7th International Conference on HIV TREATMENT AND PREVENTION ADHERENCE

Managing HCV Infection and Adherence in the Direct-Acting Antiviral Era: Learning from the HIV Experience

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Outline

- Challenges in HCV therapy
- Adherence : HCV response relationship
- Changes in antiviral adherence over time
- Barriers to adherence to HCV therapy
- Implications / future directions

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- **Challenges in HCV therapy**
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- **Barriers to adherence to HCV therapy**
- **Implications / future directions**

Case: 54 yo African-American Woman with HIV and HCV Infection

- HIV (11/2004):
  - ART: LPV/RTV, ZDV/LMV
  - 6/2011: CD4+ 354/mm^3 (22%); HIV <75 c/mL
- Chronic HCV (12/2004):
  - HCV genotype 1; HCV RNA=6.1 log IU/mL
- Past Hx: diabetes, depression
- Meds: LPV/RTV, ZDV/LMV, metformin
- Social Hx: IV heroin (1996-2004); no EtOH

Case: 54 yo African-American Woman with HIV and HCV Infection

- Exam: No hepatomegaly, stigmata of ESLD
- Laboratory data:
  - TB 0.8; Alb 3.8; INR 1.1; ALT 113
  - WBC 6.3; Hgb 14.9; platelets 138
- HCV Fibrosure=0.84 → cirrhosis
- Interleukin-28b: C/T genotype
- Abdominal U/S: No liver masses or ascites

Case: 54 yo African-American Woman with HIV and HCV Infection

- Changed ART regimen:
  - Raltegravir, tenofovir, emtricitabine
  - 4 wks later: tolerating ART; HIV <75 copies/mL
- Initiated HCV therapy
  - Peg-IFN alfa-2a 180 mcg/wk
  - Ribavirin 600 mg twice daily
  - Telaprevir 750 mg every 8 hrs

Case: 54 yo African-American Woman with HIV and HCV Infection

- Week 4 of HCV therapy:
  - Flu-like symptoms, controlled (ibuprofen)
  - Evaluation:
    - WBC 2.8 (ANC 1,020); Hgb 13.4; Plt 112
    - ALT 68
    - HCV RNA 2.1 log IU/mL (↓ 4.0 log IU/mL)

Case: 54 yo African-American Woman with HIV and HCV Infection

- Week 12 of HCV therapy:
  - ↓ flu-like symptoms, no mood changes
  - Evaluation:
    - WBC 2.1 (ANC 860); Hgb 9.4; Plt 94
    - ALT 41
    - HCV RNA undetectable ←
  - Anemia management:
    - Initiated erythropoetin 40,000 units/wk
    - ↓ ribavirin to 1,000 mg/d

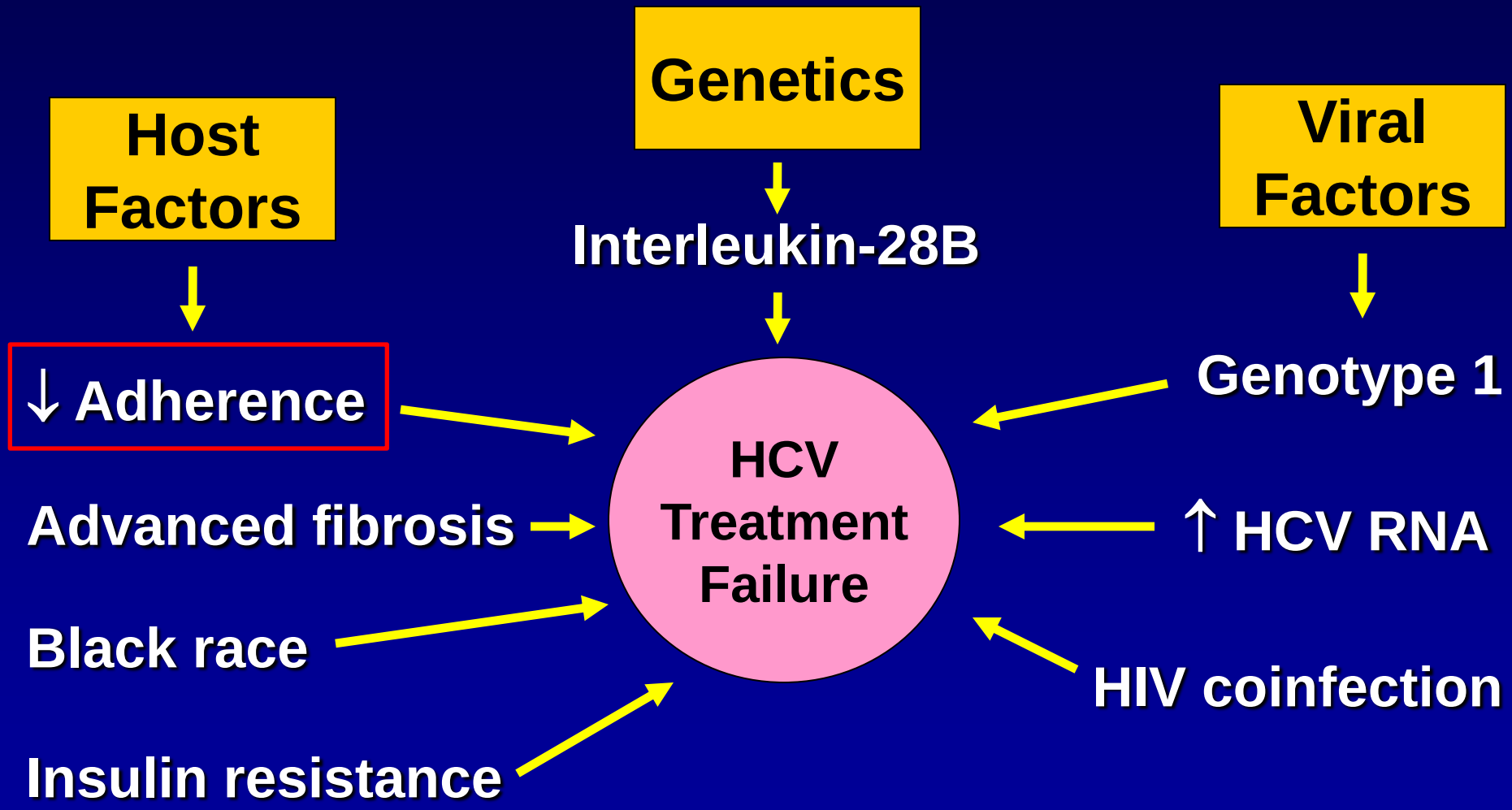
Case: 54 yo African-American Woman with HIV and HCV Infection

- Week 24 of HCV therapy:
  - Fatigue; irritability; missing ribavirin doses
  - Evaluation:
    - WBC 2.3 (ANC 940); Hgb 11.8; Plt 80
    - HIV < 75 copies/mL
    - ALT 64
    - HCV RNA 2.6 log IU/mL

Case: 54 yo African-American Woman with HIV and HCV Infection

- Week 24 of HCV therapy:
  - Fatigue; irritability; missing ribavirin doses
  - Evaluation:
    - WBC 2.3 (ANC 940); Hgb 11.8; Plt 80
    - HIV < 75 copies/mL
    - ALT 64
    - HCV RNA 2.6 log IU/mL ← Detectable, Therapy Stopped

Possible Reasons for HCV Treatment Failure



HCV Treatment Regimens With HIV Coinfection (2012)

Genotype	Therapeutic Options	Duration
1	PEG-IFN-2b + ribavirin + boceprevir^	48 wks
	PEG-IFN-2a + ribavirin + telaprevir^	48 wks
2, 3	PEG-IFN-2a or -2b + ribavirin	48 wks
4	PEG-IFN-2a or -2b + ribavirin	48 wks
	PEG-IFN + ribavirin + nitazoxanide^	48 wks

^ Off-label usage; no response-guided therapy in HIV/HCV patients.

