# HCV Controlled Human Infection Model (CHIM) Trial Design

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# Disclosures

- **Research:** Abbvie, Eiger, Gilead, GSK, Janssen, Roche, Vir
- **Consulting:** Abbvie, Gilead, GSK, Janssen, Roche, Vir

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# Outline

- Vaccine endpoints
- Population
- Design
- Indications for treatment
- Safety considerations
- Futility criteria

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# Options for Vaccine Endpoints

- **Sterilizing Immunity**
  - Prevention of initial infection
  - **Clear benefits** → no acute infection, no transmission after acute infection, easy to assess

- **Prevention of Chronic Infection**
  - Increase 'spontaneous clearance' rate
  - **Prevents long-term complications of HCV** – cirrhosis, HCC, extra-hepatic manifestations

- **Attenuated Infection**
  - Reduced severity of infection
  - **Not feasible given years/decades for HCV outcomes**

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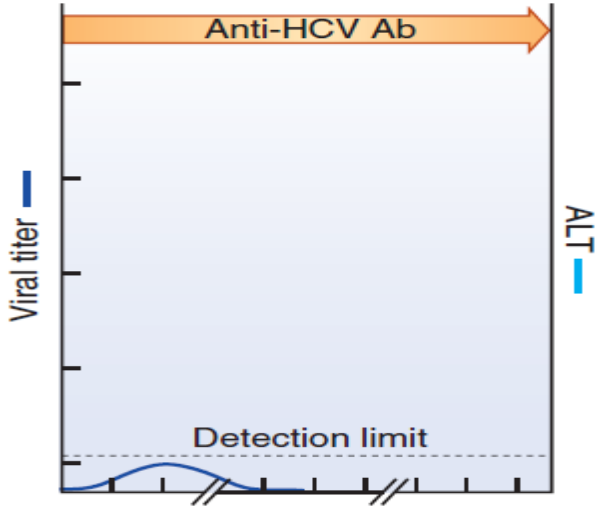
# Aim of HCV vaccination

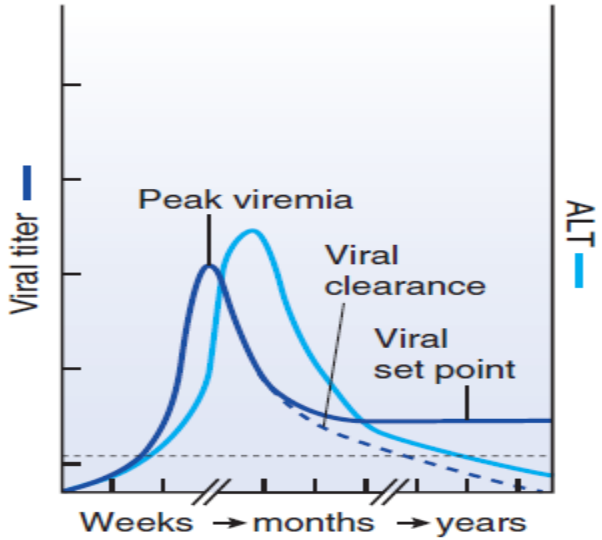
## Sterilizing Immunity




- Achieved with **homologous challenge** in chimps
- **Not seen with reinfection/heterologous challenge** in chimps

VS

## Prevention of Chronicity




- Achieved with **heterologous challenge** in chimps
- Achieved with **reinfection**

- Prevention of chronicity would **avoid major consequences of HCV** – ESLD, HCC, EHMs
- If sterilizing immunity is the goal…**may miss an imperfect but effective vaccine**
- **Primary aim of vaccine trials (incl CHIM): Prevention of chronic HCV across G1-6**

