HCV Vaccine Development: Where do we stand?

Andrea L. Cox, MD,PhD
Professor of Medicine and Oncology
Viral Hepatitis Center

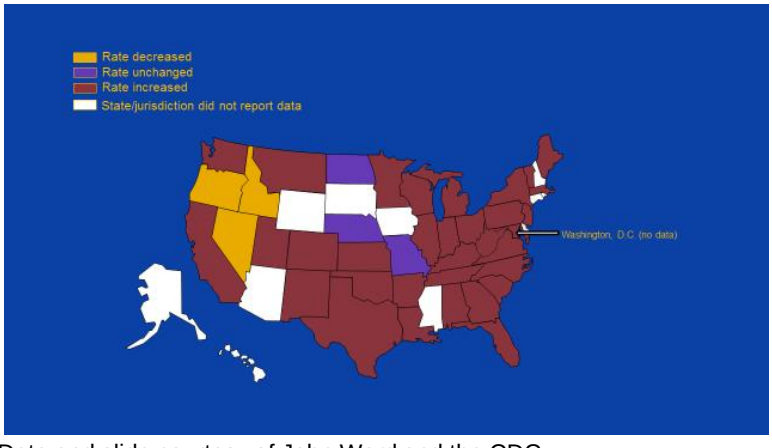
No Conflicts of Interest

HCV- Do we need a vaccine?

- Acute infection rates are not decreasing everywhere

Rising Number of New Acute HCV Cases in PWID in US

Changes in Rates of New HCV Cases Reported by State, 2010-2014



Data and slide courtesy of John Ward and the CDC

HCV- Do we need a vaccine?

- Therapies dramatically better but…

HCV- Do we need a vaccine?

- Treatment remains expensive and carries some side effects

HCV- Do we need a vaccine?

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- Finding the people who need treatment remains challenging

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Centers for Disease Control and Prevention MMWR Recomm. Rec. 47 (RR-19), 1-39 (1998), Nature Outlook Hepatitis C vol 474, 7350, S2

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- Knowledge of infection status limited
  - 5% of those infected world-wide

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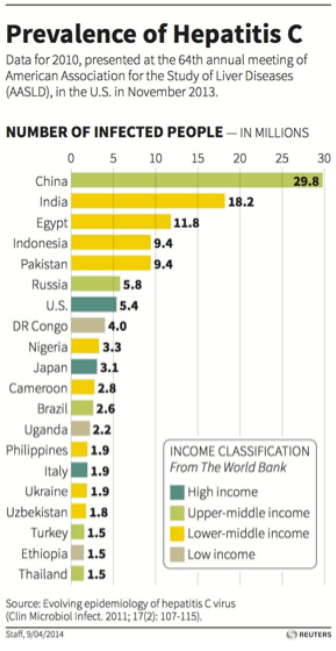
- Highest risk groups are marginalized
  - PWID
  - Living in endemic regions of the world

Centers for Disease Control and Prevention MMWR Recomm. Rec. 47 (RR-19), 1-39 (1998), Nature Outlook Hepatitis C vol 474, 7350, S2



HCV- Do we need a vaccine?

Treatment remains expensive and carries side effects

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Drugs do not provide protection against reinfection

Incidence of hepatitis C reinfection following SVR

Patients

2004–05: Treated PWID abstinent from drug use ≥6 months prior to treatment

Midgard H, et al. J. Hepatology May 2016 Volume 64, Issue 5, Pages 1020–1026

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HCV reinfection in 12 patients (12.8%)

Midgard H, et al. J. Hepatology May 2016 Volume 64, Issue 5, Pages 1020–1026

Incidence of hepatitis C reinfection following SVR

Patients: 114 HIV+ MSM with SVR

Martin TC et. al. AIDS 2013 Oct 23;27(16):2551-7

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25% of patients treated for HCV virus infection became reinfected within 2 years of follow-up.

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HCV- Do we need a vaccine?