Sustained virologic response (SVR) = HCV RNA (–) ≥24 wks after end of therapy

PEG-Interferon + Ribavirin

- **Pegylated interferon alfa**
  - Suppress viral replication
  - Two formulations: 2a, 2b
    - Alfa-2a: 180 mcg/wk SQ
    - Alfa-2b: 1.5 mcg/kg/wk SQ

PEG-IFN alfa-2a (PEGASYS®)

PEG-IFN alfa-2b (PEG-INTRON®)

- **Ribavirin**
  - Nucleoside analogue
  - Genotype 1, 4:
    - ≤75 kg: 1,000 mg/d
    - >75 kg: 1,200 mg/d
  - Genotype 2, 3: 800 mg/d

Ribavirin (Rebetol®)

Ribavirin (Copegus®)

RibaPak®

Boceprevir: HCV Genotype 1

- NS3/4A protease inhibitor
- Indicated for genotype 1 only
- Use with PEG-IFN + ribavirin

If HCV RNA >100 IU/mL at Wk 12, stop therapy

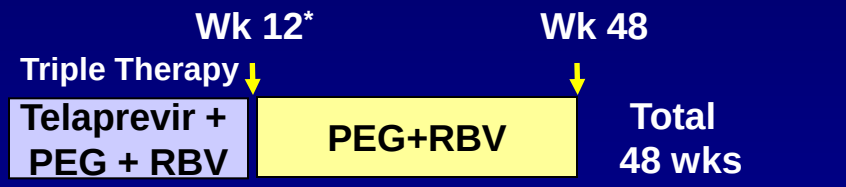
Boceprevir (VICTRELIS™)

- Dosage: 800 mg every 8 hrs
- Metabolized via CYP3A4/5, aldoketoreductase

Poordad F et al. *N Engl J Med 2011*;364:1195-206.
Bacon BR et al. *N Engl J Med 2011*;364:1207-17.

Telaprevir: HCV Genotype 1

- NS3/4A protease inhibitor
- Indicated for genotype 1 only
- Use with PEG-IFN + ribavirin:



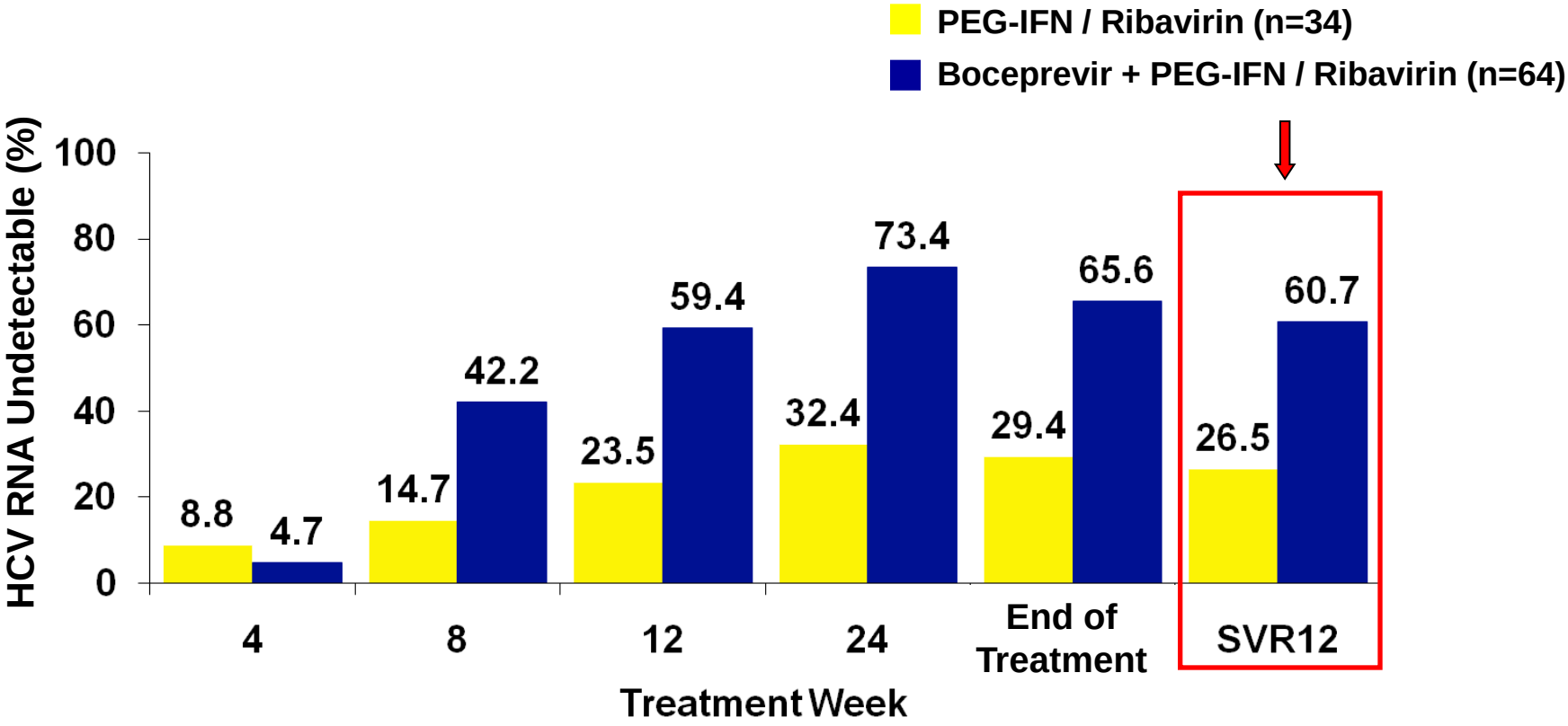
*If HCV RNA >1,000 IU/mL at Wk 4 or 12, stop therapy

- Dosage: 750 mg every 8 hrs
- Administer with 20 gm fat meal
- Metabolized via CYP3A4/5

Telaprevir (INCIVEK™)

Jacobson IM et al. *N Engl J Med 2011*;364:2405-16.
Zeuzem S et al. et al. *N Engl J Med 2011*;364:2417-28.

