Acute and Early Chronic HCV Treatment Responses within a Predominantly Injecting Drug User Population.

The Australian Trial in Acute Hepatitis C

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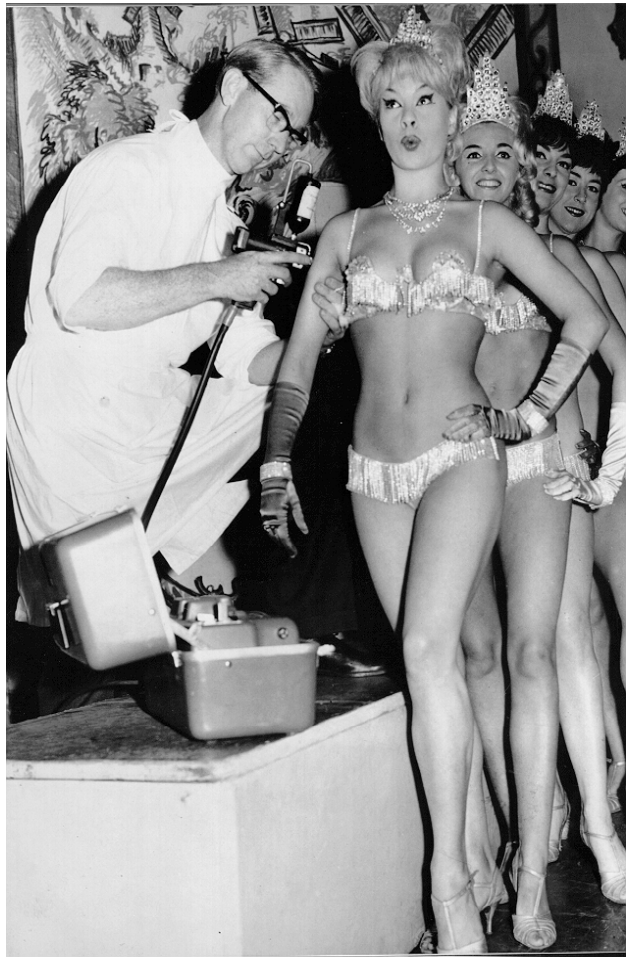
Hepatitis C infection – why should we give a toss! Estimates and modeling

- 180 – 200 million people worldwide ~ 3% of the worlds population have been exposed to HCV
- Over 240,000 Australians, ~ 1% of the population, have been exposed to HCV
- Estimated that 10,000 new HCV infections each year
- Over 80% - attributable to injecting drug use
- Between 55% and 75% of people who get infected develop a chronic infection
- Of that group - if untreated
  - 20%-30% may develop cirrhosis (10-15% overall)
  - 4%-6% - hepatocellular carcinoma (2-3% overall)
- Significant economic impact



1963- Anti-influenza injections given from a Crooks Laboratories team

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Prevention is better than cure

- Hepatitis C infection has an economic impact on the community – estimated $1-3 billion loss to the Australian economy

- Treatment is expensive and complicated
  - Drugs alone - $9,500-$20,000 (Aus) per patient per year
  - Extra costs include lab testing, health services staff
  - Not 100% effective – and varies depending on genotype
    - Genotype 1 and 4 – SVR 40-50%
    - Genotype 2 and 3 – SVR 70%-80%
  - Some patients struggle with the side effects

The pack!


Copegus® 200mg
DANGER
CONTAMINATED SHARPS ONLY
TO BE INCINERATED
Roche
Steretts
Steretts

Unfortunately to date – we have not done a brilliant job of preventing new infections

Therefore we need the treatment option

- Only 2000 Australians are treated annually for HCV
- Similar situation applies in other countries

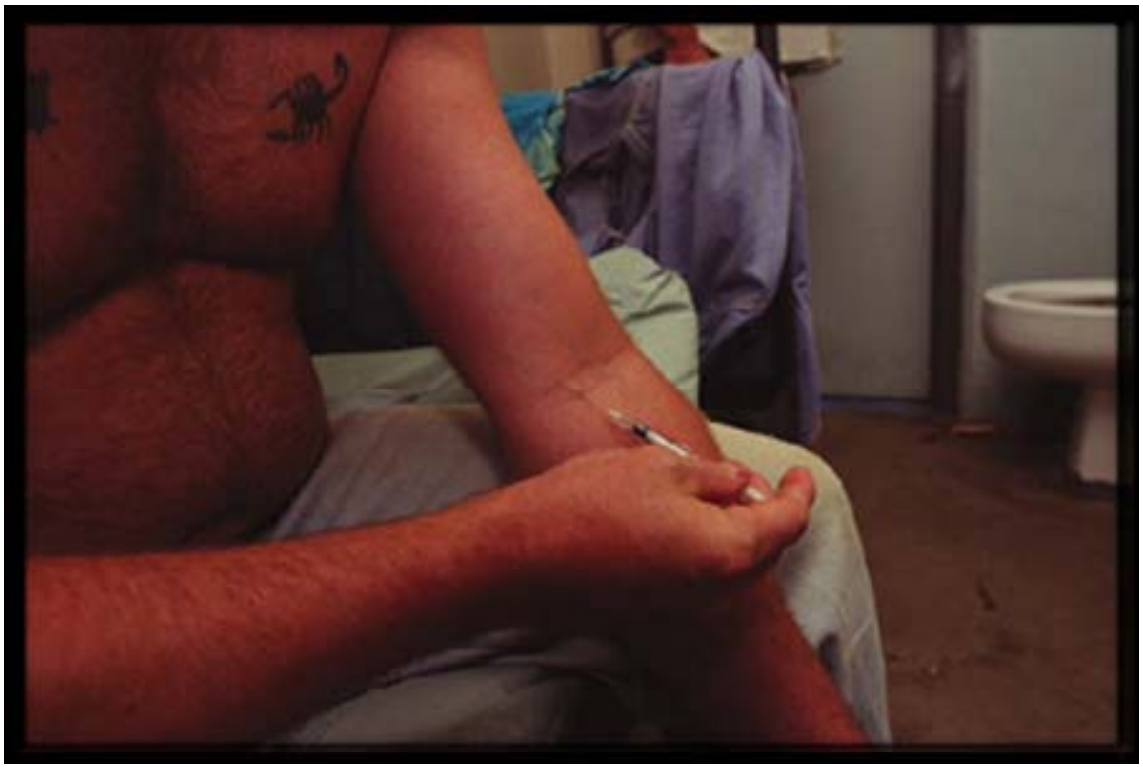
Therefore

- Need to improve IDUs access to HCV treatment
- Need to make treatment simpler
- Need to help IDUs “get through” treatment
- Some evidence that early treatment increases the chance of a SVR