Liang TJ, Nature Med 2013, Houghton Immunological Reviews 2011

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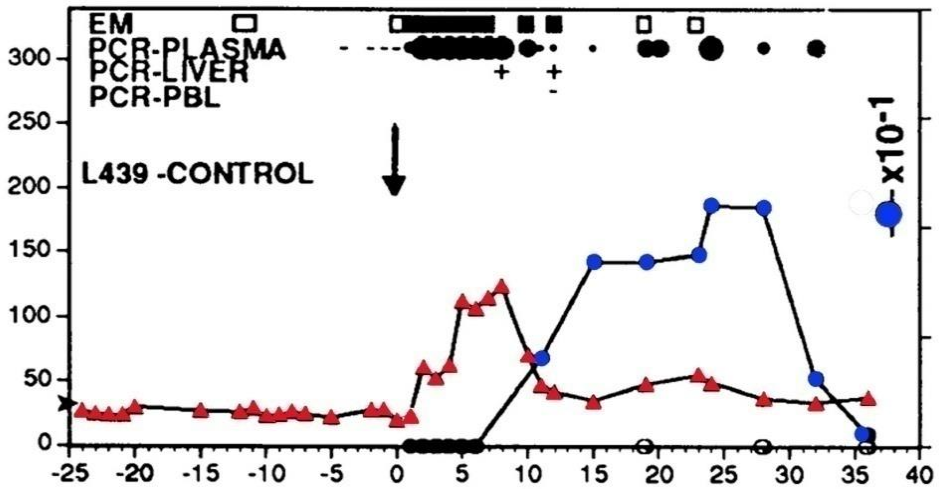
# First demonstration of HCV G1a gpE1/gpE2 vaccine efficacy in chimpanzees

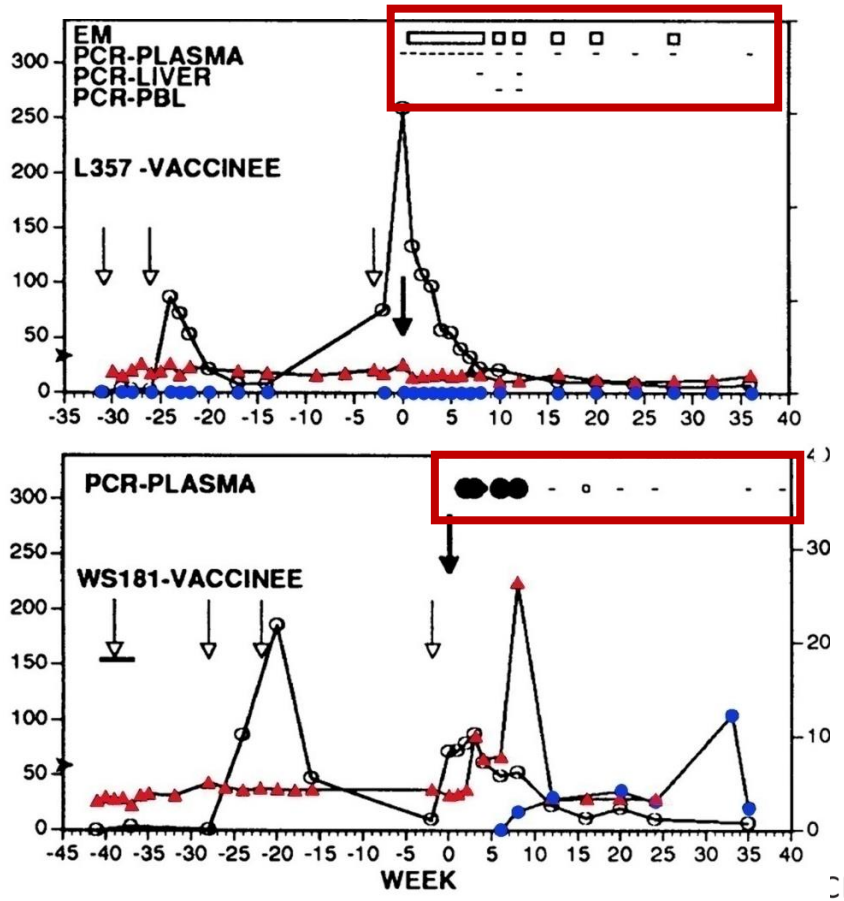
## Control Chimp – Chronic Infection




## Vaccinated Chimps – Protection

**Sterilizing**

**Acute infection with Clearance**




Q-L.Choo et al PNAS 1994

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# Prophylactic efficacy in chimp model against homologous & heterologous 1a challenge