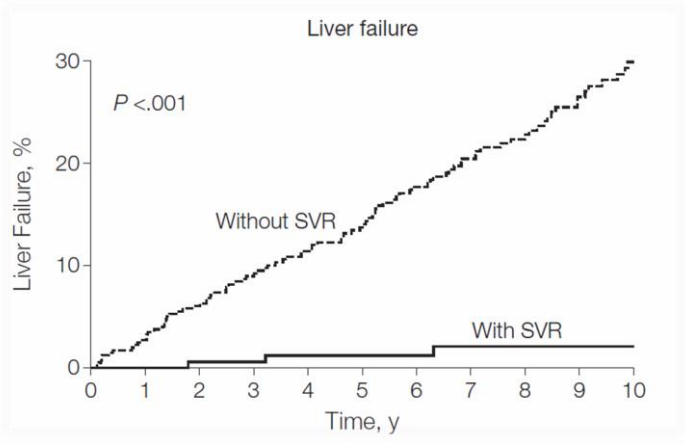
Treatment remains expensive and carries side effects

Finding the people who need treatment remains challenging

Drugs do not provide protection against reinfection

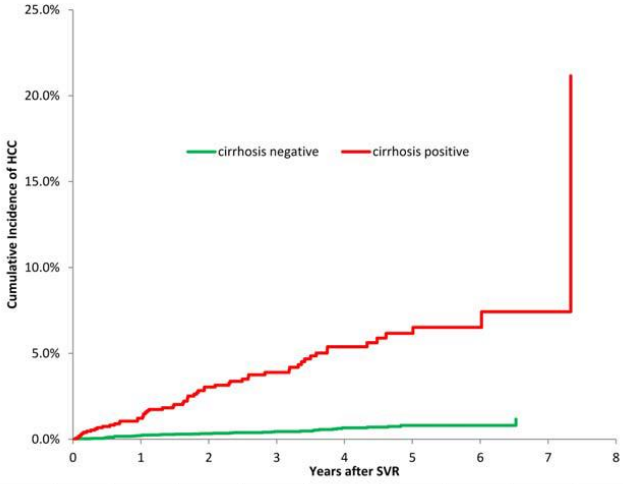
Treatment in the later stages doesn't reverse all disease

Eradication of HCV reduces but doesn't eliminate liver failure



Van der Meer JAMA 2012; Backus Clin Gastro 2011; Imazeki Hepatology 2003; Shiratori Ann Intern Med 2005; Veldt et al Ann Intern Med 2007; Berenguer Hepatology 2009;

Incidence of HCC after SVR is high in cirrhotics.



El-Serag, et. al. Risk of Hepatocellular Carcinoma after SVR in Veterans with HCV Infection, Hepatology, 2016 Jul;64(1):130-7.

HCV- Do we need a vaccine?

- Treatment remains expensive and carries side effects
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
- Treatment in the later stages doesn't reverse all disease
- Potential for DAA resistance unknown

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- Resistance in 2510 patients in Phase 2 and 3 trials who received DAAs (PTV/r-, OBV- and DSV-based regimens)

Krishnan P, et al. Antimicrob Agents Chemother. 2015 Sep;59(9):5445-54.

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- Resistance in 2510 patients in Phase 2 and 3 trials who received DAAs (PTV/r-, OBV- and DSV-based regimens)
- 67 G1a and 7 G1b failures (2.9% of total population)

Krishnan P, et al. Antimicrob Agents Chemother. 2015 Sep;59(9):5445-54.

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- NS5A RAVs persist beyond FU48
- NS3 RAVs decline to low levels by FU48
- NNI RAVs persist but not a lot of crossover across class

Krishnan P, et al. Antimicrob Agents Chemother. 2015 Sep;59(9):5445-54.