Acute Hepatitis C

PEG-IFN-based studies

	Regimen	Jaundice	IDU-acquired	Baseline ALT	Duration infection* / Diagnosis **	SVR
Jaeckel 2001 (n=44)	IFN2b 5MU daily (4wk) 5MU tiw (20wk)	68%	N=8 (18%)	885	13 weeks* (4 – 16)	98%
Kamal 2004 (n=40)	PEG-IFN2a/2b (n=20) (24 wk) PEG2a/2b+RBV (n=20) (24 wk)	3%	N=0 (0%)	570	12 weeks**	80% (PEG) 85% (PEG/RBV)
Santantonio 2005 (n=16)	PEG-IFN2b 1.5/kg (24 wk)	47%	N=2 (13%)	1019	12 weeks**	94%
Broers 2005 (n=14)	PEG-IFN2b 1.5/kg (24 wk)	14%	N=11 (79%)	800	6 weeks** (1-50)	57% (88% PP)
De Rosa 2006 (n=19)	PEG-IFN2b 1.5/kg (24 wk)	16%	N=14 (74%)	627	4 weeks** (0 – 16)	74%
Weigand 2006 (n=89)	PEG-IFN2b 1.5/kg (24 wk)	62%	N=20 (22%)	599	11 weeks* (2 – 21)	71% (89% PP)
Kamal 2006a (n=129)	PEG-IFN2b 1.5/kg (12 wk)	22%	N=12 (9%)	644	10 weeks* (8 – 11)	88%
Kamal 2006b (n=102)	PEG-IFN2b 1.5/kg (8, 12, 24 wk)	23%	N=9 (9%)	642	13 weeks*	80%



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Australian Trial of Acute Hepatitis C (ATAHC)

- Australian investigator-initiated collaborative study
- NIH/NIDA funded (5 year RO1 grant); Roche (PEG-IFN)
- Objectives:

  - examine PEG-IFN monotherapy safety and efficacy in predominantly IDU-acquired acute hepatitis C
  - examine rates and predictors of viral clearance
  - examine rates and predictors of HCV reinfection following spontaneous or treatment-related viral clearance

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ATAHC Study

- Prospective longitudinal cohort
- Untreated and Treated sub-groups, but NOT randomized
- Treatment regimen: PEG-IFN-2a 180 mcg weekly for 24 weeks (PEG-IFN/RBV for HIV/HCV)
- All HCV-RNA positive subjects at screening eligible for treatment assessment, including normal ALT
- Median follow-up 3 years

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Definition of acute or newly acquired hepatitis C

- Anti-HCV antibody positive within previous 6 months

AND EITHER

- Anti-HCV antibody negative within 24 months prior to initial positive

OR

- Acute clinical hepatitis within 12 months prior to initial positive

RECRUITMENT

- HCV enhanced surveillance

  Difficult, time consuming, ethical issues, doctors act as “gate keepers”

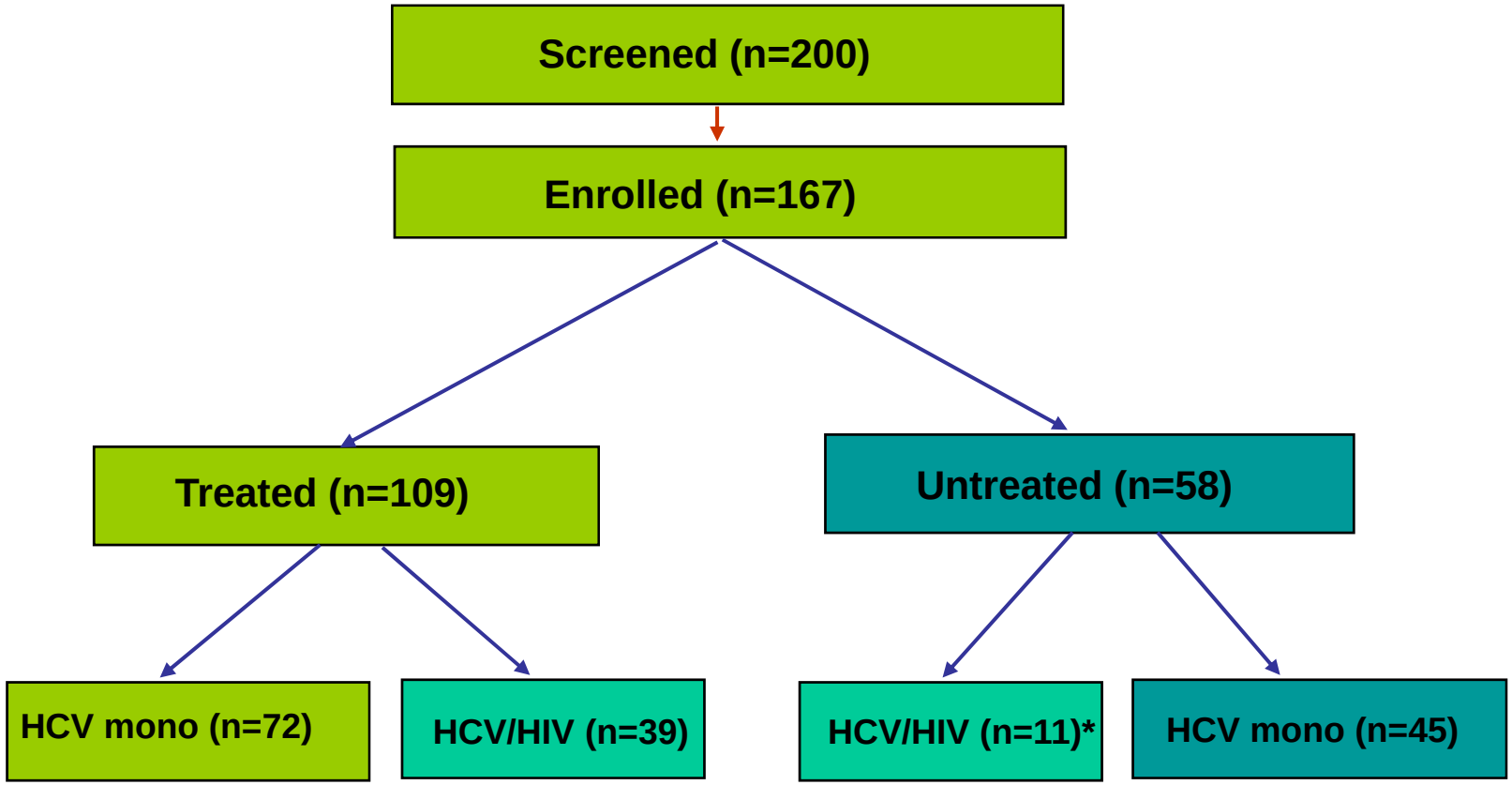
- Referrals from tertiary hospitals sites

- Referrals from GPs, drug treatment service, primary health care services

- Other

  Self referral, other research studies, prisons

ATAHC enrollment



* HCV RNA <3200 at screening in 8/11

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First 100 participants recruited into ATAHC

- What were the characteristics of the group?
- Were there factors that decreased the likelihood of participants undertaking treatment?