| Viral challenge | Group | Total | Acute infections | Chronic infection (%) | |
|---|---|---|---|---|---|
| Homolog HCV-1 | gpE1/gpE2 | 12 | 7 | 2(17) | P=0.03 |
| | Unimmunized | 10 | 10 | 7(70) | |
| Heterolog H77 | gpE1/gpE2 | 19 | 19 | 3(16) | P=0.02 |
| | Unimmunized | 14 | 14 | 8(57) | |
| Total | gpE1/gpE2 | 31 | 26 | 5(16%) | P=<0.001 |
| | Unimmunized | 24 | 24 | 15(63%) | |

- Sterilizing immunity achieved ONLY with virus used for vaccine design (homologous challenge)
- But prevention of chronic infection with heterologous challenge → still a major benefit

Houghton Immunological Reviews 2011

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# Next question – How do we define chronic infection?

- The real question:
  - How long do we need to 'leave' people infected before rescuing with DAA treatment to avoid missing spontaneous clearance?
  - If we treat too early → we may abandon a good vaccine
  - If we treat too late → we expose participants to a longer duration of infection

- Chronicity typically defined as '>6m of infection'
- True definition is transition to immune exhaustion after which spontaneous clearance is extremely rare
  - Immune exhaustion is difficult to evaluate in real-time
  - Need to decide on a standard duration of infection for CHIM/Vaccine trials that balances missing late clearance against duration of infection

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# Can we predict clearance before 6m?

- Literature is sparse
  - Precise timing of infection rarely known
  - Few with standardized and frequent sampling of HCV RNA

- Review of VIP trial, BBASH and INC3 cohorts
  - Cohorts of PWID prospectively followed for clearance
  - n>1000 but exclude:
    - Prior infection
    - Treated
    - Vaccinated,
    - HIV coinfection
    - And Require >2 HCV RNA measurements and known outcome of infection