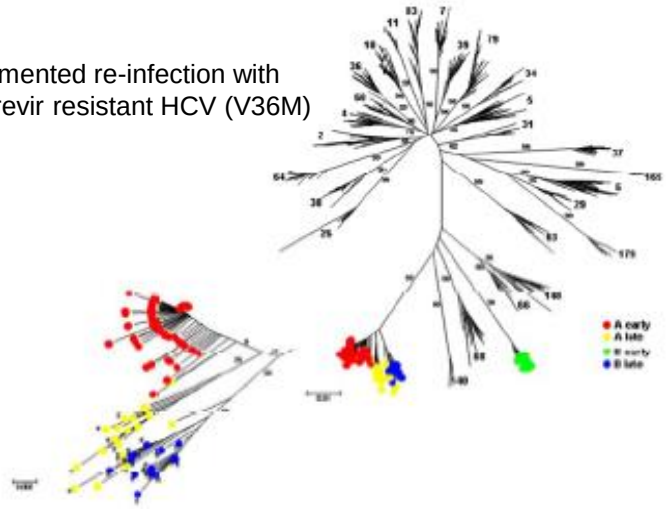
Reinfection with DAA resistant HCV

HIV-infected male sexual partners with HCV:
SVR in one
DAA failure in the other with documented telaprevir resistant HCV (V36M)

Franco et al. Gastroenterology 2014

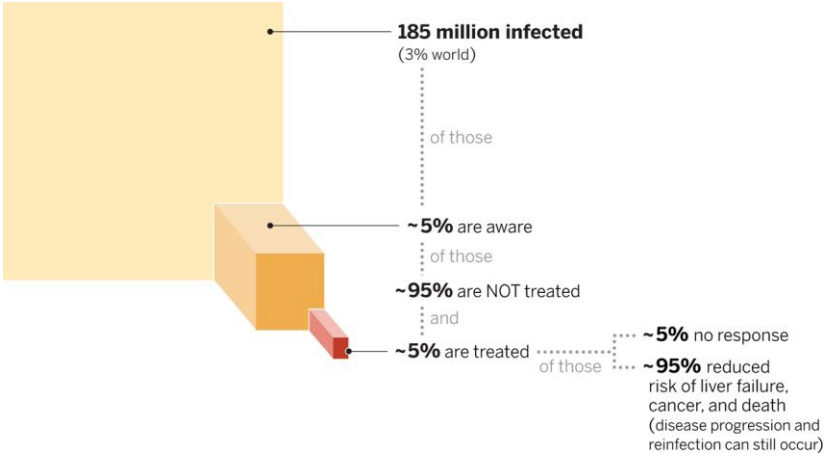
Reinfection with DAA resistant HCV

Documented re-infection with telaprevir resistant HCV (V36M)



Franco et al. Gastroenterology 2014

The global reach of HCV infection.



Andrea L. Cox Science 2015;349:790-791

Science AAAS

Is protective immunity possible?

Is protective immunity possible?

- Reinfection does not always result in clearance- no protective immunity

Is protective immunity possible?

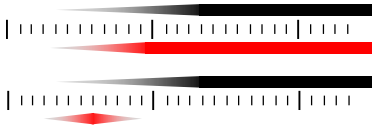
- Reinfection does not always result in clearance- no protective immunity
- Some evidence that says yes…

BBAASH Cohort

Baltimore **B**efore and **A**fter **A**cute **S**tudy of **H**epatitis

18-35yo Active IDU
HCV EIA & RNA neg

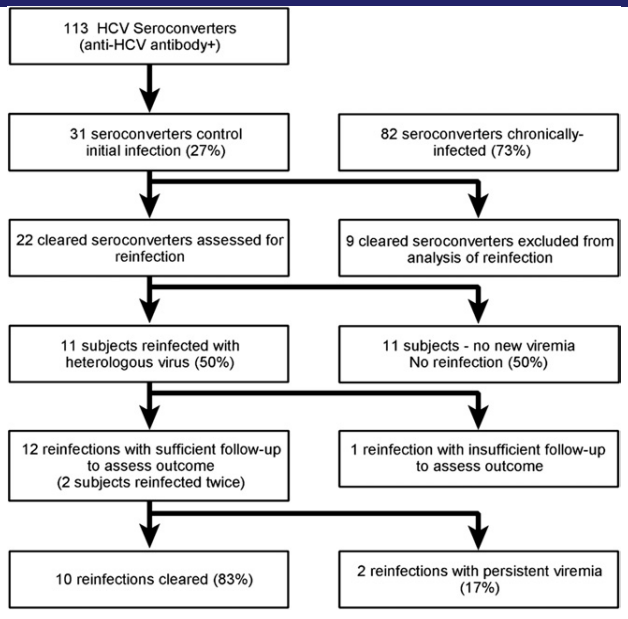
Anti-HCV Ab = black bar **HCV = red bar**