First 100 Recruited

Predictors of HCV treatment uptake – univariate analysis

	Not treated n = 21	Treated n = 67	OR	95 % CI	p-value	p-value
Education						
Secondary/other	18	37	1.00			
TAFE/trade	1	11	5.37	0.64-44.89	0.121	0.036
Tertiary/post grad	2	19	4.79	0.81-28.45	0.085	
Employment						
Full-time employment	2	24	1.00			
Part-time employment/other	18	43	0.20	0.04 – 1.01	0.052	
Duration of injecting						
< 6 years	4	32	1.00			
>=6 years	12	21	0.23	0.06 - 0.80	0.021	0.020
Missing/not injector	5	14	0.32	0.07 - 1.41	0.13	
Major depression (current)						
No	16	61	1.00			
Yes	5	5	0.29	0.07 - 1.18	0.085	
Duration of infection						
<24 weeks	12	26	1.00			
>=24 weeks	9	41	2.53	0.89 – 7.14	0.081	
HCV viral load (screening)						
<400,000 copies/ml	16	32	1.00			
>=400000 copies/ml	5	35	3.30	1.07 – 10.23	0.038	

First 100 Recruited

Predictors of HCV treatment uptake – multivariate analysis

	OR	95 % CI	p-value	p-overall
Duration of infection				
<24 weeks	1.00			
>=24 weeks	3.95	1.02 – 15.30	0.047	
HCV RNA viral load (copies/ml)				
<400000	1.00			
>=400000	6.53	1.49 – 28.56	0.013	
Duration of injecting				
< 6 years	1.00			
>=6 years	0.13	0.03 - 0.56	0.006	0.005
Missing/not injector	0.29	0.05 – 1.69	0.17	
Employment status				
Full-time	1.00			
Part-time	0.16	0.03 – 0.93	0.041	

Treatment outcome

First 50 mono-infected patients

- First 76 patients enrolled
  - 50 (66%) commenced treatment
  - Majority - history of injecting drugs (82%)
  - Estimated duration infection - 40 weeks
  - 70% - early chronic HCV infection

First 50 Treated

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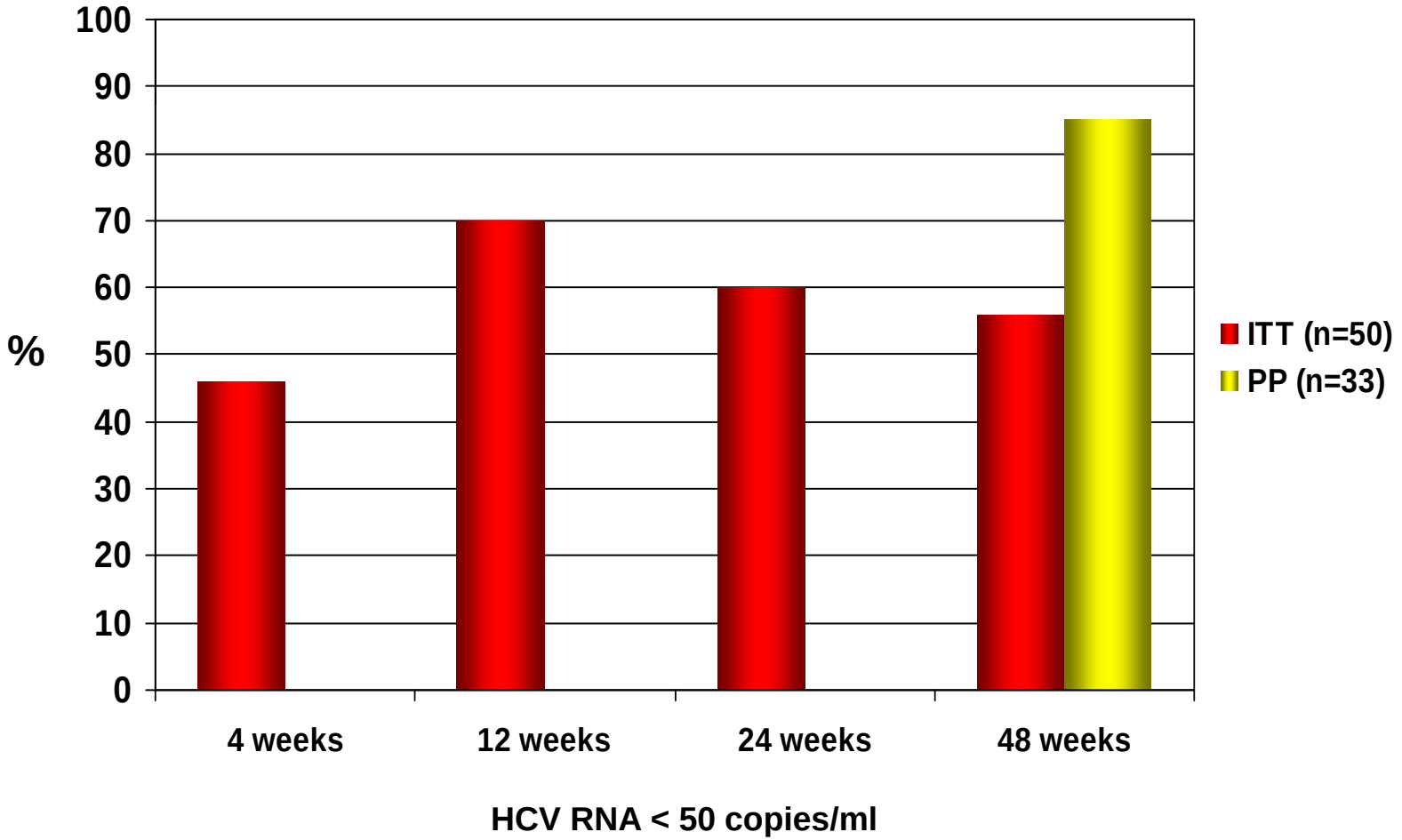
Clinical characteristics at baseline: 50 treated HCV monoinfected subjects

HCV virology	
Genotype 1	25 (50%)
Genotype 2/3	22 (44%)
Genotype missing	3 (6%)
Baseline HCV RNA (median, copies/ml)	380,000
Clinical	
Acute symptomatic illness	23 (46%)
Estimated duration of HCV infection (mean, weeks)	**40**
ALT (mean peak, IU/ml)	811
ALT (mean baseline, IU/ml)	204

HCV treatment response: HCV mono (PEG) (n=50)



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First 50 treated – predictors of SVR (univariate analysis)

	No SVR	SVR	Total	OR (95% CI)	P value
Mode of HCV infection					
Other	2	7	9	1.00	
IDU	20	21	41	0.30 (0.06 – 1.62)	0.16
Injected within 6 months prior to treatment					
No	3	14	17	1.00	
Yes	**10**	**13**	**23**	**0.28 (0.06 – 1.24)**	**0.094**
Missing	**9**	**1**	**10**	**0.02 (0.00 – 0.27)**	**0.002**
Estimated duration of HCV infection					
<= 24 weeks	8	7	15	1.00	
> 24 weeks	14	21	35	1.71 (0.51 – 5.80)	0.39

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First 50 treated – predictors of SVR (univariate analysis)