**Only 45**

  - Of 45 → 29 chronic and 16 clearance by 12m

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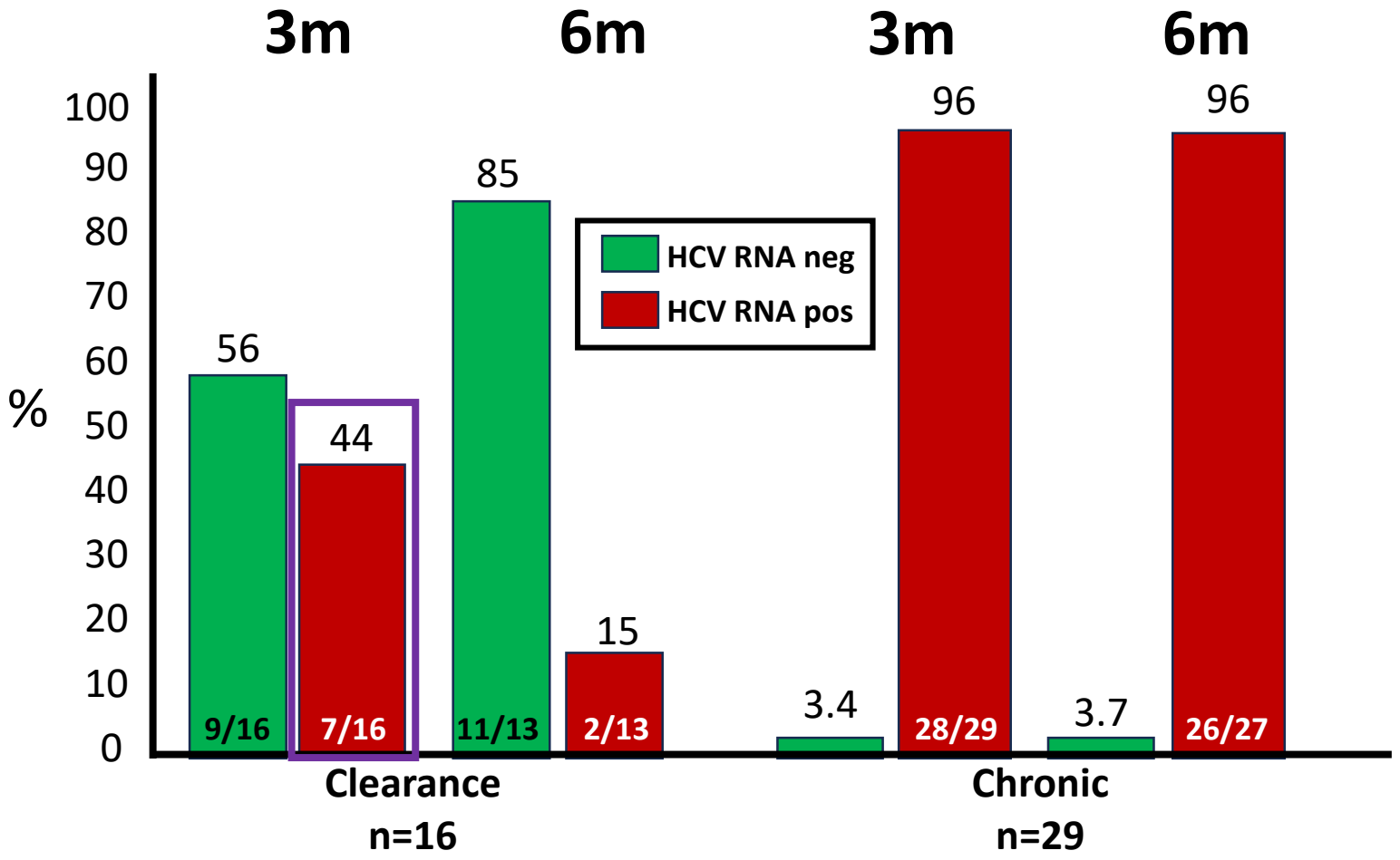
# 6m looks like the most reliable timepoint




**At 3m**

NPV for clearance = **90%**

PPV for chronicity = **80%**

**At 6m**

NPV for clearance = **92%**

PPV for chronicity = **93%**

- Limited numbers but **starting treatment at 3m will likely miss clearance episodes**
- **Consequence:** Underestimate clearance → overestimate vaccine efficacy
- CHIM – standard inoculum, no reinfection – **may allow for better prediction**

Data courtesy of D. Thomas, A Cox, K Page

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# Population

- Important to study people at risk for HCV but safety is paramount
  - Safety to participant
  - Safety to non-study population – transmission risk

- **Initial CHIM studies:**
  - Healthy population – young, no medical problems, no liver disease, no substance use, barrier contraception and notification of intimate partners

- **Subsequent CHIM studies:**
  - Critical to document safety and effectiveness in PWID
  - Consider including people on stable OAT vs real-world effectiveness

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# Participant Compensation & Consent

- Different from other challenge studies due to duration of infection

- Discussions with ethicists and Community Advisory Board
  - People at risk or with lived/living experience of HCV
  - People with experience in challenge studies

- Test of comprehension for all participants
- Hourly wage for study visits + travel or other cost reimbursement
- Weekly stipend for duration of infection through to end of treatment to acknowledge QoL effects of HCV infection

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# Design – Multi-stage approach

1. **Establishment of Inoculum**
   - Generate an acute inoculum to be used for future CHIM
   - 1 to 4 genotypes – genotypes 1 and 3 +/- others
2. **Sentinel cohorts**
   - Reliable infection - viremia
   - Acute, non-severe hepatitis
   - Reliable (universal) cure with DAAs
3. **Spontaneous Clearance cohorts**
   - Clarify spontaneous clearance rate for each inoculum
4. **Vaccine Cohorts**
   - Vaccinated prior to infection
   - Matched to spontaneous clearance cohort on: sex, race, IFNL4 genotype