Persistent Infection

Spontaneous Clearance

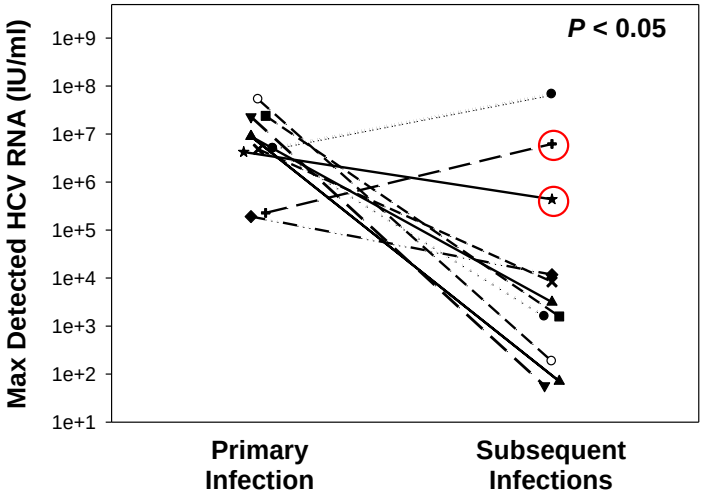
Protection from Persistent HCV



(*P =.001)*

Osburn et. al. Gastroenterolgy 2010;138:315–324

Decreased magnitude of viremia during reinfection



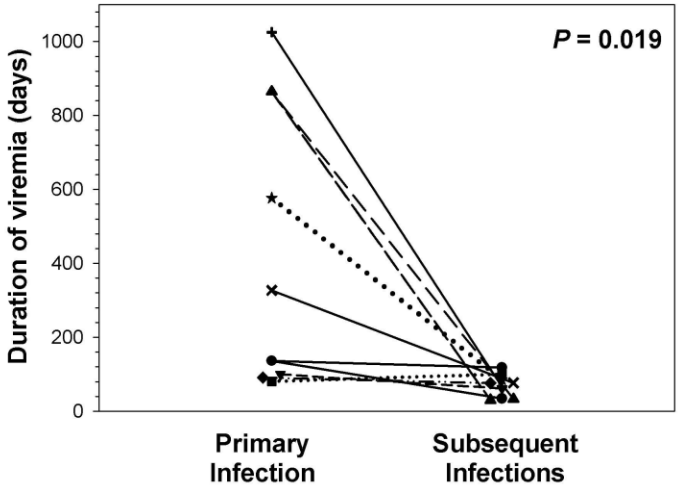
includes persistently reinfected subjects

Osburn et. al. Gastroenterolgy 2010;138:315–324

Evidence of protective immunity

- Peak HCV RNA level significantly lower during reinfection than primary infection
  - Mehta et. al. Lancet 2002,
  - Grebely et. al. Hepatology 2006
  - Sacks-Davis et. al. JID 2015

Shorter duration of viremia during reinfection



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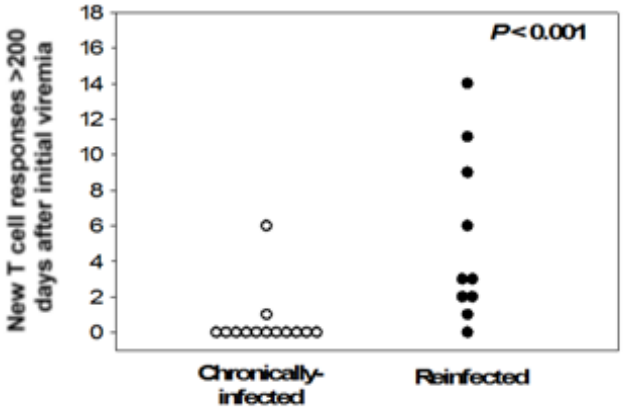
Broadening of T cell responses in HCV Reinfection



