells/ μ L and viral load suppression below 300 copies/ml. The cohort was established to determine the longitudinal virologic, immunologic, and clinical characteristics. We report here on the full results including baseline characteristics and follow-up.

Results: The median age at presentation was 53 years (41-75 years). The median duration of HIV was 17.5 years (4-25 years). The majority of patients had an undetectable viral load and all had CD4 count greater than 330 at baseline. Two had prior history of visceral KS. All have now been on ART for at least two years with maintenance of HIV viral load suppression and high CD4 count. All continue to have relatively indolent cutaneous KS lesions, none have developed new visceral KS lesions. One patient has been diagnosed with lymphoma, the remainder have been without AIDS-related opportunistic infections or illnesses other than KS.

Conclusion: Unlike typical patients with HIV-associated KS, the patients in our cohort have persistently high CD4 count and low HIV viral load. The occurrence of KS in these patients raises questions about underlying immune system abnormalities that may not be captured by CD4 count. Practitioners should be encouraged to report similar patients or clusters in order to establish how widespread this phenomenon is and to pool information on effective treatments.

V-1622

Chronic Hepatitis B Virus (HBV) Infection in the HIV Outpatient Study, 1996-2006: Prevalence in the Era of Evolving Interventions

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Background: Co-infection with HBV is an important cause of chronic liver disease among patients infected with HIV.

Methods: We calculated the prevalence of chronic HBV infection annually from 1996-2006 by age, gender, risk factor for HIV, and race/ethnicity in the HOPS, a multi-site observational cohort study of HIV-infected patients. Prevalence was defined as the number of patients with a positive HBsAg or HBeAg or detectable HBV DNA divided by the number of patients tested for chronic HBV infection.

Results: Of the 7,050 patients in the HOPS during 1996 to 2006, 4,315 (61.2%) were tested for chronic HBV infection. Of these, 369 (8.6%) were positive for HBsAg or HBeAg or detectable HBV DNA. Annual chronic HBV infection prevalence ranged from 8.0% to 8.7% over the study period with downward but statistically insignificant trend. Prevalence was highest among patients aged 40-49 years, men, and men who have sex with men.

Conclusions: The prevalence of chronic HBV infection in the HOPS was unchanged over the past decade among patients in all demographic and HIV risk groups, but overall was 20 times greater than national prevalence estimates (0.42%). Although HBV infection treatment options now exist for co-infected patients, vaccination of persons at risk for HBV infection remains the most essential intervention.

V-1629

Sharp Decline in The Seroprevalence of Hepatitis C Virus Among HIV-infected Patients in Spain

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Background: The HIV epidemic is experiencing some changes in Spain, mainly due to a decrease in the transmission of the infection by injection drug use (IDU). We hypothesized that this change may have important repercussions in the epidemiology of HIV/HCV coinfection in our country.

Methods: We collected data from 5170 HIV-positive ART-naïve patients of two different cohorts, who initiated care in Spanish institutions: (i) a retrospectively assembled cohort, from Jan 1997 to Dec 2003 (CoRIS-MD); and (ii) a prospective cohort, from Jan 2004 to Nov 2006 (CoRIS). Variables related to sociodemographic characteristics, HIV and HCV infections were collected. Univariate analysis and logistic regression were performed in Stata 10® Software.

Results: The prevalence of HCV steadily decreased from 70.8% (IC95: 73.7-68.0) in patients who entered the study in 1997, to 16.3% (IC95: 13.5-19.0) in patients who entered in 2006. During the same period, the proportion of IDU decreased from 67.1% (IC95: 64.1-70.0) to 14.5% (IC95: 11.8-17.1). HCV infection was strongly associated with IDU (OR 36.4; IC95: 27.7-47.9, p=0.0000) taking patients who acquired HIV by heterosexual transmission as the reference category.

Conclusions: Seroprevalence of hepatitis C coinfection in HIV+ ART-naïve patients initiating care in Spain has decreased from 1997 to 2006. This decrease is driven by a change in HIV transmission patterns.

V-1631

Does the Choice of peg-IFN Formulation Affect Safety or Efficacy in HIV/HCV-Coinfected Patients Receiving Weight-adjusted Ribavirin?

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Background: There is scant information on differences in treatment outcome in HCV/HIV-coinfected patients according to peg-IFN formulation.

Methods: To assess the outcome of HCV treatment according peg-IFN formulation in 174 consecutive HIV patients starting their first cycle of peg-IFN-a2a (n=93, 53%) or peg-IFN-a2b (n=81,47%) plus weight-adjusted RBV. Univariate/multivariate regression analyses were used to assess baseline predictors of SVR.