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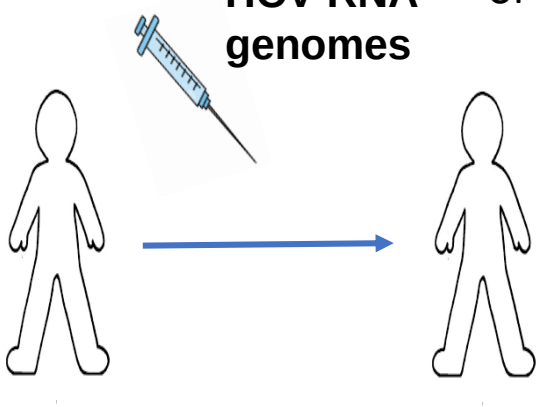
# Stage 1 – Establishment of Inoculum

**3,000 free HCV RNA genomes** or **RNA LNP**



**CHIM Donor**
***Chronic HCV***

Gt 1a, 1b, 2a, 3a
Cured with DAAs

**Initial Recipient & CHIM Donor**
***Acute HCV***

**n = 1 per gt (up to 4)**

**Pre-viremia** | **Viremia** → **Treatment DAAs**

- HCV RNA 2x/wk
- ALT 2x/wk

1. **HCV Ab + OR**
2. **Severe hepatitis* OR**
3. **After 2nd plasmapheresis**

- HCV RNA – biweekly until >10e6 IU/mL
- Labs – weekly
- **Plasmapheresis x 2 after >10e6 IU/mL**
  → **Acute inoculum for future CHIM**

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# Primary Endpoint

Establishment of a controlled human infection model that can be used for vaccine assessment as assessed by all of the following criteria:

1. **Reliable establishment of viremia**
   - **All participants** develop viremia for selected inoculum size, defined as quantifiable HCV RNA on at least 2 occasions separated by >1 week with peak HCV RNA >1,000 IU/mL

2. **Development of acute, non-fulminant hepatitis**
   - No cases of fulminant acute HCV with signs of acute liver failure

3. **Universal cure of infection**
   - All participants who do not spontaneously clear infection are successfully cured with HCV DAAs (1$^{st}$ or 2$^{nd}$ course of treatment)

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# Why use an acute donor?

- **Chronic HCV**
  - All Ab+, limited free ‘uncomplexed’ HCV RNA – **large inoculum size**
  - Chronically infected people and chimps range from 10 to 1,000 CID/ml with rare reported cases of higher levels of CID

- **Acute HCV**
  - Prior to Ab development – all/most free HCV RNA – **very small inoculum size**
  - Acute Phase H strain – 10e6 CID/mL

Hijikata J Virol 1993, Choo PNAS 1994, Houghton Nature 2005, Bradley J Virol Methods 1985

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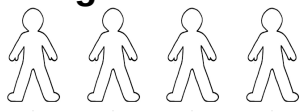
# Stage 2 – Sentinel Cohorts – Dose Finding and Confirmation of Safety & Cure 12w and 24w

## 12 week Cohort

**3,000 free HCV RNA genomes**



**n = 4 per gt (up to 16)**

**1. Severe hepatitis* OR**
**2. 12 wks**
**3. PI or Participant choice**

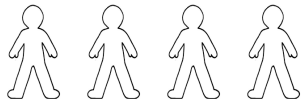
**Pre-viremia** → **Viremia** → **Treatment DAAs**

- HCV RNA 2x/wk
- ALT 2x/wk

- Symptoms/AEs - weekly
- HCV RNA – weekly
- Labs – weekly
- PBMCs – weekly x 4 then q2w
- Leukapheresis – 8-12w & 24w