Updated from Osburn et. al. Gastroenterology 2010;138:315–324

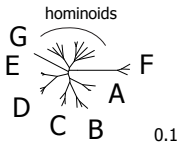
Broadening of T cell responses in HCV Reinfection

- Confirmed in Montreal Acute Hepatitis C Injection Drug User Cohort:
  - Increased magnitude and breadth
  - Higher T cell proliferative capacity

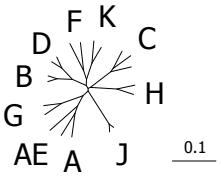
Abdel-Hakeem, M et. al. Gastroenterolgy 2014, 147;870-881

HCV- Can we make an effective vaccine?

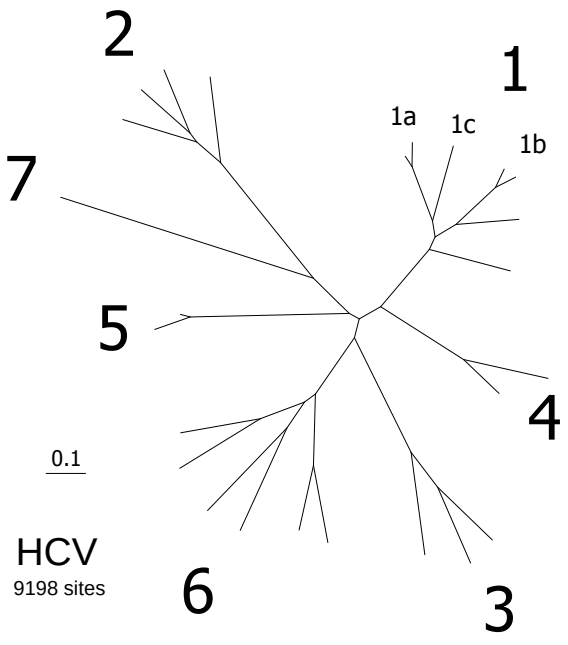
- Challenges parallel to HIV
  - Highly diverse virus



HBV
3181 sites



HIV
8316 sites



Ray SC and Thomas DL. *PPID* 7th ed, Chapter 154 2009

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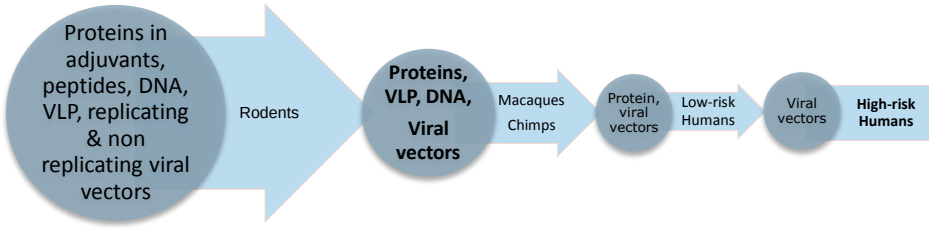
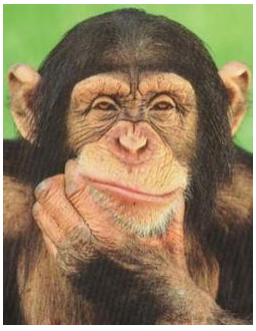
  - Increasing interest in vaccines that induce robust T cell responses
  - Current focus is to use vectors to deliver viral antigens in a system that induces robust innate and adaptive immune responses
    - Preexisting vector immunity limits responses

Efforts to develop a prophylactic HCV vaccine



Vaccines for Hepatitis C, 25 Years After the Discovery of Hepatitis C, Springer, in press

Preventing pre-existing anti-vector immunity from limiting vaccine efficacy



- Adenoviruses derived from chimpanzees (ChAd) differ from human adenovirus primarily in hexon (surface) proteins, making Ab cross reactivity low

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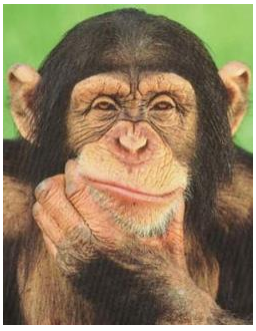
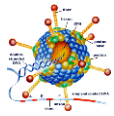