Results: Peg-IFN-a2b subjects were younger (p=0.001), with less duration of HCV infection (p=0.029), higher AST and GGT values (p=0.012 and p=0.015), and a trend to more patients with F3/F4 (p=0.07). During therapy there were not differences in HCV-RNA levels at weeks 4, 12 or 24, nor in the rate of SVR (41% vs 49,5%, p=0.24). There were not differences in the rates of peg-IFN (p=0.21) or RBV (p=0.59) dose adjustments, nor in the rates of early withdrawals (18,5% vs 15%, p=0.54) By univariate analysis, baseline HCV-RNA (p=0.0001), HCV-genotype (p=0.0001), fibrosis scoring (p=0.036), baseline CD4 counts (p=0.035), and a GGT value ≥ 100 U/l (p=0.004) were associated with SVR. By multivariate analysis, HCV-genotype 1 or 4 (OR 7.59, 95%CI 2.53-22.77, p=0.0003), and higher baseline HCV-RNA levels (OR 3.27, 95%CI 1.55-6.90, p=0.0018) or fibrosis scoring (OR 1.74, 95%CI 1.16-2.60, p=0.0066) remained independently associated with failure to reach SVR.

Conclusions: In our HIV-cohort both peg-IFN formulations plus weight-adjusted RBV showed similar safety and effectiveness profiles. HCV-genotype 1 or 4, and higher HCV-RNA levels or fibrosis were independently associated to failure.

V-1634

HCV Treatment Eligibility in ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans)

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Background: Treatment eligibility rates for hepatitis C virus (HCV) infection are unknown.

Methods: We assembled a national cohort of HCV-infected veterans-in-care from 1998-2003, using the VA National Patient Care Database, Pharmacy Benefits Management database and the Decision Support Systems database. We compared the HCV monoinfected and HCV-HIV coinfecting subjects for treatment indications and eligibility using the current treatment guidelines.

Results: Of the 86,530 subjects, 27,452 subjects with HCV and 1,225 with HCV-HIV coinfection had complete clinical and laboratory data. Of those, 74% and 85% had indications for therapy and within this group, 56.1% of the HCV monoinfected and 28.4% of the HCV-HIV coinfecting subjects were eligible for treatment. Anemia, decompensated liver disease (DLD), chronic obstructive pulmonary disease (COPD) and substance abuse were among the most common contraindications. Among those eligible for treatment, 23% of the HCV and 15% of the HCV-HIV coinfecting subjects received any treatment for HCV.

Conclusions: Most veterans with HCV are not eligible for treatment according to the current guidelines. Several contraindications are modifiable and aggressive management of those may improve treatment prescription rates. 1

V-1637

Low HCV Treatment Rates after a Liver Biopsy

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Background: At the CORE center, we have an on-site hepatitis clinic and pts have access to HCV therapy regardless of insurance status. Few HCV+ genotype (gn) 1 pts have been treated. A liver biopsy (LB) is done in gn1 pts who are treatment (Rx) candidates. The aims of this study were to determine (1) the rate of HCV Rx post LB and (2) reasons for non-treatment post LB.

Methods: Retrospective review of the CORE hepatitis database to identify all HCV+ genotype 1 pts (with or without HIV co-infection), who had a LB. LB Staging was done using Ludwig-Bartts scale: F0 (no fibrosis) to F4 (cirrhosis).

Results: Between 8/01 and 8/06, 163 HCV+gn1 pts had a LB ; 83 (51%) were HIV+ (mean CD4, cells/mm 428). Mean age 47yrs; 75% male, 63% African American (AA), 20% Hispanic, 16%Caucasian. On LB, 58% had Fibrosis \geq F2 and 11% F4. 61/163 [37%] pts received HCV Rx post LB. Women were more likely to be Rx post LB (50% vs 32%, p=0.05) and AA were less likely (27% vs 50% p=0.01) to be Rx. Pts were more likely to start Rx if they had \geq F2 48% vs 22% (p=0.001) or cirrhosis 70% vs 34% (p=0.001) . On multivariate analysis, predictors of Rx were race (p=0.01) and fibrosis \geq F2 (p=0.001). There were delays in Rx, with 45% starting Rx >1yr post LB; women were more likely to delay Rx (65% vs 35% p=0.05). Reasons for non-Rx were; mild fibrosis F0-F1 (53%), pt declined(20%), lost to follow up (19%). If only pts with \geq F2 were considered Rx eligible, then 46/93 [49%] of eligible pts received Rx. In the 47 untreated pts with \geq F2 fibrosis, HIV+ pts were more likely to decline Rx (57% vs 27%) and less likely to be LTFU (23% vs 59%) (p=0.04) when c/w HIV- pts. In the 61 Rx pts, sustained virologic response (SVR) was 26% (14%HIV+ vs 38% HIV-) (p=0.04)

Conclusions: In HCV+ gn1 pts, only 37% overall and 49% of those with \geq F2 fibrosis received HCV Rx post LB. Most untreated HIV co-infected pts, continued to follow up in the hepatitis clinic post LB, but declined Rx and this underscores the urgent need for more effective and better tolerated therapies for HCV.