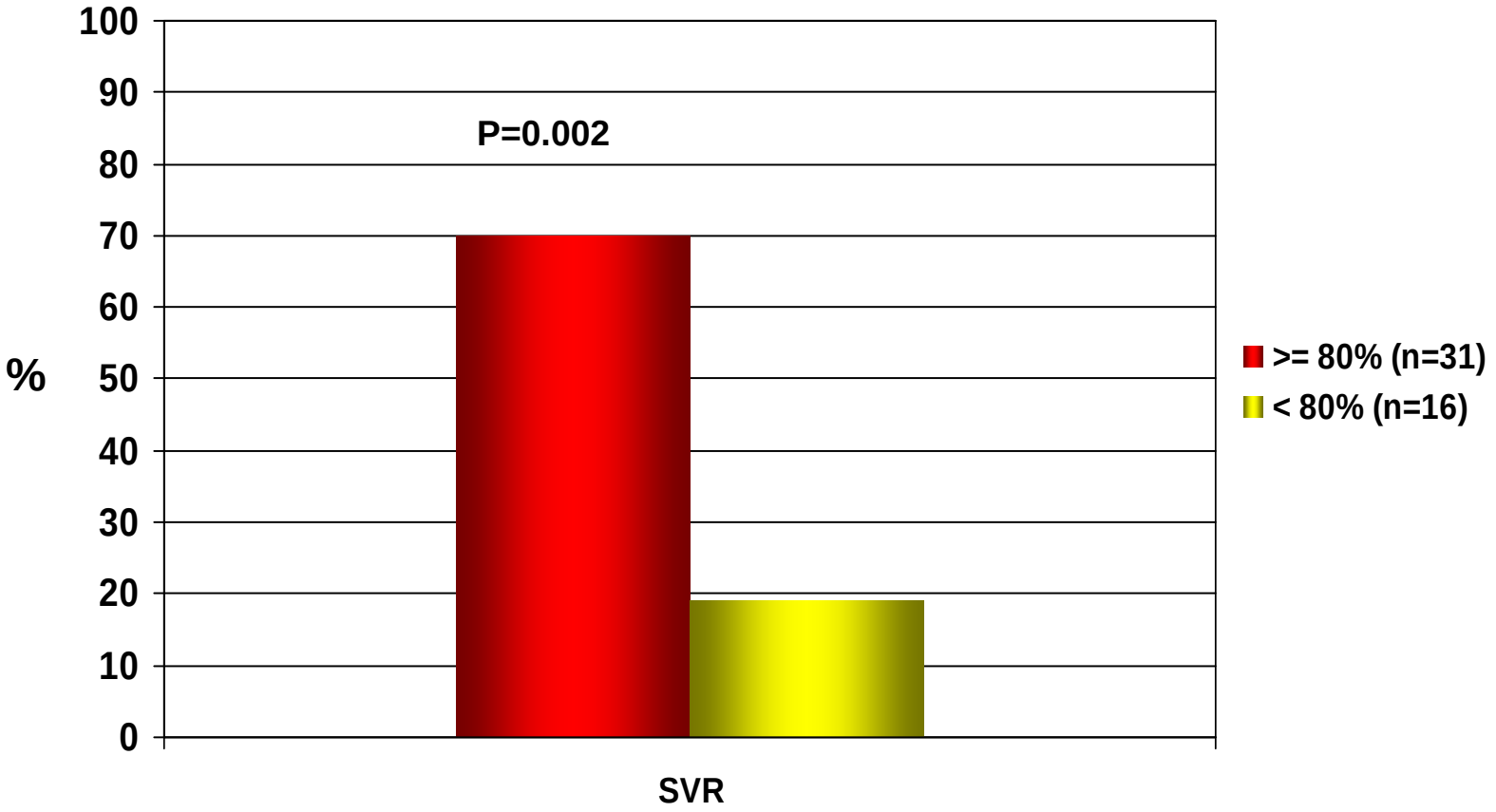
	No SVR	SVR	Total	OR (95% CI)	P value
Major depression at baseline					
No	20	24	44	1.00	
Yes	1	4	5	3.33 (0.34 – 32.27)	0.30
Major depression during treatment or follow-up					
No	11	14	25	1.00	
Yes	6	14	20	1.83 (0.53 – 6.34)	0.34
Missing	5	0	5		
Injected during treatment or follow-up					
No	**3**	**14**	**17**	**1.00**	
Yes	**10**	**13**	**23**	**0.28 (0.06 – 1.24)**	**0.094**
Missing	**9**	**1**	**10**	**0.02 (0.00 – 0.27)**	**0.002**
Interferon injections received					
<80%	**13**	**4**	**17**	**1.00**	
>=80%	**9**	**24**	**33**	**8.67 (2.23 – 33.68)**	**0.002**

First 50 treated – predictors of SVR (multivariate analysis)

- The only factor associated with improved SVR
  - 80% treatment adherence

  (OR=5.64, 95% CI=1.25 – 25.45, p=0.024).

HCV treatment response: SVR by adherence



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Conclusion

- Population with recently acquired HCV infection – some acute, others early chronic
- Predominantly infected due to injecting drug use
- PEG-IFN monotherapy resulted in good treatment outcomes among adherent participants
- Strategies are required to enhance HCV treatment adherence

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Potential explanations for poorer treatment outcomes

- **High proportion of IDU**
- **Lack of supervised treatment**
- **Later commencement of treatment**
- **Lack of combination therapy**

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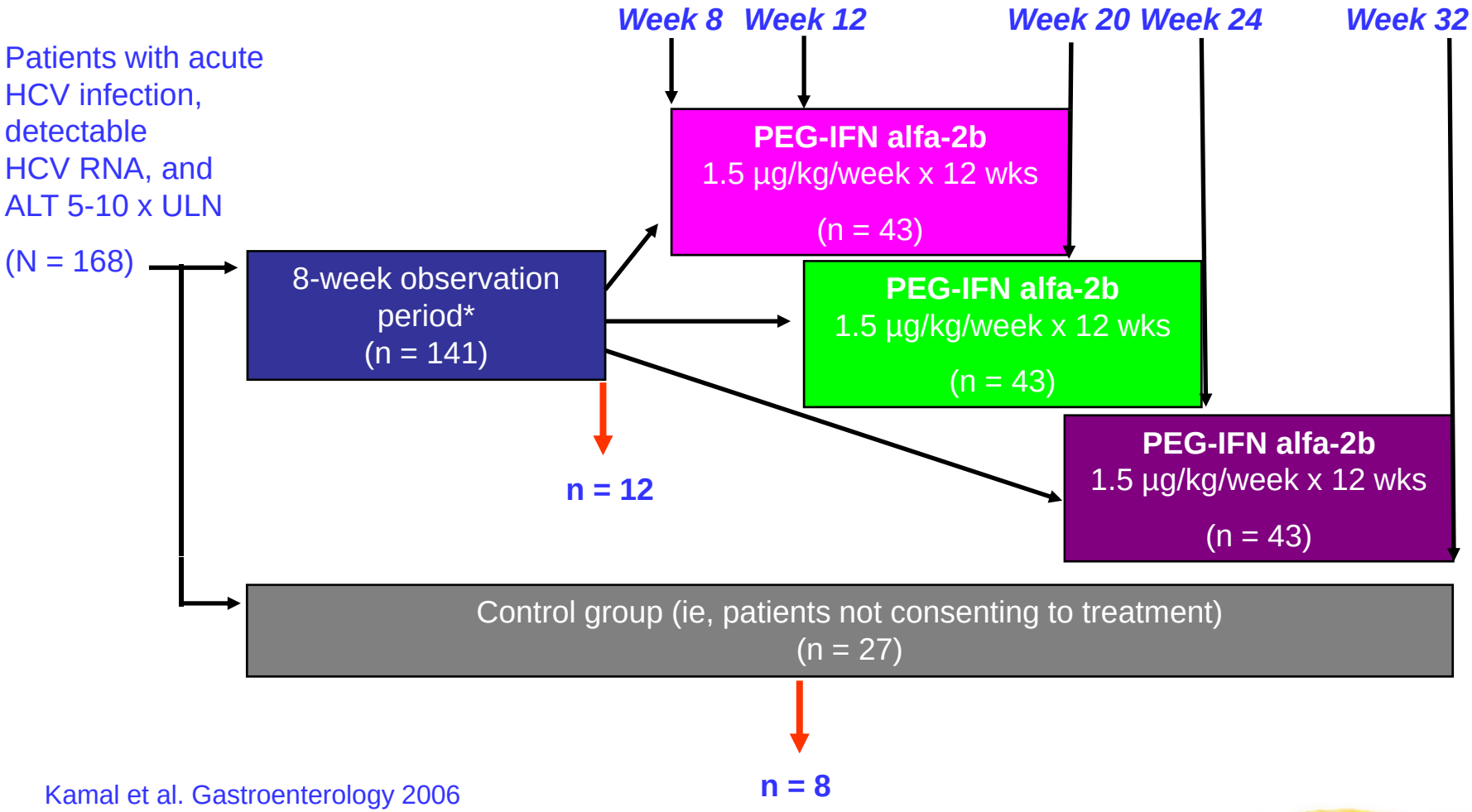
So where to from here?