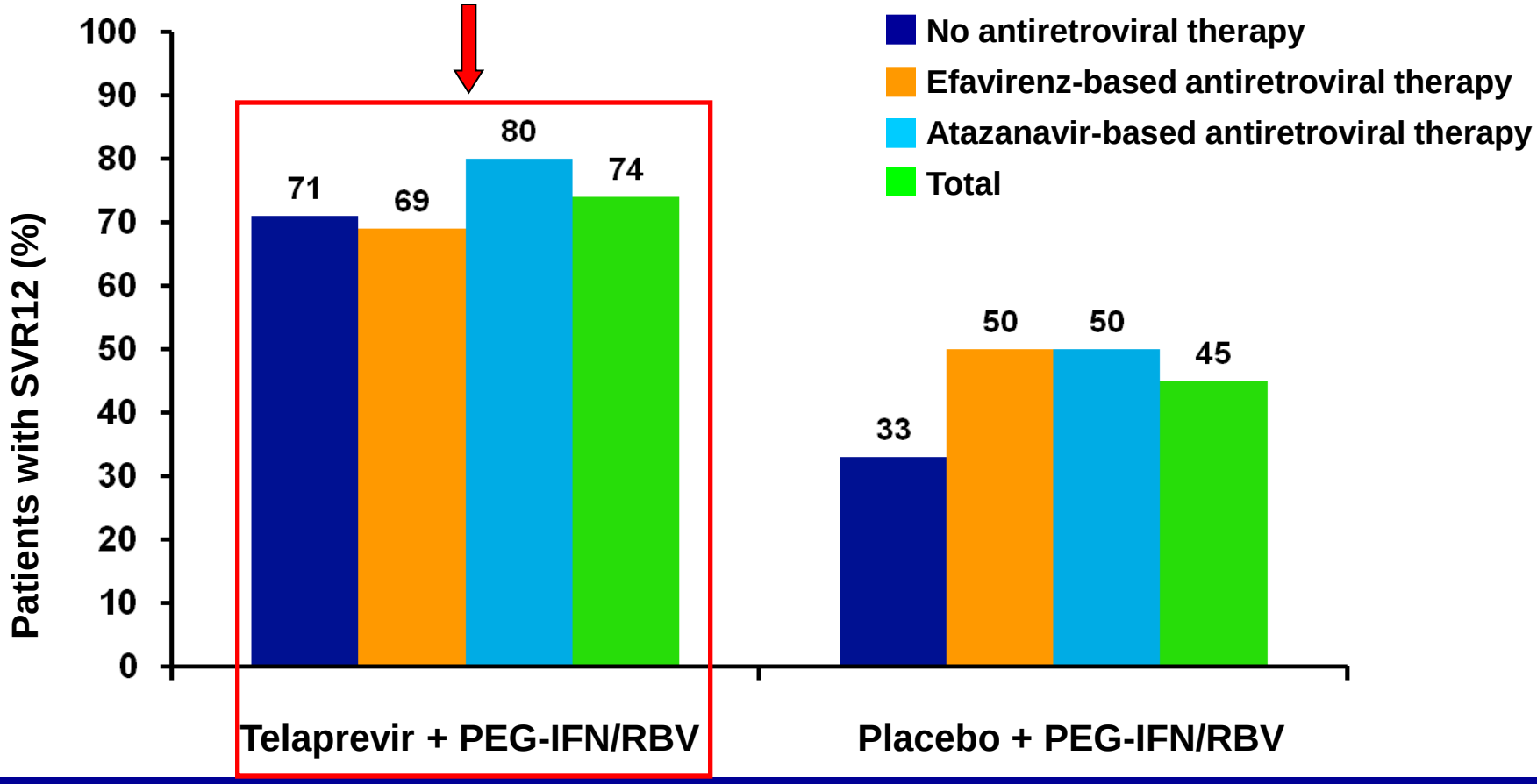
SVR12 Rates with Boceprevir for HCV Genotype 1 in HIV



SVR12 = Undetectable HCV RNA 12 weeks after treatment cessation

Sulkowski MS et al. 19th CROI. Abstract 47.

SVR12 Rates with Telaprevir for HCV Genotype 1 in HIV



SVR12 = Undetectable HCV RNA 12 weeks after treatment cessation

Dieterich D et al. 19th CROI. Abstract 46.

Toxicities of HCV Therapy

- Tend to dominate treatment of HCV
- Adverse events affect:
  - Quality of life
  - Follow-up
  - Adherence to antiviral therapy

Notable Toxicities of PEG-IFN / Ribavirin in HIV Trials

Pegylated Interferon

Adverse Effect	% Reported
Fatigue	44%
Pyrexia	44%
Myalgia	36%
Depression	29%
Insomnia	26%
Thyroid dysfunction	6%

Ribavirin

Adverse Effect	% Reported
Hemolytic anemia	16%

Torriani FJ et al. *N Engl J Med* 2004;351:438-50.
Carrat F et al. *JAMA* 2004;292:2839-2848.

Notable Toxicities of Boceprevir / Telaprevir in HIV Trials

Boceprevir[1]

	BOC+P/R (N=64)	P/R (N=34)
Anemia	41%	26%
Pyrexia	36%	21%
Asthenia	34%	24%
Anorexia	34%	18%
Diarrhea	28%	18%
Dysgeusia	28%	15%
Vomiting	28%	15%
Flu-like illness	25%	38%
Neutropenia	19%	6%
Erythropoietin use	38%	21%

Telaprevir[2]

	TVR+P/R (N=38)	P/R (N=22)
Pruritus	39%	9%
Headache	37%	27%
Nausea	3%	23%
Rash	34%	23%
Pyrexia	21%	9%
Depression	21%	9%
Neutropenia	24%	23%
Anemia	18%	18%
Insomnia	13%	23%
Anorexia	11%	18%

[1]Sulkowski MS et al. 19th CROI. Abstract 47.
[2]Dieterich D et al. 19th CROI. Abstract 46.

Challenges in HCV Therapy

- Complex treatment regimen
- Frequent monitoring of laboratory results
- Office visits to evaluate adverse effects
- Toxicities of HCV treatment
- May need to change ART regimen
- Suboptimal adherence → ↓ response

Adherence to HCV Therapy

- **Prior data:**
  - **↓ drug exposure from dose reduction: ↓ SVR**
  - **Few data: ↓ drug exposure from missed doses**
- **Unanswered questions:**
  - **Levels of adherence for virologic response**
  - **Differences between PEG-IFN, ribavirin**
  - **Changes in antiviral adherence over time**
  - **Risk factors for non-adherence**

McHutchison JG et al. *Gastroenterology* 2002;123:1061-9.
Reddy KR et al. *Clin Gastroenterol Hepatol* 2007;5:124-9.