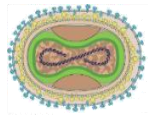
- Adenoviruses derived from chimpanzees have low Ab cross reactivity
- many are highly immunogenic

Prophylatic vaccines to generate T cell immunity based on viral vectors

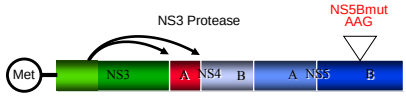
- Low seroprevalence chimpanzee derived Adenovirus – ChAd3



- MVA attenuated strain, non-replicating in mammalian cells



Prophylatic vaccines to generate T cell immunity based on viral vectors



- Vectored HCV antigen: “NSmut”

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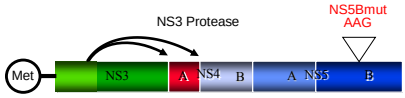
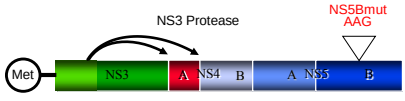


- Vectored HCV antigen: "NSmut"
  - NS3-NS5B (NS = 1985 aa)
  - Several known human CD4 and CD8 T cell epitopes
  - Most conserved HCV region
  - Genotype I, subtype 1b

Prophylatic vaccines to generate T cell immunity based on viral vectors



- Vectored HCV antigen: **"NSmut"**

Aim: induce antiviral immunity with functional characteristics analogous to those associated with viral control in natural infection – broadly targeted, durable, functional CD4+CD8+ T cell response

HCV Vaccine Healthy Volunteer Trial Summary

- AdCh3NSmut prime with MVANSmut boost is a highly potent inducer of T cell responses.

Swadling L et al., *Science Translational Medicine;* 5 November 2014; 6:(261)