## 24 week Cohort

**3,000 free HCV RNA genomes**



**n = 4 per gt (up to 16)**

**1. Severe hepatitis* OR**
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**Pre-viremia** → **Viremia** → **Treatment DAAs**

- HCV RNA 2x/wk
- ALT 2x/wk

- Symptoms/AEs - weekly
- HCV RNA – weekly
- Labs – weekly
- PBMCs – weekly x 4 then q2w
- Leukapheresis – 8-12w & 24w

**Higher dose (30,000 free HCV RNA genomes - if required)**

***Severe hepatitis** = ALT>1000 U/L, bilirubin> 100µmol/L and/or signs of acute liver failure

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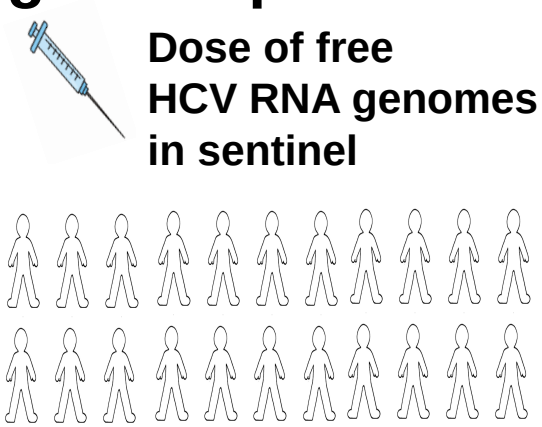
# Stage 3 – Spontaneous Clearance Cohorts



**Dose of free HCV RNA genomes in sentinel**

**n = 24 per gt (up to 96)**

**1. Severe hepatitis* OR**
**2. 24 wks**
**3. PI or Participant choice**

**Pre-viremia** | **Viremia** → **Treatment DAAs**

- HCV RNA 2x/wk
- ALT 2x/wk

- Symptoms/AEs - weekly
- HCV RNA – weekly
- Labs – weekly
- PBMCs – weekly x 4 then q2w
- Leukapheresis – 8-12w & 24w

**Primary Endpoint: Spontaneous Clearance Rate @ 24w**

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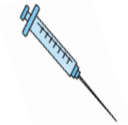
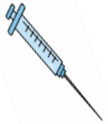
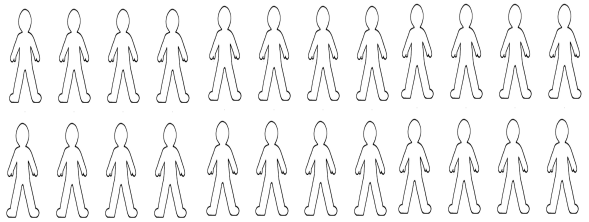
# Stage 4 – Vaccination Prior to Infection



Vaccine



Dose of free
HCV RNA genomes
in sentinel



n = 24 per gt (up to 96)

1. Severe hepatitis* OR
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**Pre-viremia** | **Viremia** → **Treatment DAAs**

- HCV RNA 2x/wk
- ALT 2x/wk

- Symptoms/AEs - weekly
- HCV RNA – weekly
- Labs – weekly
- PBMCs – weekly x 4 then q2w
- Leukapheresis – 8-12w & 24w

**Primary Endpoint: Clearance Rate without Treatment @ 24w vs Stage 3 (per genotype)**

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# Additional Endpoints

- Many additional endpoints to be studied
  - Virological
  - Immunological
  - Clinical
  - Ethical/Qualitative

- **Inform vaccine design**
  - Detailed immunological and virological studies in CHIM would inform vaccine design if initial candidates are not successful

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# Indications for treatment

- **Stage 1 – Establishment of inoculum**
    1. Anti-HCV positivity (reduced infectivity)
    2. ALT >1,000 U/L
    3. Bilirubin elevation >2x ULN
    4. Participant request
    5. PI assessment
    6. 12 weeks if none of above met earlier