Outline

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- Adherence : HCV response relationship
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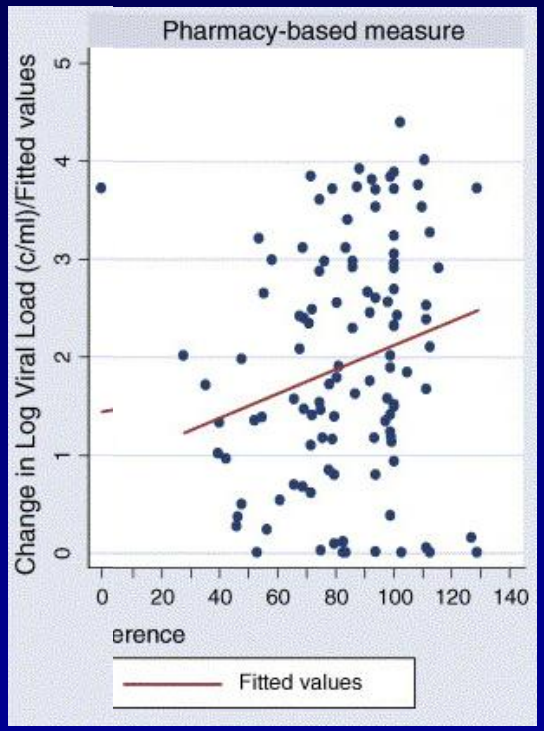
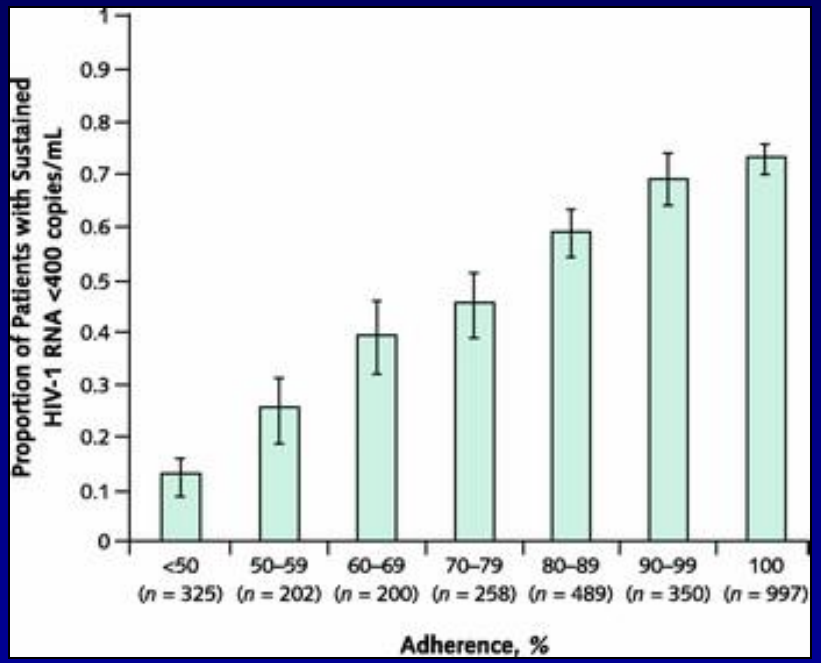
Learning from the HIV Experience: ART Adherence and HIV Response





ART Adherence : ↓ in HIV RNA

ART Adherence : HIV Suppression

Grossberg R et al. *J Clin Epidemiol* 2004;57:1107-10.
Nachega JB et al. *Ann Intern Med* 2007;146:564-73.

Study 1: Adherence and HCV Suppression

- Aim: Evaluate relation between adherence to PEG-IFN + ribavirin and HCV suppression over initial 12 weeks of HCV therapy
  - Adherence: Pharmacy refill measure
  - Hypothesis: ↑ adherence → Greater decline in HCV RNA

Lo Re V et al. *Clin Infect Dis* 2009;48:186-93.

Study Design / Setting

- Design: Retrospective cohort study
- Setting: Philadelphia VA Med Center
  - Majority of veterans receive meds through VA*
  - PEG-IFN + ribavirin dispensed monthly
  - Patients must initiate contact to obtain refills
  - Dispensing of antivirals not linked
  - Prescribing info recorded in database

*Steiner JF et al. *Med Care* 1988;26:814-23.

Study Subjects

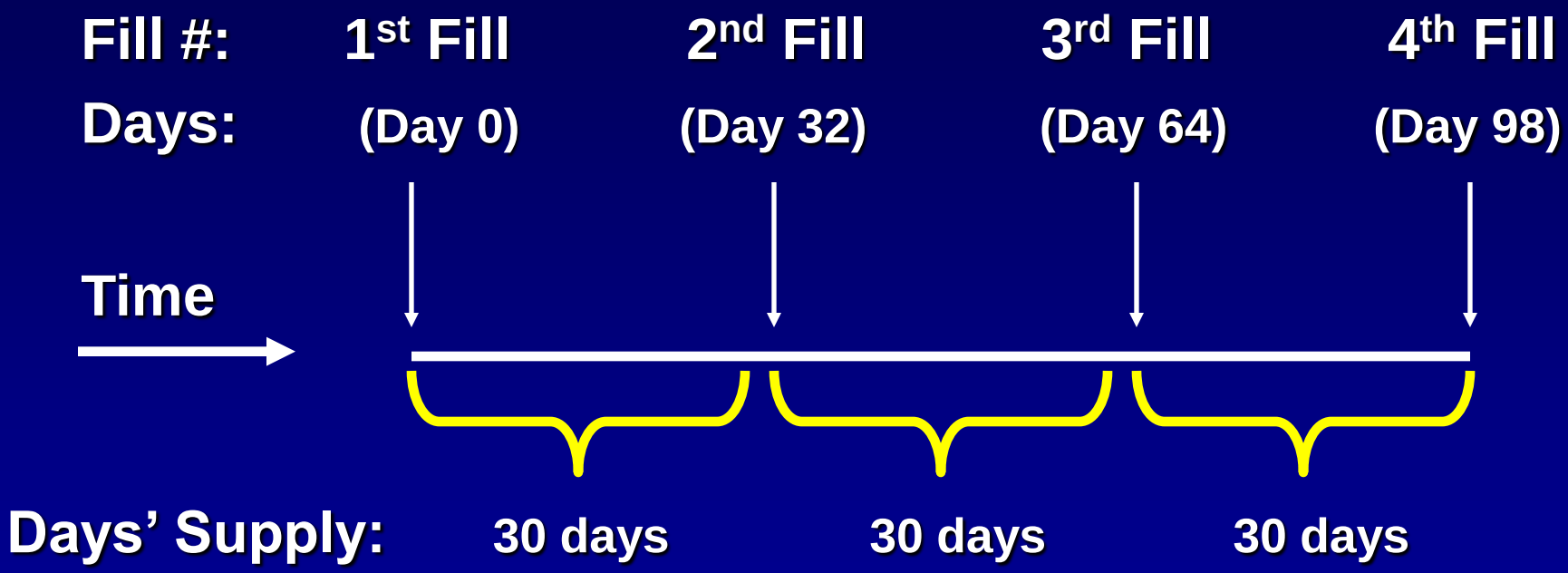
- **Eligibility criteria:**
  - **HCV RNA+**
  - **Received at least one pharmacy refill of both PEG-IFN and ribavirin**
  - **HCV RNA prior to treatment and at 12 weeks**
- **Exclusion:**
  - **Started rx outside VA, switched formulation**
- **Identification (VA pharmacy database):**
  - **Prescribed PEG-IFN + ribavirin, 1/1/01–12/31/07**

Adherence: Pharmacy Refills

- Compares actual versus expected refills
- Valid indicator of actual adherence
- Advantages:
  - Relatively simple to collect
  - Does not require patient recall
  - Permits determination of PEG-IFN and ribavirin adherence separately

Grossberg R et al. *J Clin Epidemiol* 2004;57:1107-10.

