

Progression of Decompensated Liver Disease in Patients with HIV

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Scope of Problem

- HIV accelerates HCV progression
- HAART slows HCV progression
- ESLD progression is increasing
 - HCV #1 cause mortality in HIV/HCV coinfection
 - HIV(+) pre-transplant survival is shorter than HIV(-); sepsis, MOF

Suggests: period of clinical vulnerability in HIV(+) ESLD

immune dysfunction of HIV and HCV

Problem: No established predictors of ESLD progression

HCV End-Stage Liver Disease

- **ESLD in HIV(+), HIV(-):**

- Gastrointestinal bleeding – portal hypertension

- Ascites

- Hepatic encephalopathy

- Subacute bacterial peritonitis

- Non-obstructive jaundice

- Cirrhosis by biopsy

- Hepatocellular carcinoma

- **Impact of HIV Infection on ESLD:**

- Ascites commonly first presenting sign

- Cirrhosis often silent – increasing proportion affected

- Patients may come to attention late

Screening: End-Stage Liver Disease

- **ESLD Screening:**

- | | |
|--------------------------------|---|
| Gastrointestinal bleeding | – Guaiac, MCV, Fe, INR , endoscopy |
| Ascites | – Exam, U/S, CT scan |
| Hepatic encephalopathy | – Hx, exam, mental status, sleep, NH3 |
| Subacute bacterial peritonitis | – If fever, tap & culture |
| Non-obstructive jaundice | – Bilirubin , alkaline phosphatase |
| Cirrhosis | – Biomarkers, CT scan, biopsy |
| Hepatocellular carcinoma | – Alpha feto-protein, CT scan |

- **MELD - Model for Endstage Liver Disease:**

Validated as a predictor of mortality in liver transplant candidates

$[0.957 \text{ Ln (creatinine mg/dL)} + 0.378 \text{ Ln (bilirubin mg/dL)} + 1.120 \text{ Ln (INR)} + 0.643] \times 10$

HCV/HIV Co-Infection & ESLD

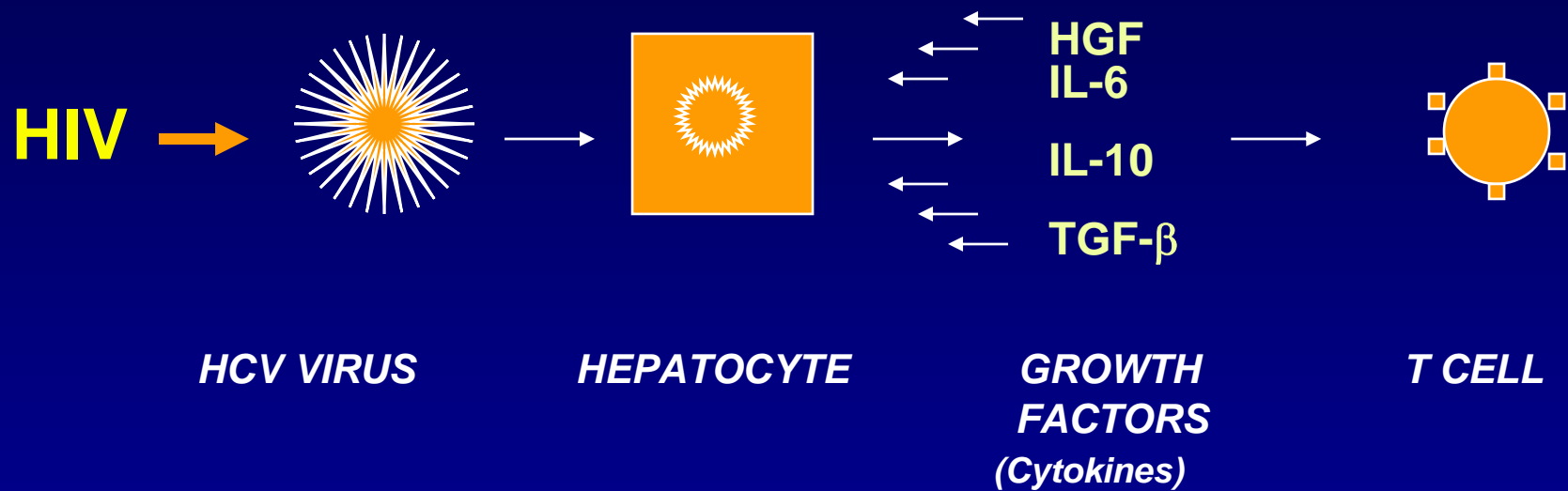
- Pre-transplant mortality

- Risk factors, predictors poorly understood
- Disease severity: MELD validated in HIV(-) ESLD
- In HIV(+):
 - Greater fibrosis progression rate
 - Increased hepatotoxicity with HIV drugs
 - Poorer SVR response to HCV treatment
 - Demise rapid, recognition slow
 - Increasing competition for OLTX
 - Increasing pre-transplant mortality rate