- **Stage 2, 3 and 4 – 12- and 24-week Sentinel cohorts**
    1. ALT >1,000 U/L
    2. Bilirubin elevation >100 µmol/L (~6 mg/dL)
    3. Participant request
    4. PI assessment
    5. 12 or 24 weeks respectively if none of above met earlier

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# Rationale for treatment indications

Prevent fulminant hepatitis

Miss spontaneous clearance

Jaundice is a marker of more severe hepatitis

Jaundice associated with clearance (primary endpoint of vaccine trials)

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# Data on ALT & Bilirubin in acute HCV

- INC3 cohort – collection of multiple cohorts of PWID with acute/recent HCV
- 643 with acute/recent infection – 173 (26%) with spontaneous clearance
  - Peak median ALT
    - Clearers 463 (IQR 72, 2316) vs Persistent HCV 470 (IQR 99, 944) p=0.43

- Prospective study of acute HCV in 124 individuals
  - 56 of 108 (52%) had bilirubin > 30 µmol/L
  - Mean bilirubin 79 +/- 89 µmol/L
  - Jaundice associated with clearance → 56% vs 8%, p=0.04
  - ALT >20x ULN (800 U/L) ~assoc with clearance → 49% vs 24%, p=0.07

- Multiple other studies – no threshold identified to predict evolution to fulminant hepatitis/acute liver failure
- Many people with ALT>1,000 U/L and bilirubin>100 µmol/L with **no cases of fulminant hepatitis or liver failure**

Hajarizadeh PLoS One 2015, Wang JID 2007, Tillman Gastroenterology 2010, Beinhard J Hepatol 2013

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# Futility Criteria

## 1. Inability to establish viremia

- If >25% of participants in Part 2 or 3 do not establish viremia, the protocol will be halted and the the inoculum will be further characterized in liver human-chimeric mice before further CHIM

## 2. Acute Liver Failure*

- Any cases of acute liver failure due to HCV → protocol will be halted

## 3. Treatment Failure

1. If any participant is not cured after 2nd DAA course → protocol will be halted
2. If 3 or more participants are not cured with 1st DAA course → protocol will be halted

## 4. HCV Transmission*

- If infection of contact of a study participant occurs, the virus will be sequenced to confirm it is the CHIM inoculum and if confirmed, the protocol will be halted

* Issues for full program, others for specific genotype

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# Risk mitigation strategies

## 1. Donor Characteristics

- No coinfections
- No IDU > 5 years (risk of unrecognized infection in ‘window’ period)
- Eligible as blood donor by questionnaire & testing (except HCV+)
- No cirrhosis (exclude more virulent strain)

## 2. Pathogen Testing

- Standard pathogen panel – repeat post-SVR to exclude window period

## 3. HCV

- Full-length sequencing – no relevant DAA resistance associated substitutions
- Donor will be treated with CHIM DAA regimen – used only after confirmation of SVR

## 4. Storage

- Under GMP conditions at -80C
- Serial testing q6m to confirm HCV RNA stability & infectivity in humanized mouse model

## 5. Stepwise evaluation

- Small sentinel cohorts with sequential enrolment & clear treatment criteria
- DSMB with careful oversight
- Long-term follow-up offered to all participants

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# Sample size considerations

- **Sentinel cohorts**
  - No specific sample size calculation
  - Aim to give prediction of reliable infection
  - Allow for dose escalation if infection unsuccessful
- **Spontaneous clearance cohorts**
  - Aim to develop a relatively robust estimate of clearance rate
  - Need to consider factors associated with spontaneous clearance:
    - Female sex
    - IFNL4/IL28B genotype
    - Race/ethnicity
- **Vaccine Cohorts**
  - Will depend on goal – de-risk candidate to justify larger trial vs efficacy trial
  - Spontaneous clearance rate will greatly influence numbers required