Acute Hepatitis C

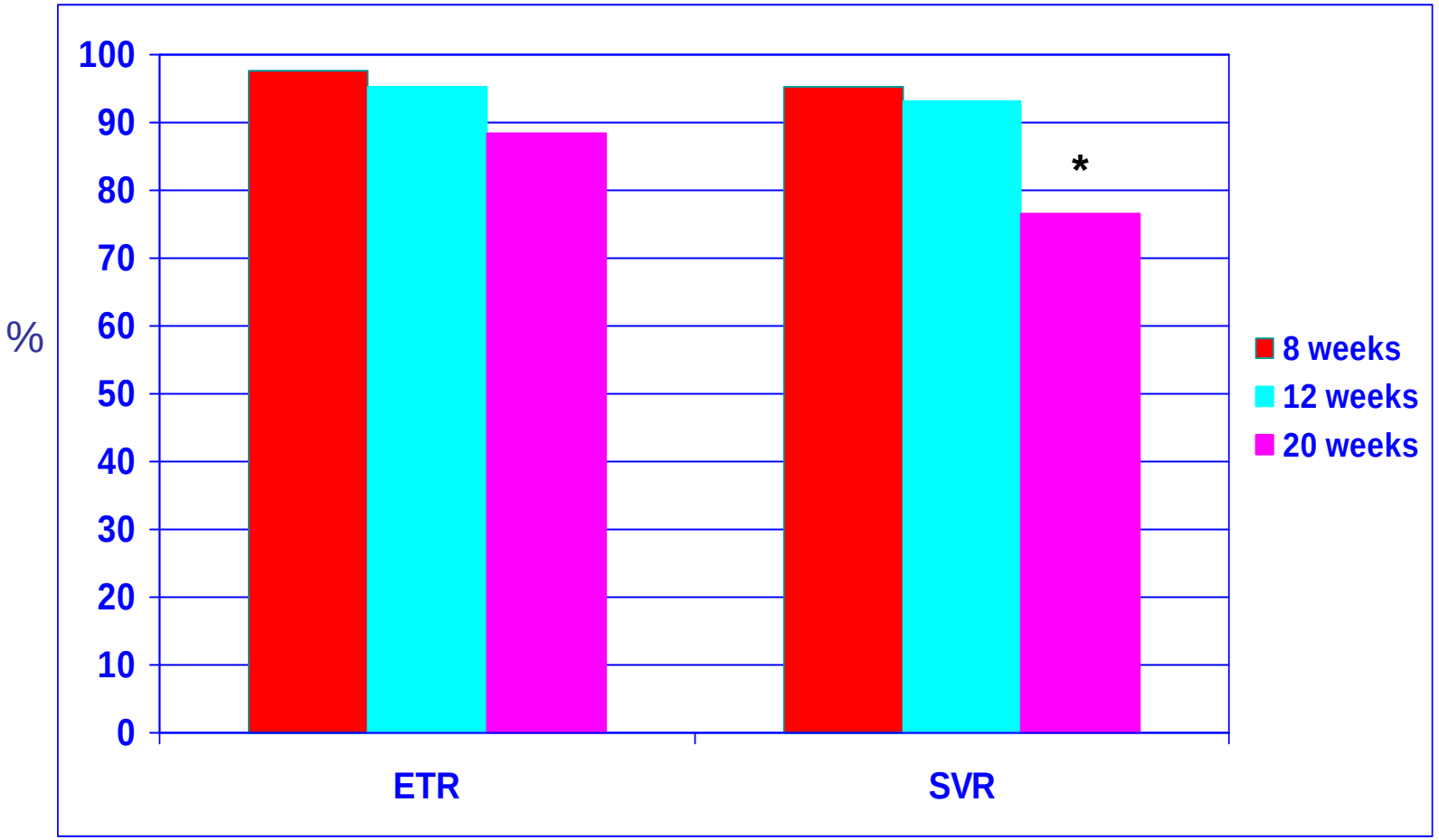
Impact of timing of treatment



Kamal et al. Gastroenterology 2006

Acute Hepatitis C

PEG-IFN 2b (12 weeks): impact of timing of treatment



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