HCV/HIV Co-Infection & ESLD

- Is it HAART therapy?
 - Improved immune function, HIV survival
 - Living long enough to develop ESLD
 - Increasing demand for OLTX
- Is it the immune system?
 - HIV impairs an already ineffective T cell response
 - HIV increases HCV persistence, HCV RNA
 - HIV dysregulates cytokine production
 - HIV accelerates fibrosis progression

HIV Impact on HCV Progression



- **HIV** impairs an already ineffective T-cell response to HCV
- **HIV** upregulates, dysregulates cytokines causing liver fibrosis
- **HIV** increases persistence of HCV viremia, RNA, accelerates FPR

HIV Impact on HCV Progression

- Is it the timing of HIV in the course of HCV?

Initial infection:

- Cellular immune response to HCV critical
- Innate immunity & HCV-specific CD4, CD8 expansion
- Sequence evolution, HIV escape, T cell dysfunction

- In HCV(+) hemophilia, HIV occurred years later:

- Further worsened CD4 response, CD8 memory response to HCV
- Further promoted loss of protective immunity against HCV
- Accelerated HCV disease progression, ESLD

HCV Infection in Hemophilia

- Among hemophiliacs, 90% HCV (+)
 - *Exposure with first transfusion (1970,80s)*

- Among hemophiliacs, 80% HIV(+)
 - *Exposure 10+ years after HCV, peak 1982*

HIV-HCV co-infection: 40% of HCV(+), 97% of HIV(+)

Fibrosis increasing, predictors ESLD, mortality known



HIV: Impact on Natural History of HCV

Study group: 157 HCV+ hemophilic men
(85 HIV+, 72 HIV-)

Outcome: ESLD, ESLD risk

		<u>Relative Risk: HIV(+) vs HIV(-)</u>	
HIV:	ESLD	3.72	[95% CI, 1.25-11.09]
	ESLD Death	3.81	[95% CI, 1.19-12.16]
Risk factors:	Age of HCV	1.94	P = 0.0001
	Past, current HBsAg +	5.47	P = 0.0061
	Alcohol use	3.72	P = 0.019
	With each decade HCV+	2.26	P = 0.0006
	With each decade HIV+	2.18	P = 0.0013
	CD4+ number	0.32	P = 0.10
	HAART	0.14	P = 0.045

Impact of HAART on ESLD Progression

HAART: Slows HCV progression

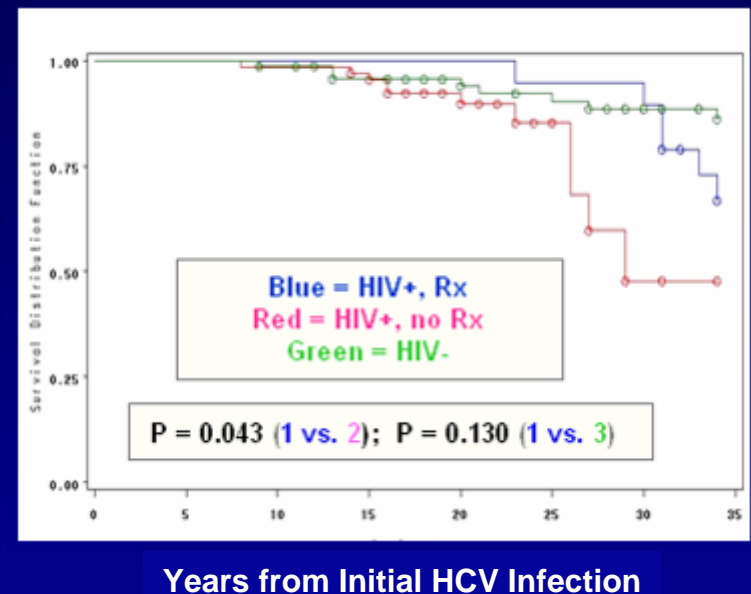
Study group: 157 HCV+ hemophilic men
(85 HIV+, 72 HIV-):
 ≥ 25 yr HIV(+)
 ≥ 15-30 yr HCV(+)

Outcome: ESLD: By HIV status, HAART rx

Results:

	Group 1	Group 2	Group 3
HIV Infection	+	+	-
HAART Rx	+	-	-
Time to ESLD (median, yr)	30.3 yr	20.0 yr	27.9 yr
	p=0.043 (1 vs. 2); p=0.130 (1 vs. 3)		

Problems: Observational, small sample, few IFN/RBV



HCV End-Stage Liver Disease

- Natural History of HCV progression to ESLD

Study: Prospective cohort (IVDU, transfusion recipients)

Endpoint: ESLD, ESLD mortality

Population: 1011 Rx-naïve HIV/HCV, pre-HAART & HCV Rx

Demography: 86% M, 34 yr age, 5,070 pt-yr FU, biannual U/S, labs

Incidence: 58 (6%) baseline, 59 (5.8%) followup, 1.16 per 100 pt-yr

Presentation: Ascites 61%, HE 27%, PHGB 7%, HCC 2%, SBP 1%

Mortality: 92% 5-yr survival, 1.36 per 100 pt-yr

Predictors: Age, CD4, HIVVL, HAART

HCV End-Stage Liver Disease

- Predictors of ESLD mortality:

Multivariate analysis

- Older age (> 33 yr) P = 0.011
- HIV CDC stage \geq C P = 0.007
- Cirrhosis at baseline P < 0.001
- <100/ μ l CD4 gain on HAART P = 0.002
- HIV VL < 400 \leq 60% time P < 0.001

Not predictive: Type or duration HAART, compliance

HAART & HIV+ OLTX Survival

Multicenter Study

Six sites, 1997-2001

23 HIV+ liver transplant (OLTX) recipients

90% 12-month survival

Comparable to HIV(-) transplant survival

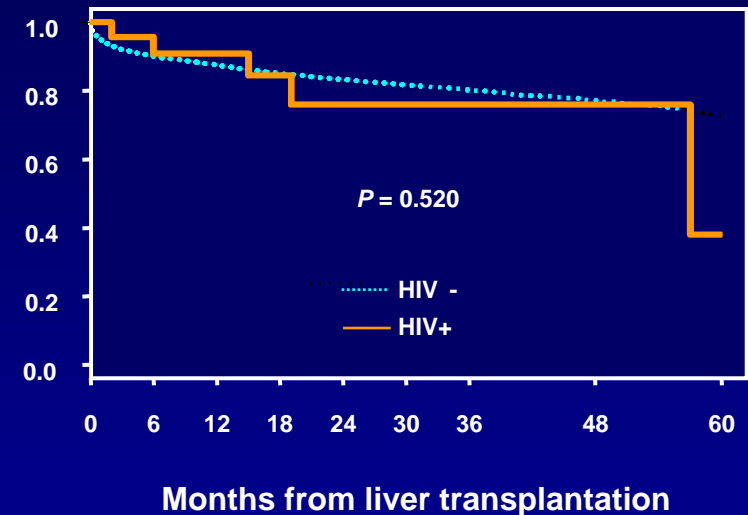
Factors associated with survival

CD4 Count: Post-OLTX, not baseline

HIV RNA PCR: Post-OLTX, not baseline

ART post-OLTX: PI, NNRTI better than NRTI

HAART Tolerance: Post-OLTX, not baseline



Ragni M, et al. *J Infect Dis.* 2003; 188:1412-20

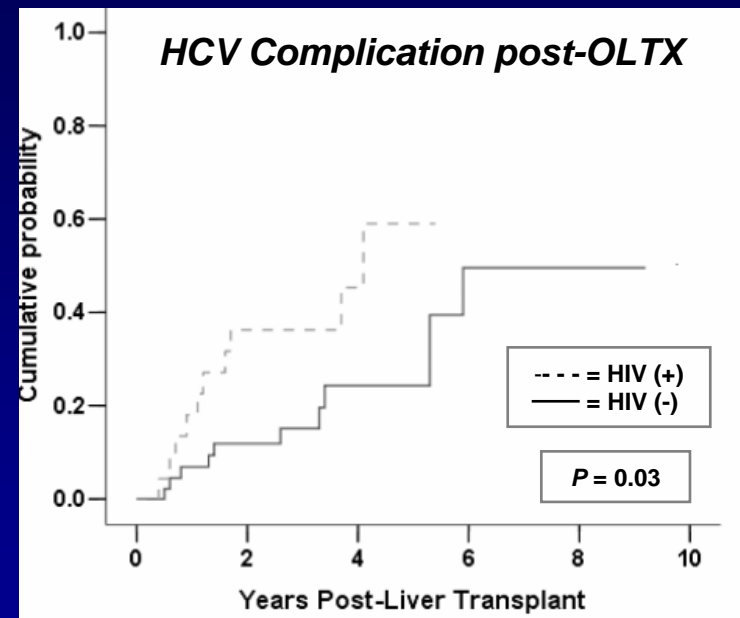
HIV(+) OLTX & HCV Complications

Recurrent HCV: HCV Complications after OLTX

Probability:

	Post-OLTX		
	1yr	3yr	5yr
HIV (-)	7%	15%	24%
HIV (+)	18%	36%	59%

P = 0.03



Devera M, et al., *Am J Transplant.* 2006; 6: 2983-93

Pre-Transplant Survival: HIV+ vs. HIV-

Pitt OLTX Study

OLTX evaluation:* 1997 – 2002

* CD4, HIV VL OK, if suppressed by HAART

Prospective FU study: OLTX, death

ESLD group: 58 HIV (+)

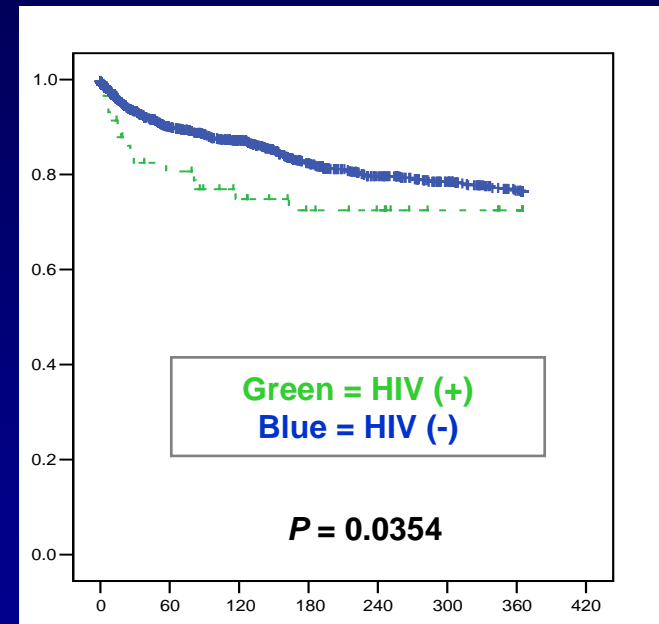
UNOS group: 1359 HIV (-)

(Matched age, gender, race, HCV)

Results

All	<u>HIV(+)</u>	<u>HIV(-)</u>	
OLTX	25.9%	63.3%	
Died pre-OLTX	48.8%	15.5%	$P < 0.001$
Cum. survival (day)	880	1427	$P = 0.0354$
MELD	16	15	ns

<u>HIV(+)</u>	<u>Died</u>	<u>Survived</u>	
MELD	15	13	ns
CD4	230	327	ns
HIV VL	<400	<400	ns
HAART intolerance	47.6%	45.4%	ns
HCV infection	76.2%	72.3%	ns



Days from initial transplant evaluation

Pre-Transplant Survival: HIV+ vs. HIV-

NIAID Multi-OLT_X Study

OLT_X evaluation:* 2003 – 2007

*CD4 >100, HIV VL undetectable

Prospective FU Study: OLT_X, death

ESLD group: 167 HIV (+)

UNOS group: 792 HIV (-)

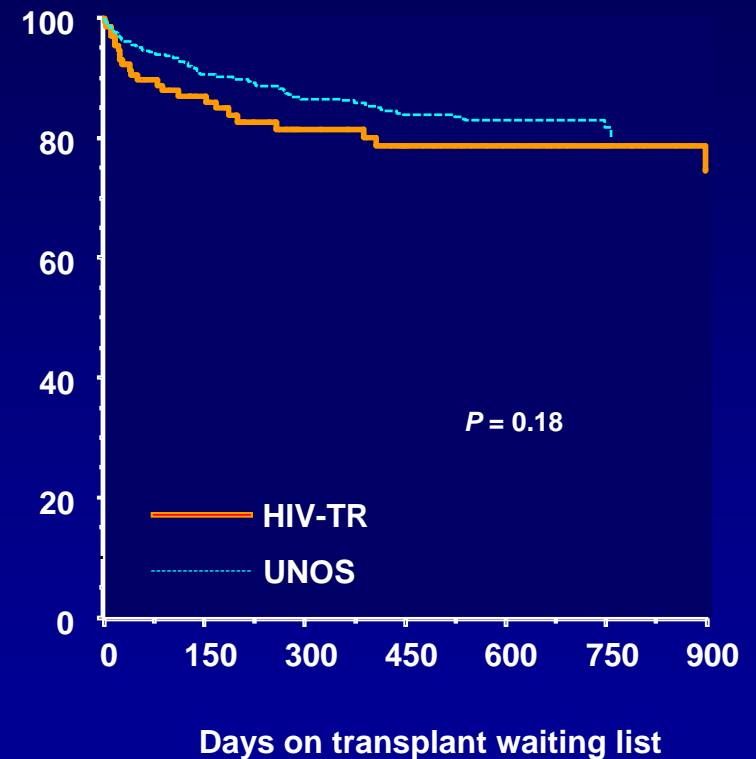
(Matched 1:5: age, gender, race, HCV)