Data Analysis: Calculation of Adherence



$$\% \text{ Adherence} = \frac{\text{Days' Supply over 12 weeks}}{\text{Days Between 1st \& Final Fills}} \times 100$$

% Adherence = 90 days / 98 days = 92%

Main Study Outcome

- Decline in HCV RNA (log IU/mL) from baseline at 12 weeks
  - Week 12 RNA: Obtained weeks 11 – 13

Data Collection / Analysis

- Data abstracted from VA medical records
  - Baseline: closest to, prior to start of therapy
    - Demographic: age, sex, race, weight, height
    - Laboratory: HCV genotype / viral load, HIV, HBV
    - Pharmacy: fill dates, # dispensed, frequency, dose
  - Longitudinal: antiviral rxs, dose, week 12 RNA
- Mixed effects regression model:
  - Adherence and ↓ in HCV viral load

Results: Patient Characteristics

Characteristic	All Subjects (N=188)
Median age (yrs, IQR)	52 (48-56)
Male sex (no., %)	181 (96%)
Black race (no., %)	91 (48%)
Injection drug use (no., %)	124 (66%)
HCV viral load >800,000 IU/mL (no., %)	107 (57%)
HCV genotype 1 or 4 (no., %)	152 (81%)
HIV coinfection (no., %)	15 (8%)

Results: Medication Dosing

PEG-Interferon

- 135 (72%) treated with PEG-IFN alfa-2a
  - 133 (99%) started at / maintained 180 μg/week
- 53 (28%) treated with PEG-IFN alfa-2b
  - 38 (72%) started on / maintained at least 1.4 μg/kg/wk

Ribavirin

- Genotype 1/4: 7 (5%) sub-optimal ribavirin dose
  Week 12: 9 had ↓ ribavirin dose
- Genotype 2/3: 0 sub-optimal ribavirin dose

Results: Medication Dosing

PEG-Interferon

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- 53 (28%) treated with PEG-IFN alfa-2b
  - 38 (72%) started on / maintained at least 1.4 µg/kg/wk

Ribavirin

- Genotype 1/4: 7 (5%) reduced ribavirin dose
  Week 12: 9 had ↓ ribavirin dose
- Genotype 2/3: 0 reduced ribavirin dose

Results: HCV Viral Load Decline in Good Vs. Poor Adherers

Population	12-Week Adherence	Mean HCV Viral Load (log Iu/mL) HCV Decline	Difference	P-Value
All patients	<85%	2.57		
	≥85%	3.23	0.66	0.04
Genotype 1 or 4	<85%	2.28		
	≥85%	2.95	0.67	0.05
Baseline HCV RNA >800,000 IU/mL	<85%	2.77		
	≥ 85%	3.45	0.68	0.09
Baseline HCV RNA ≤800,000 IU/mL	<85%	2.26		
	≥85%	2.95	0.69	0.1

Results: Exclusion of Subjects With Reduced Doses

- 16 subjects with reduced ribavirin doses:
  - Overall:
    - ↓ in HCV RNA: 1.0 log IU/mL > for good adherers (p=0.01)
  - Genotypes 1 / 4:
    - ↓ in viral load: 1.09 log IU/mL > for good adherers (p=0.01)
- 17 subjects with reduced PEG-IFN doses:
  - Differences in viral load ↓ between good and poor adherers similar to those with full PEG-IFN dose

Study 2: Adherence and HCV Response

- Aim: Evaluate relation between adherence to PEG-IFN, ribavirin and virologic response
  - Hypothesis: ↑ adherence → ↑ HCV response

Lo Re V et al. *Ann Intern Med* 2011;155:353-60.

Study Design / Setting

- Retrospective cohort study
- Setting: U.S. VA Hepatitis C Case Registry
  - Extract of VA records from HCV+ veterans
  - Demographic, administrative, lab data
  - Dispensing data on meds
  - Advantages:
    - Majority receive meds through VA*
    - Initiate contact for refills (not automatic)
    - Dispensing of antivirals not linked

*Steiner JF et al. *Med Care* 1988;26:814-23.

Study Subjects

- **Inclusion criteria:**
  - **HCV RNA+, HCV genotype 1 – 4**
  - **PEG-IFN + ribavirin rx: Jan 2003 → Dec 2006**
  - **HCV RNA prior to, after treatment start**
- **Exclusion criteria:**
  - **Clinical trial, switched IFN formulation, HIV**
- **Selection: first treatment course**

Adherence: Pharmacy Refills

- Calculated over 12-wk intervals:
  - 0 – 12 wks
  - 13 – 24 wks
  - 25 – 36 wks
  - 37 – 48 wks
- Initial fills: closest to wks 13, 25, 37
- Included in analyses: fill during interval
- Observed fills analyzed in each interval

Study Outcomes

- **Early virologic response (EVR)**
  - **≥2 log ↓ in HCV RNA copies/ml at 12 wks**
  - **Defined wk 12 HCV RNA: wks 9 – 15**
- **Sustained virologic response (SVR)**
  - **Undetectable HCV RNA in all follow-up viral load tests 24 wks after treatment end date**
  - **Collected HCV RNA → Dec. 2008**

Data Analysis

- Calculated adherence separately
- Adherence categorized into 7 strata
  - Examined virologic response in each stratum
  - Chi-square tests for trend

Results: Subject Selection

9,468 HCV genotype 1 - 4
Prescribed PEG-IFN + Ribavirin

3,762 Excluded:

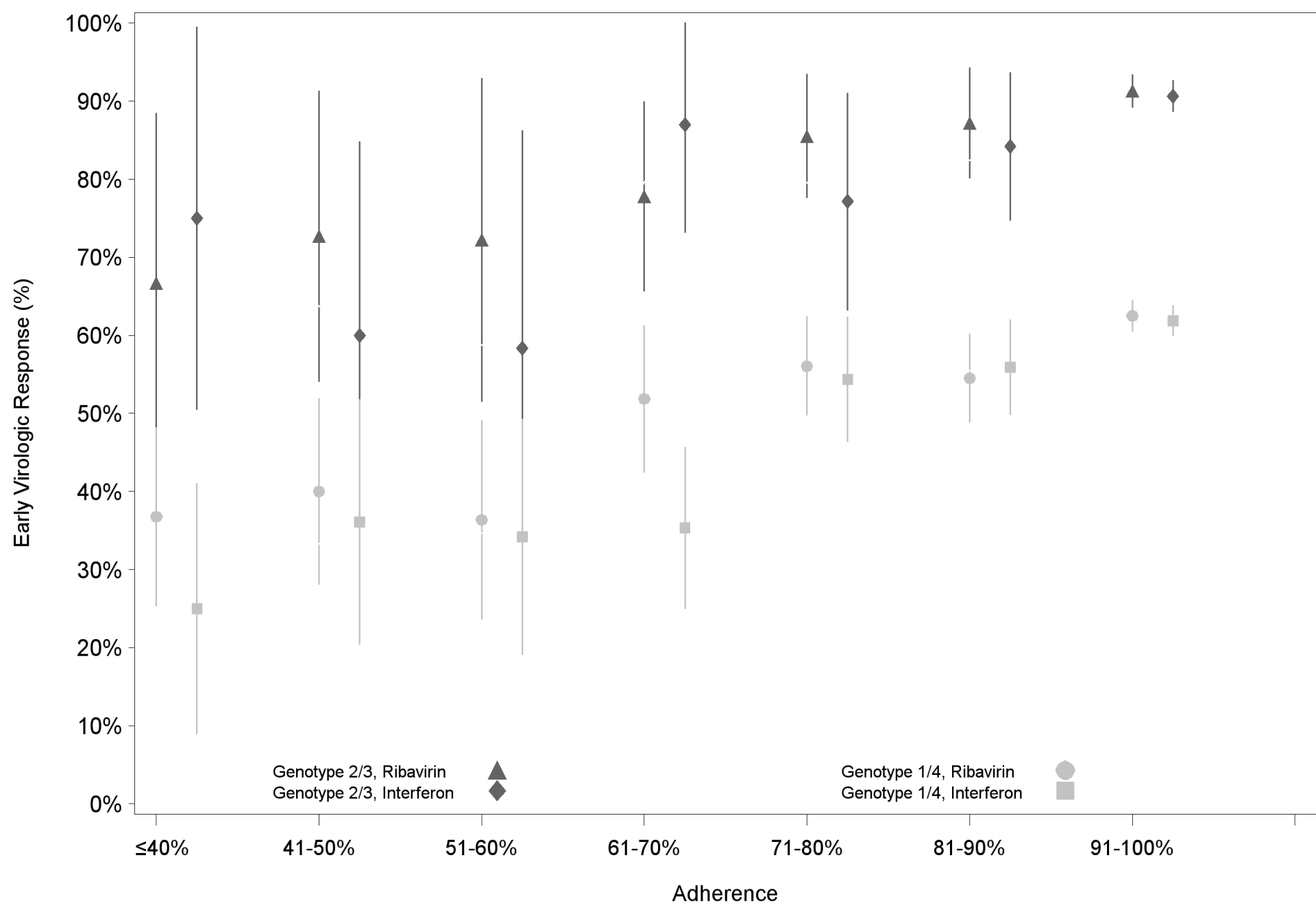
- **3,416 No HCV RNA prior to, after start of therapy**
- **48 Received antivirals in clinical trial**
- **75 Switched IFN formulation**
- **205 HIV-infected**
- **18 Infected with genotype 5 or 6**

5,706
Patients Included

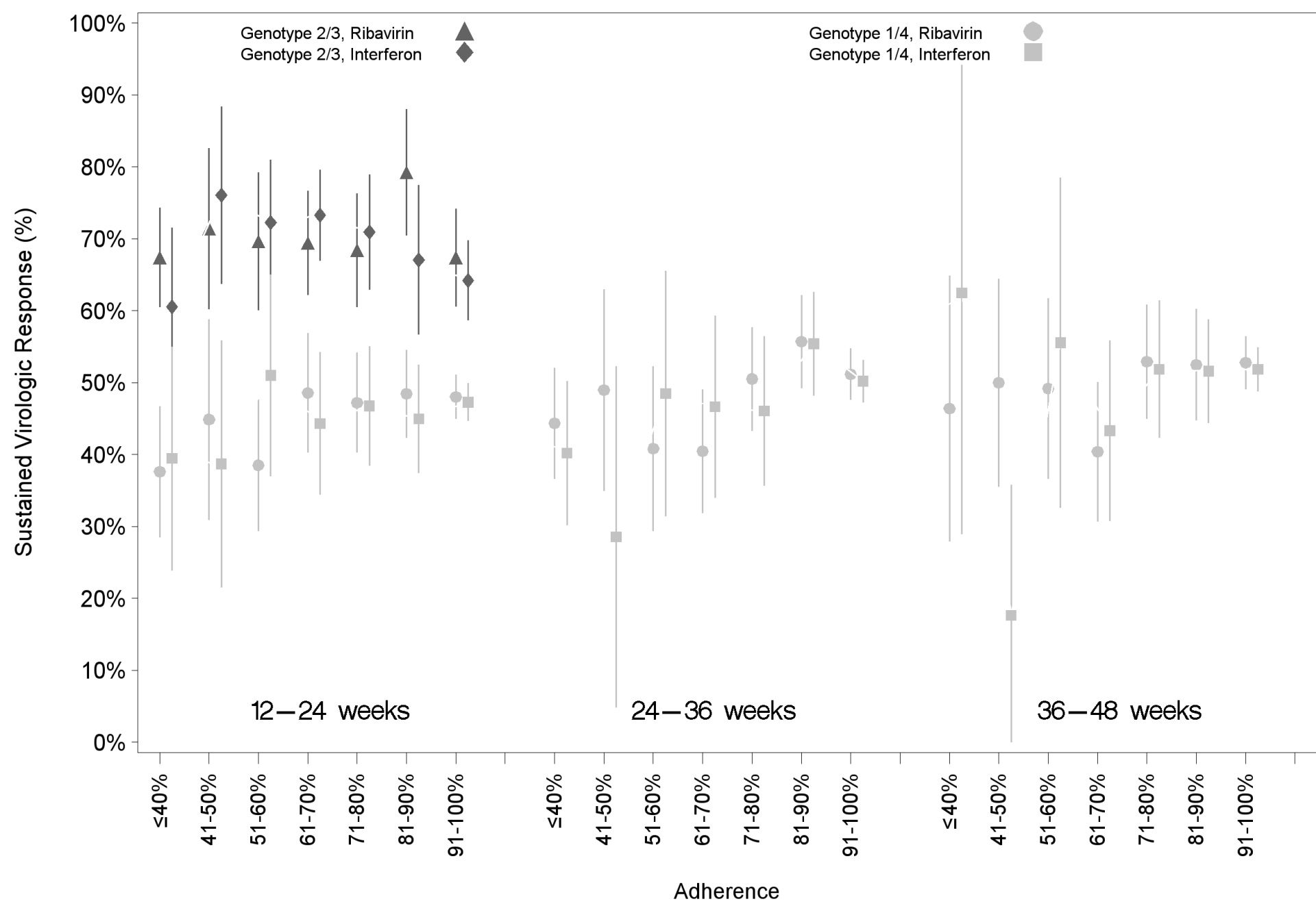
3,992
Available for
EVR Analyses

Results: Patient Characteristics

Characteristic	All Subjects (n=5,706)
Mean age (yrs, SD)	52 (6)
Male sex (no., %)	5,482 (96%)
Race (no., %)	
African-American	1,080 (19%)
Caucasian	3,397 (60%)
HCV genotype 1 or 4 (no., %)	4,207 (74%)
HCV viral load >400,000 IU/mL (no., %)	3,158 (55%)



Lo Re V et al. *Ann Intern Med* 2011;155:353-60.