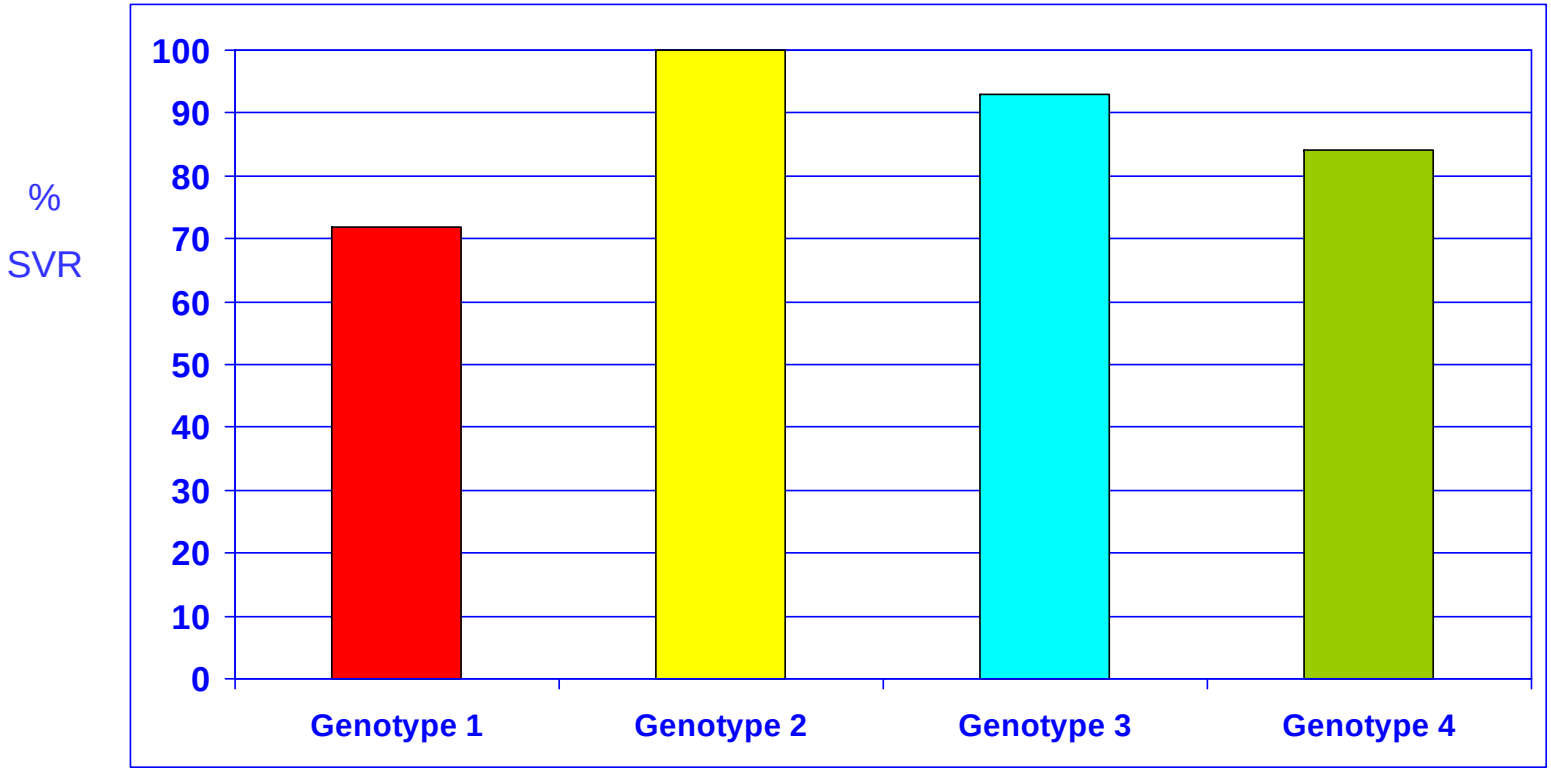
PEG-IFN 2b (12 weeks): impact of genotype



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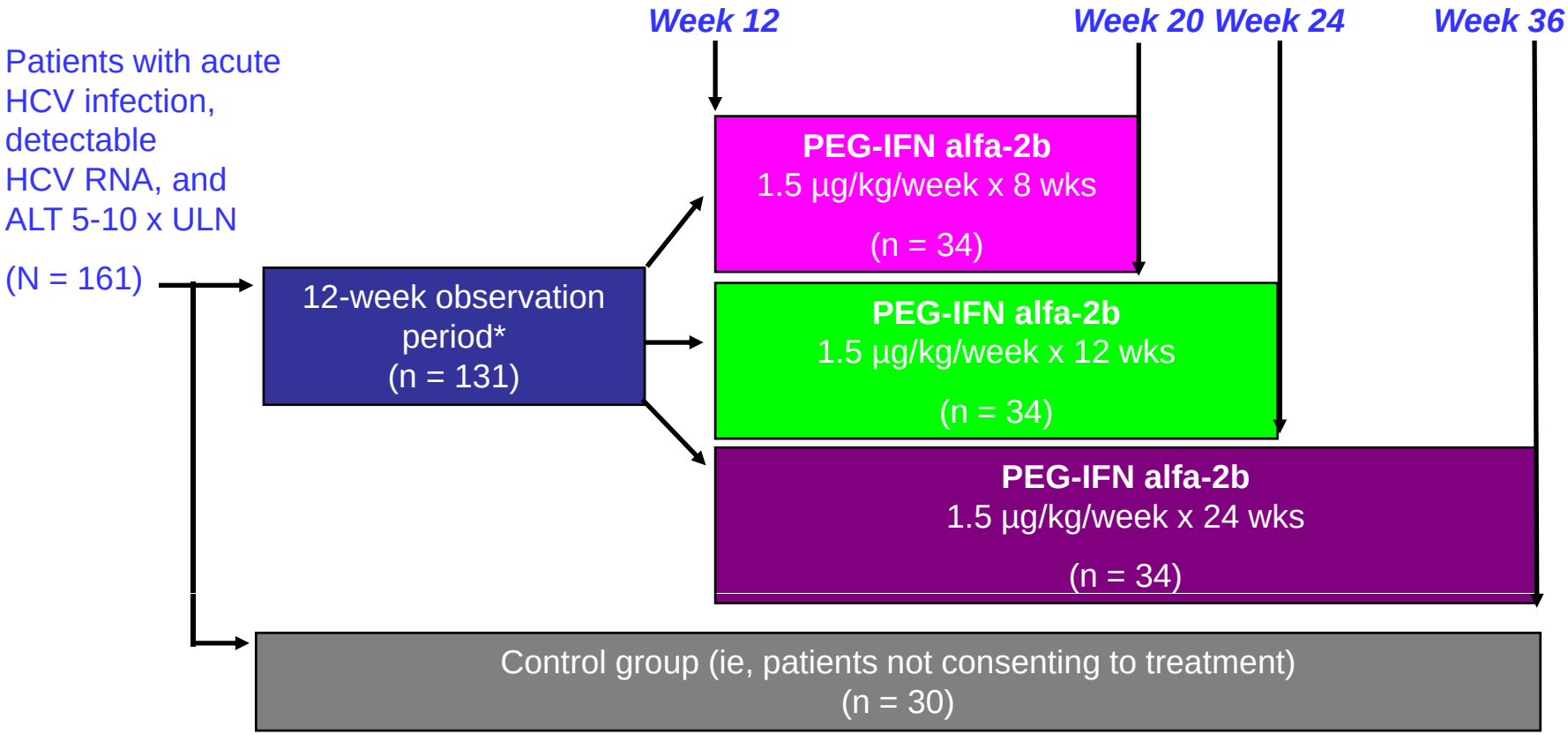
Baseline predictors of SVR:
low HCV RNA, non-1 genotype