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Figure 2c

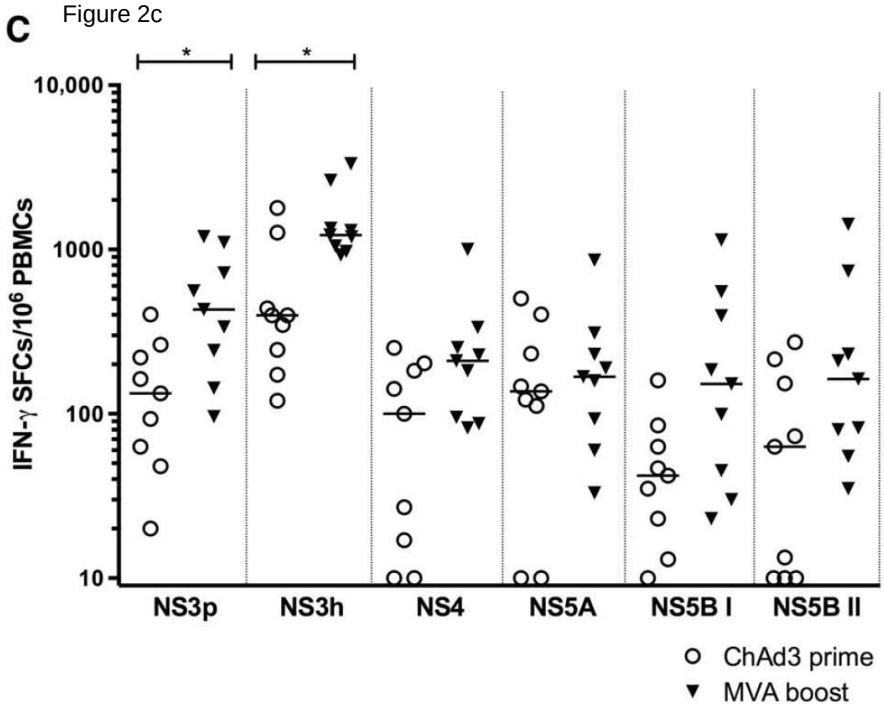

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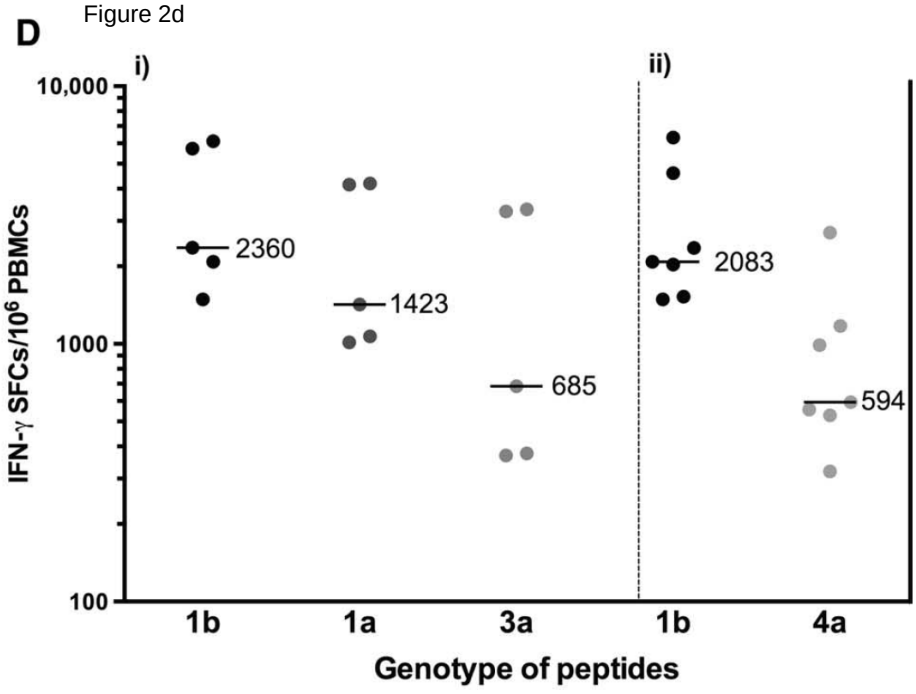
Figure 2d



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- T cells responses across genotypes detected.
- Vaccines safe and well tolerated.

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VIP: Vaccine is Prevention

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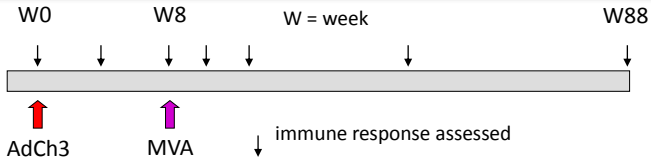
- **Population**: 18-45 yo active injection drug users at high risk for but not infected with HCV RNA at screening
- **Size:** Total N=540
- **Goal:** assessment of safety, induction of HCV specific immune responses, and efficacy in preventing chronic HCV infection

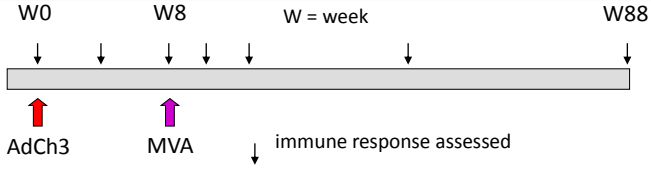
VIP Design

- **Two injections administered at 0 and 8 weeks:**
  AdCh3NS$_{mut1}$ & MVA-NS$_{mut}$
- Immune responses assessed



VIP Design

- **Two injections administered at 0 and 8 weeks:**
  AdCh3NS$_{mut1}$ & MVA-NS$_{mut}$
- Immune responses assessed
- HCV RNA tested monthly



Conclusions

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- A prophylactic HCV vaccine is needed.
  - Comprehensive strategy
    - Prevention, harm reduction
    - Diagnosis
    - Treatment

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- As with HIV, it will not be easy to create a successful vaccine.

Conclusions

- A prophylactic HCV vaccine is needed.
- Protective immunity likely exists *in vivo*.
- As with HIV, it will not be easy to create a successful vaccine.
- A new prophylactic vaccine is in trials for the first time in at risk subjects- data due out in early 2017

Acknowledgements

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Stefania Capone
Antonella Folgori
Alfredo Nicosia
Elisa Scarselli

Thank you!!!

- Questions?