Results

All	<u>HIV(+)</u>	<u>HIV(-)</u>
OLT _X	34.7%	47.6%
Died pre-OLT _X	14.4%	11.1%

HIV(+) (at enrollment)

	<u>Hazard</u>	<u>Death</u>
MELD	HR=1.2	<i>P</i> <0.0001
MELD ≥25	HR=21.8	<i>P</i> <0.0001
CD4 <200	HR=2.1	<i>ns</i>
HIV VL >400	HR=1.4	<i>ns</i>



The Problem With Predictors of ESLD Mortality

- **ESLD risk groups**
 - May vary by age at or duration of HIV, HCV infection or by other risk factors for ESLD: HBsAg, ETOH
- **MELD as a predictor**
 - May depend on stage at presentation but may not predict mortality in HIV(+) ESLD
- **ESLD onset too late**
 - Infectious complications, mortality may be inevitable as ESLD alters inflammatory, endothelial, coagulation function
- **Cirrhosis, fibrosis earlier marker**
 - May be asymptomatic and missed unless biopsies routine
- **Study design**
 - May differ in size, power, design, endpoints, duration

Making Sense of Studies to Date

- Problems interpreting clinical studies
 1. Lead bias: Early or late ESLD; time of biopsy, FPR
 2. Sample size, risk group: IVDU or hemophilia, tx recipient
 3. Study aim: Drug, marker, biopsy, OLTX, epi study
 4. Study design: Retrospective or prospective; follow-up
 5. Duration HCV, HIV: HCV before, after HIV, short- or long-term
 6. Duration HAART: Effect of HAART, toxicity on progression
 7. Data collection uniformity: Initial, serial, follow-up efficiency
 8. Risk factors: Control for: age, race, sex, duration HIV, CD4, HIV VL, HAART, ETOH, smoke

Predictors of HCV Progression

- Problems with predictors of HCV progression

CD4: May also reflect splenic sequestration in ESLD

MELD: May better predict progressive ESLD in HIV- than HIV+

ALT: May also reflect adverse drug rx, mitochondrial toxicity

HIV VL: May also indicate HAART resistance or intolerance

IFN, RBV: May further reduce CD4, decision re OLTX

Predictors of HCV Progression (cont)

- Lead bias
 - Are HIV(+) ESLD evaluated early enough for OLTX?
 - Are HIV(+) ESLD transplanted early enough?
- Predictors
 - Is MELD sufficiently sensitive to HIV effects?
 - Is there a better marker?

CD4-MELD

CD4 <200-duration MELD

HIV (and/or HCV) duration-MELD

Immune marker-MELD

Duration MELD 25

Summary

- ***What is needed to move field ahead?***
 1. More effective HCV treatment, prevention
 2. Carefully designed, prospective studies of HCV, ESLD
 3. Earlier referral of HIV co-infected patients
 4. Earlier knowledge of cirrhosis: better markers, biopsy
 5. Better predictors of ESLD, early biopsy
 6. Earlier patient recognition of warning signs, symptoms
 7. Public health campaign, targeting PCP, HIV docs

Studies Needed in the Future

- ***Comparability of data***
 1. Early assessment: symptoms versus scan cirrhosis
 2. Consistent fibrosis marker: biopsy or scan
 3. Uniform patient selection – risk group, power
 4. Adjustment for duration HAART treatment; toxicity
 5. Adjustment for risks – demographic
 6. Prospective studies
 7. Early enrollment of patients

HIV/ HCV Co-infection: Guidelines

1. Screen HIV(+) for anti-HCV

- If negative, monitor
- If positive, check HCV RNA

2. If HCV RNA positive, consider IFN+RBV

- Psych, genotype, race, ETOH, drug use, biopsy

3. Check noninvasive markers of fibrosis

- APRI, FIB-4, FibroScan, FibroSURE

4. Initiate therapy

- When CD4 < 200, SVR with IFN+RBV lower, anti-HIV Rx is priority

5. Management

- Current Rx: Limited effectiveness of IFN+RBV
- Newer Rx: Resistance, toxicity with NS3, NS5B protease inhibitors