Acute Hepatitis C

Impact of duration of treatment



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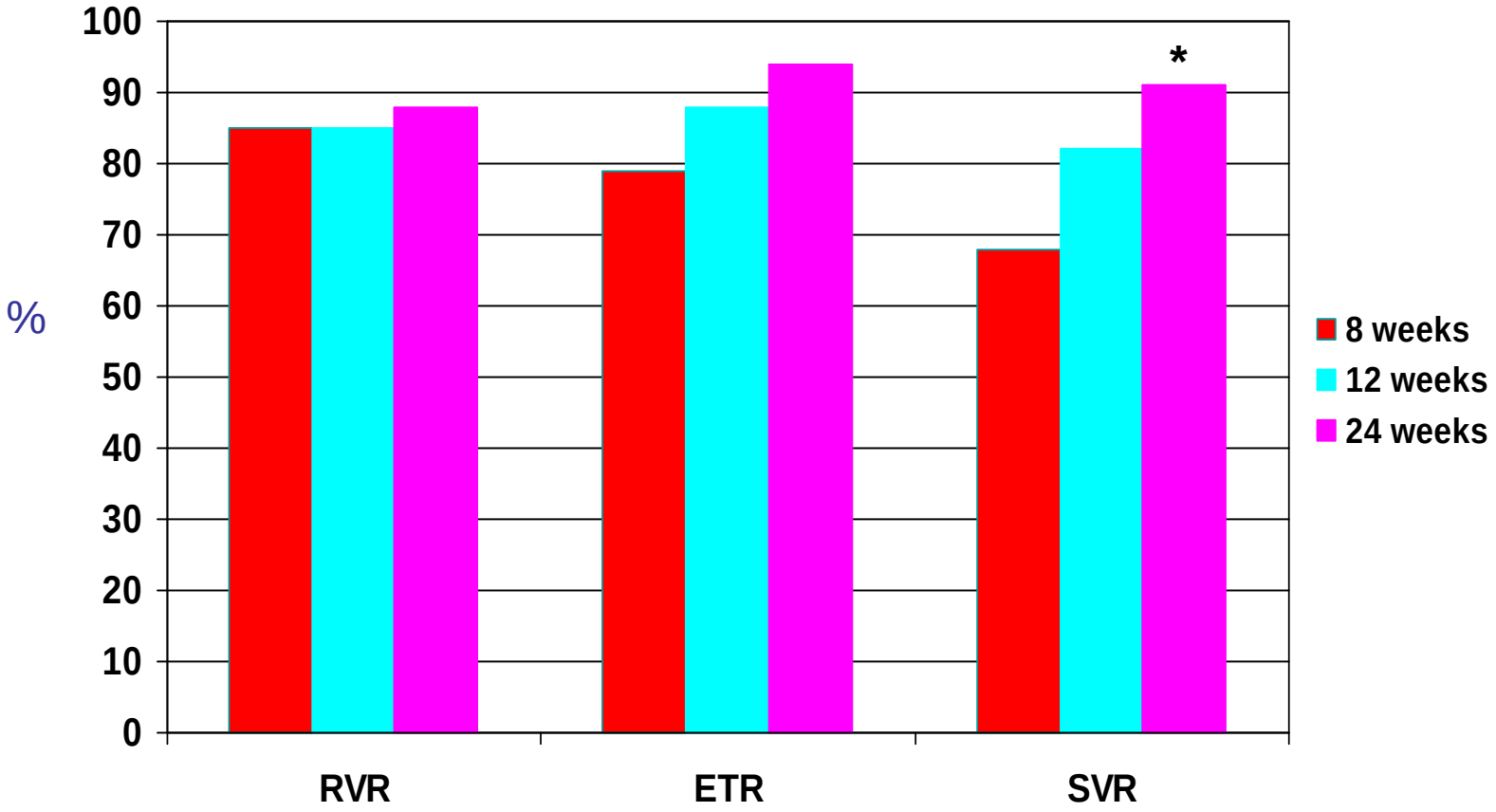
PEG-IFN 2b monotherapy: impact of duration of treatment



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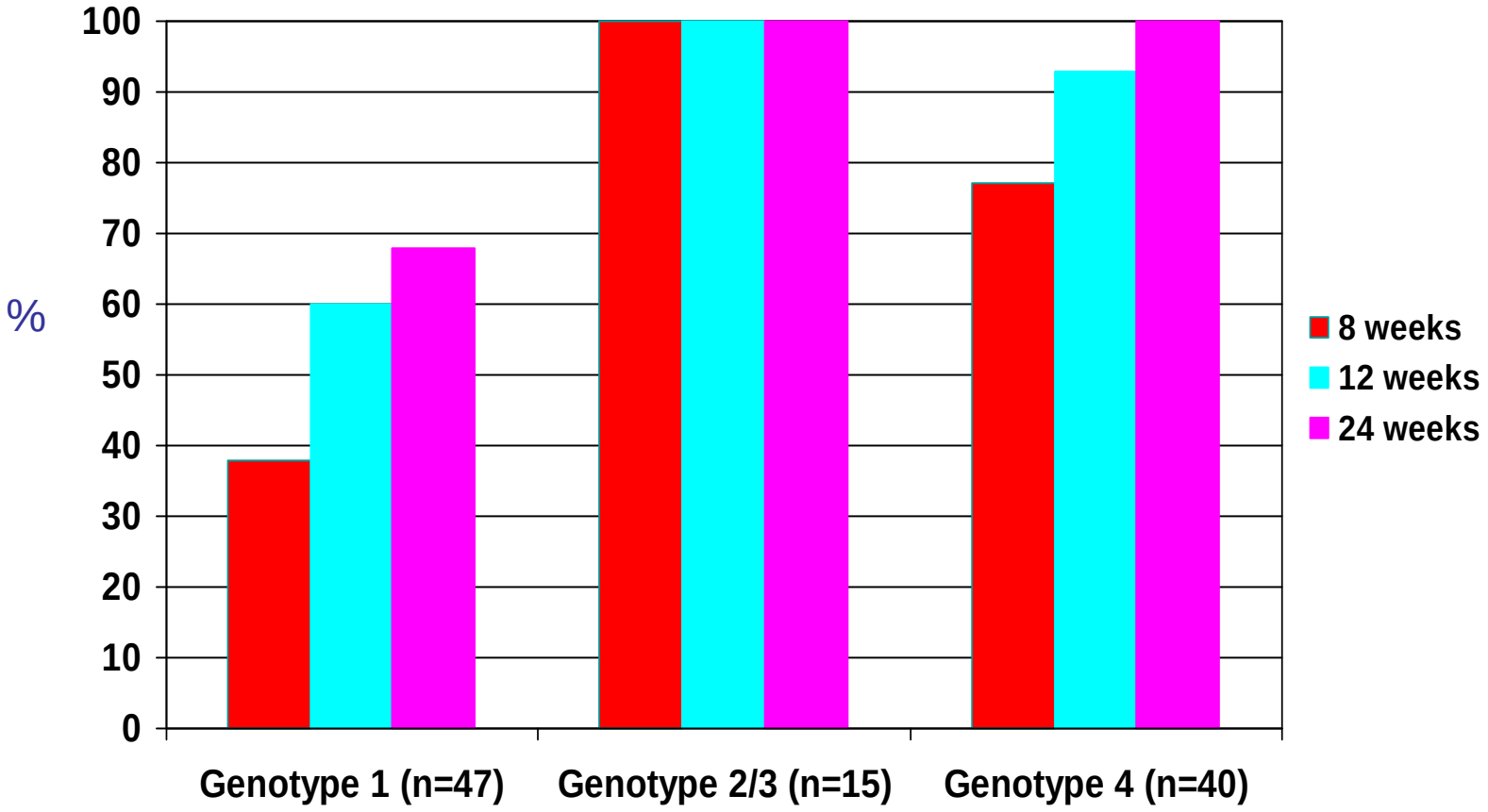
PEG-IFN 2b monotherapy: impact of duration of treatment