Lo Re V et al. *Ann Intern Med* 2011;155:353-60.

Potential Limitations

- Overestimate actual adherence
  - Patients may not take meds after refill
    - Assoc. with biological surrogate that only responds to antiviral therapy
- Retrospective design
  - No standardized HCV RNA testing
- Generalizability

Conclusions

- ≥85% adherence associated with ↑ HCV viral suppression over initial 12 weeks
  - Viral load ↓ greater with optimal ribavirin dose
- ↑ EVR and SVR with higher levels of adherence to PEG-IFN and ribavirin

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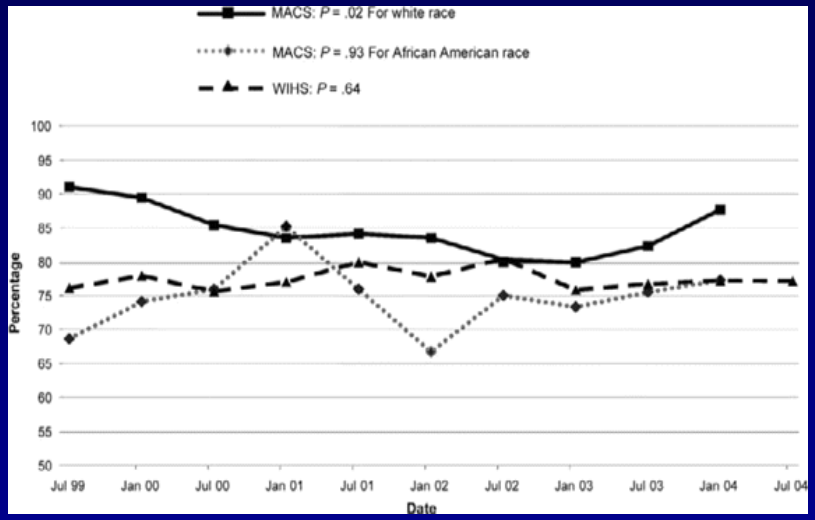
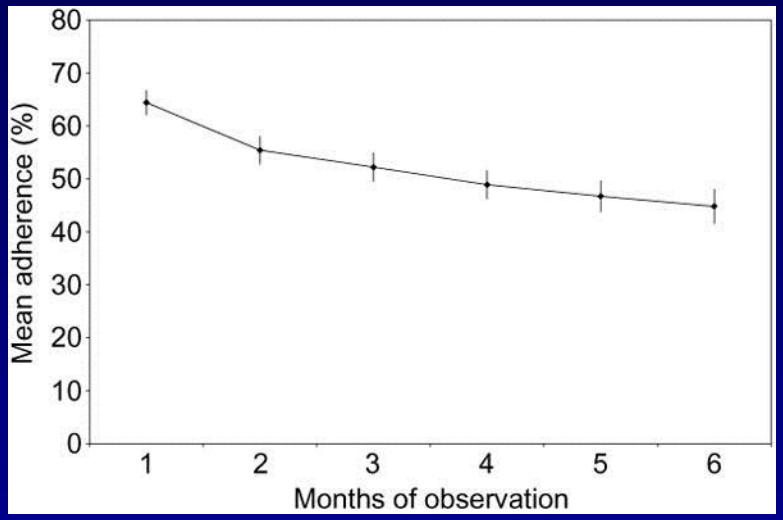
Learning from the HIV Experience: Change in Adherence Over Time



ART Adherence Over Time, MACS and WIHS



ART Adherence Over Time, HIV Epidemiology Research Study

Lazo M et al. *Clin Infect Dis* 2007;45:1377-85.
Howard AA et al. *AIDS* 2002;16:2175-82.

Adherence Over Time: HCV-Monoinfected

Adherence Interval (Weeks)	Mean PEG-Interferon Adherence (%, SD)		Mean Ribavirin Adherence (%, SD)		P-Value‡
	N	Adherence	N	Adherence	
0-12	5,706	100% (23%)	5,706	97% (38%)	<0.001
13-24	3,542	95% (23%)	3,497	86% (38%)	<0.001
25-36	2,501	94% (24%)	2,453	84% (38%)	<0.001
37-48	904	89% (30%)	860	76% (40%)	<0.001

Mean ↓: 3.5% / 12 wks p<0.001

Mean ↓: 6.8% / 12 wks p<0.001

‡ P-values via paired t-tests

Lo Re V et al. *Ann Intern Med* 2011;155:353-60.

Adherence Over Time: HIV/HCV-Coinfected

Adherence Interval (Weeks)	Mean PEG-Interferon Adherence (%, SD)		Mean Ribavirin Adherence (%, SD)		P-Value‡
	N	Adherence	N	Adherence	
0-12	333	99% (27%)	333	93% (38%)	<0.001
13-24	239	96% (23%)	234	87% (38%)	<0.001
25-36	150	100% (24%)	145	89% (38%)	<0.001
37-48	106	88% (30%)	102	78% (40%)	<0.001

Mean ↓: 2.5% / 12 wks p<0.001

Mean ↓: 4.1% / 12 wks p<0.001

‡ P-values via paired t-tests

Conclusions

- Within person, differing antiviral adherence
  - PEG-IFN adherence higher than ribavirin
  - HIV: differing adherence to ARVs reported*
- Adherence to anti-HCV drugs ↓ over time
  - More so for ribavirin than PEG-IFN

*Garner EM et al. *AIDS* 2008;22:75-82.