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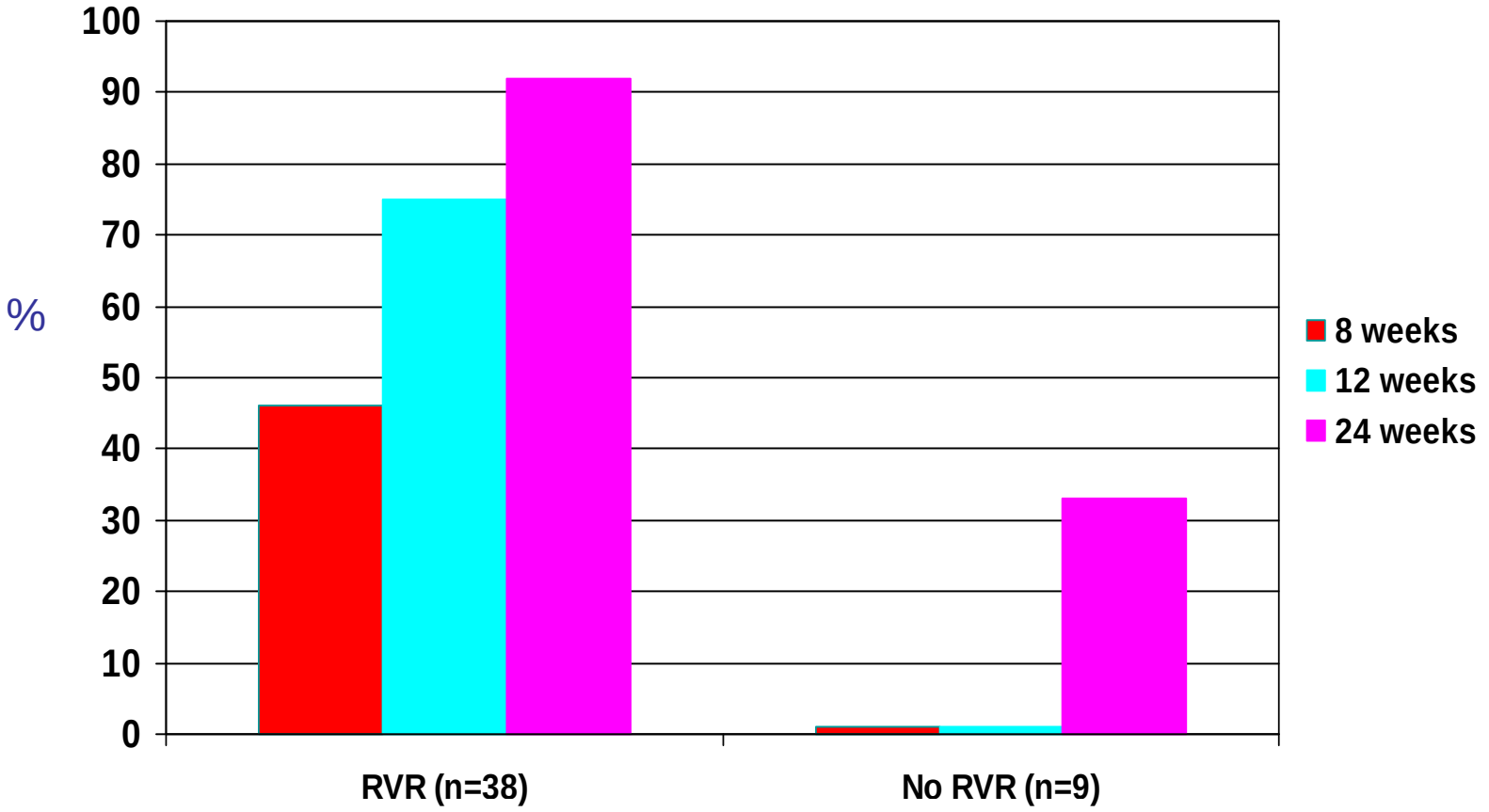
PEG-IFN 2b monotherapy: impact of RVR (genotype 1)



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Future directions

- NIH (NIDA) RO1 renewal submission July 2008
- Continued focus on acute and early chronic HCV among IDU
- Possible smaller recruitment network
- Look at reducing length of treatment
- Consider taking genotype and if person has RVR in to account
- Role of combination therapy in some population
- Immunovirology sub-study opportunities

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Recruitment – initial contact

Very important – usually research nurse or outreach worker

Apart from ensuring “eligibility” criteria need to reassure about privacy & confidentiality

Also – need to provide study information in a simple clear way, need to ensure participants are aware of need for long follow up

Very early on (via telephone) ensure have multiple contact details because often it is hard to get them the first clinic visit – need a persistent research nurse

Where appropriate discuss study about treating HCV, not drug use and that they do not have “stop” using

Follow up

- Support to get to clinic
- Reminders of appointment times
- Clinic structure
- Clinicians – interest in working with the patient group
- Nursing support –well informed about HCV and open minded, patient and persistent
- Outreach worker
- Easy access to psychiatrist and drug and alcohol service
- Social work support

ATAHC Study Group

Participating Sites	Principal Investigators & Study Coordinators
Alfred Hospital Infectious Disease Unit (VIC)	Margaret Hellard, Oanh Nyugen, Christine Bowtell-Harris
St Vincent's Hospital (NSW)	Greg Dore, Gail Matthews, Zoe Potgieter
Kirketon Road Centre (NSW)	Ingrid van Beek, Anna Doab, Therese Carroll
Royal Prince Alfred Hospital (NSW)	Paul Haber, Sue Mason, Sineal Shiels, Louise Campbell
Holdsworth House GP Practice (NSW)	Mark Bloch, Ruth Hutchison, Collin Anderson
407 Doctors (NSW)	David Baker, Robyn Vale
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Nepean Hospital (NSW)	Nghi Phung, Vince Fragomeli, Sara Twohill
Alfred Hospital Gastroenterology Unit (VIC)	Stuart Roberts, Caroline Day
Royal Melbourne Hospital (VIC)	Joe Sasadeusz, Maxine Giourouski, Joanne Patterson
Monash Medical Centre (VIC)	Bill Sievert, Sherryne Warner
Royal Adelaide Hospital (SA)	David Shaw, Catherine Ferguson
Fremantle Hospital (WA)	Lindsay Mollison, Crystal Connelly
Princess Alexandra Hospital (Qld)	Darrell Crawford, Julie Roggeveen, Fiona Giddon
Protocol Steering Committee: John Kaldor, Greg Dore, David Baker, Nick Crofts, Kate Dolan, Geoff Farrell, Rose Ffrench, Steve Liebke, Gail Matthews, Margaret Hellard, Paul Haber, Andrew Lloyd, Geoff McCaughan, Annie Madden, Bill Rawlinson, Bill Sievert, Ingrid van Beek, Peter White	
NCHECR ATAHC Study Team: Barbara Yeung, Carolyn Day, Gail Matthews, Pip Marks, Anna Doab, Therese Carroll	
Sponsors: NIH/NIDA; Roche Products	


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