Hypotheses

- Possible reasons for ↓ ribavirin adherence:
  - Fatigue, loss of concentration common
  - ↑ frequency of ribavirin administration may make it more vulnerable to missed doses
- PEG-IFN:
  - Patient select day of week to inject
  - Scheduling routine may promote ↑ adherence

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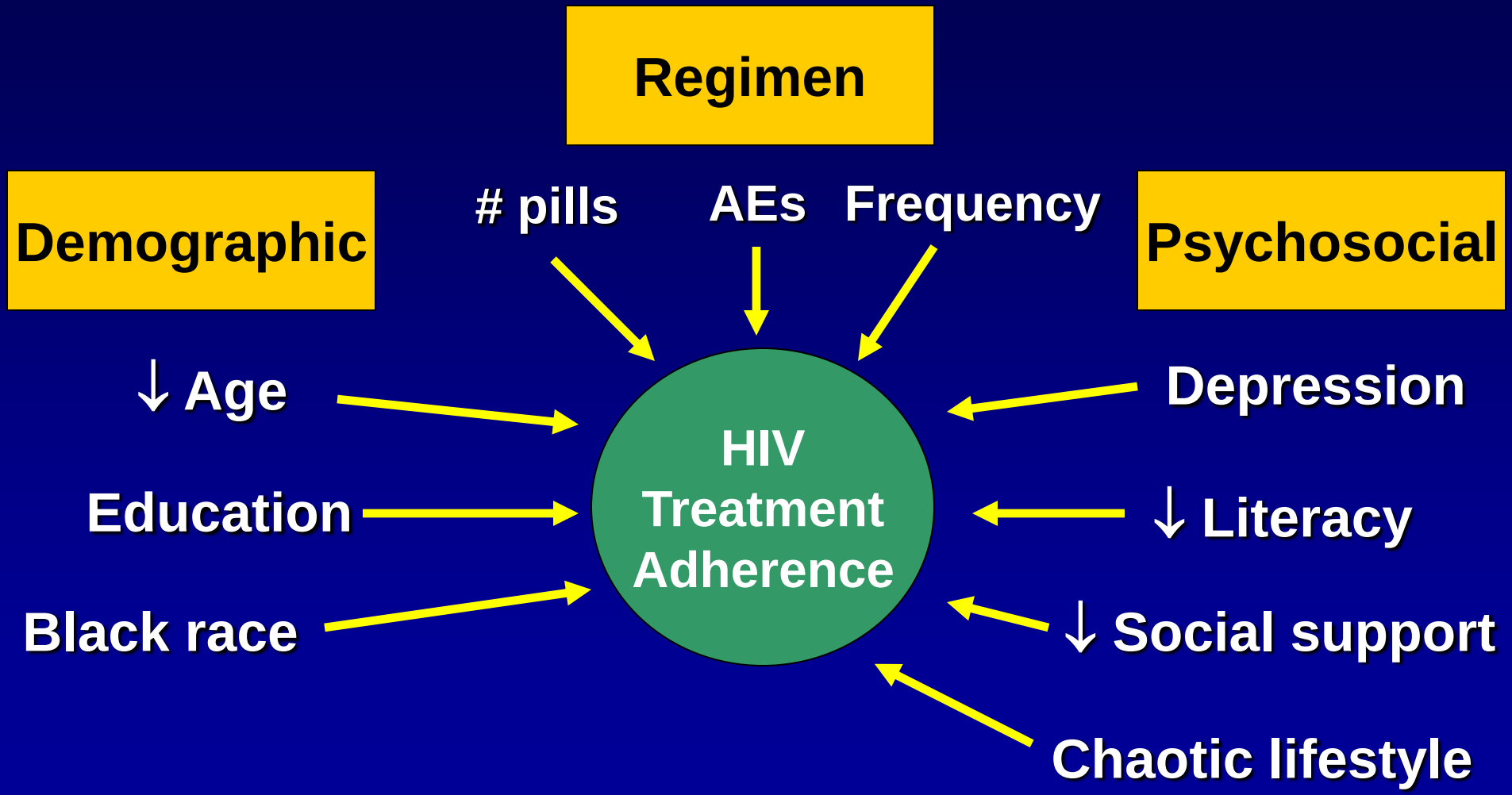
Learning from the HIV Experience: Risk Factors for Non-Adherence



Determinants of HCV Adherence: HCV-Monoinfected

Risk Factor	Mean Ribavirin Adherence Percent (95% CI)		
	With Factor	Without Factor	P-Value
Depression	90.1%	90.1%	0.9
Schizophrenia	89.9%	90.1%	0.6
Methadone	88.9%	90.2%	0.2
New thyroid med	91.9%	89.9%	0.02
New growth factor	91.0%	89.7%	0.02

Lo Re V et al. *Ann Intern Med* 2011;155:353-60.

Determinants of HCV Adherence: HIV/HCV-Coinfected

Risk Factor	Mean Ribavirin Adherence Percent (95% CI)		
	With Factor	Without Factor	P-Value
Depression	87.3%	89.2%	>0.5
Schizophrenia	90.2%	88.4%	>0.5
Methadone	76.7%	89.4%	0.04
New thyroid med	94.9%	88.4%	0.5
New growth factor	97.7%	84.8%	<0.001

Conclusions

- Patients prescribed growth factors had higher mean adherence to both antivirals
- Methadone use associated with lower mean adherence to PEG-IFN, ribavirin in HIV/HCV-coinfected

Hypotheses

- Growth factors to manage side effects
  - Relieve toxicities, ↑ adherence
  - Require more frequent visits, ↑ attention from clinical care team
- Methadone use in HIV/HCV
  - Cognitive dysfunction, ↓ adherence

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Implications

- Adherence is key to effective HCV therapy
- Emphasize adherence throughout course
  - Adherence to anti-HCV drugs ↓ over time
- Addition of direct-acting antivirals:
  - ↑ complexity of HCV therapy
  - Might affect HCV treatment adherence

Integrating Hepatitis C Care into HIV Practice

- Establish multidisciplinary management team
- Provide support and education
- Treat psychiatric disorders / substance abuse
  - Administer CES-D and AUDIT
- Provide anti-HCV therapy
- Education to prepare for HCV therapy
- Offer weekly HCV adherence visits, monitoring

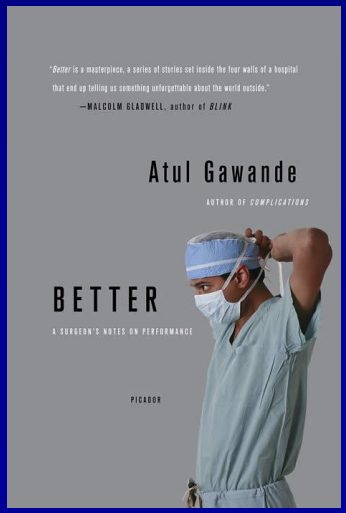
Lo Re V et al. *Clin Liver Dis* 2008; 12:587-609.

Future Directions in HCV Treatment Adherence

- Conceptual model: barriers to adherence
- Evaluate adherence to direct-acting antivirals
  - Adherence : response relationship
  - Differences in adherence to regimens, ART
  - Adherence → antiviral resistance
- Methods to measure adherence in real time
  - Identify non-adherence as soon as it occurs
- Develop adherence interventions
  - Modify successful HIV adherence interventions

"Arriving at meaningful solutions is an inevitably slow and difficult process. Nonetheless, better is possible. It does not take genius. It takes diligence. It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try."

- Atul Gawande



7th International Conference on HIV TREATMENT AND PREVENTION ADHERENCE

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