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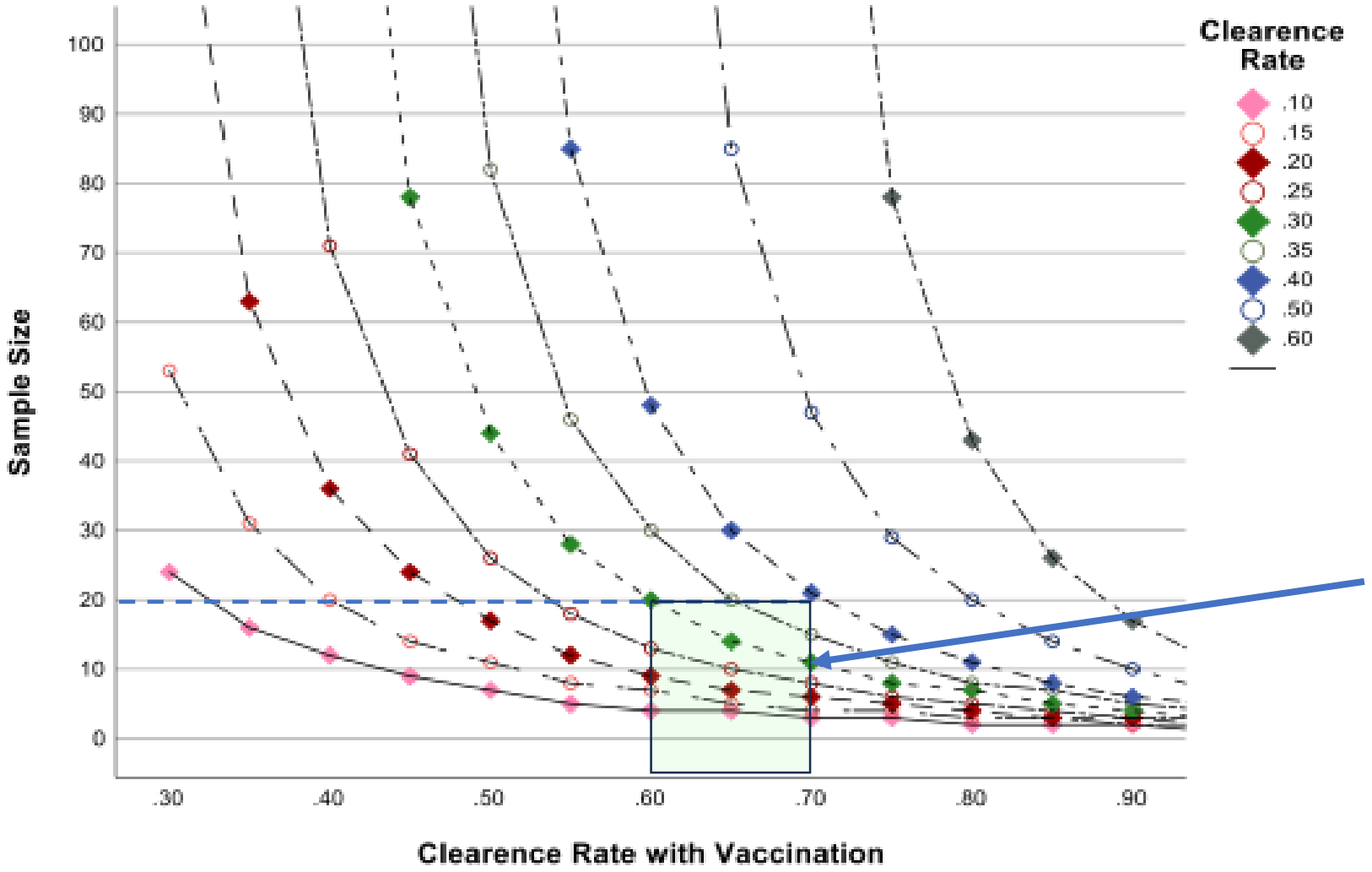
# Sample size considerations – Vaccine Cohorts




Each colour – spontaneous clearance rate

Sample size required for 80% power

With spont clearance of 20-30%
10-20 participants per inocoulm to show vaccine effectiveness of 60-70%

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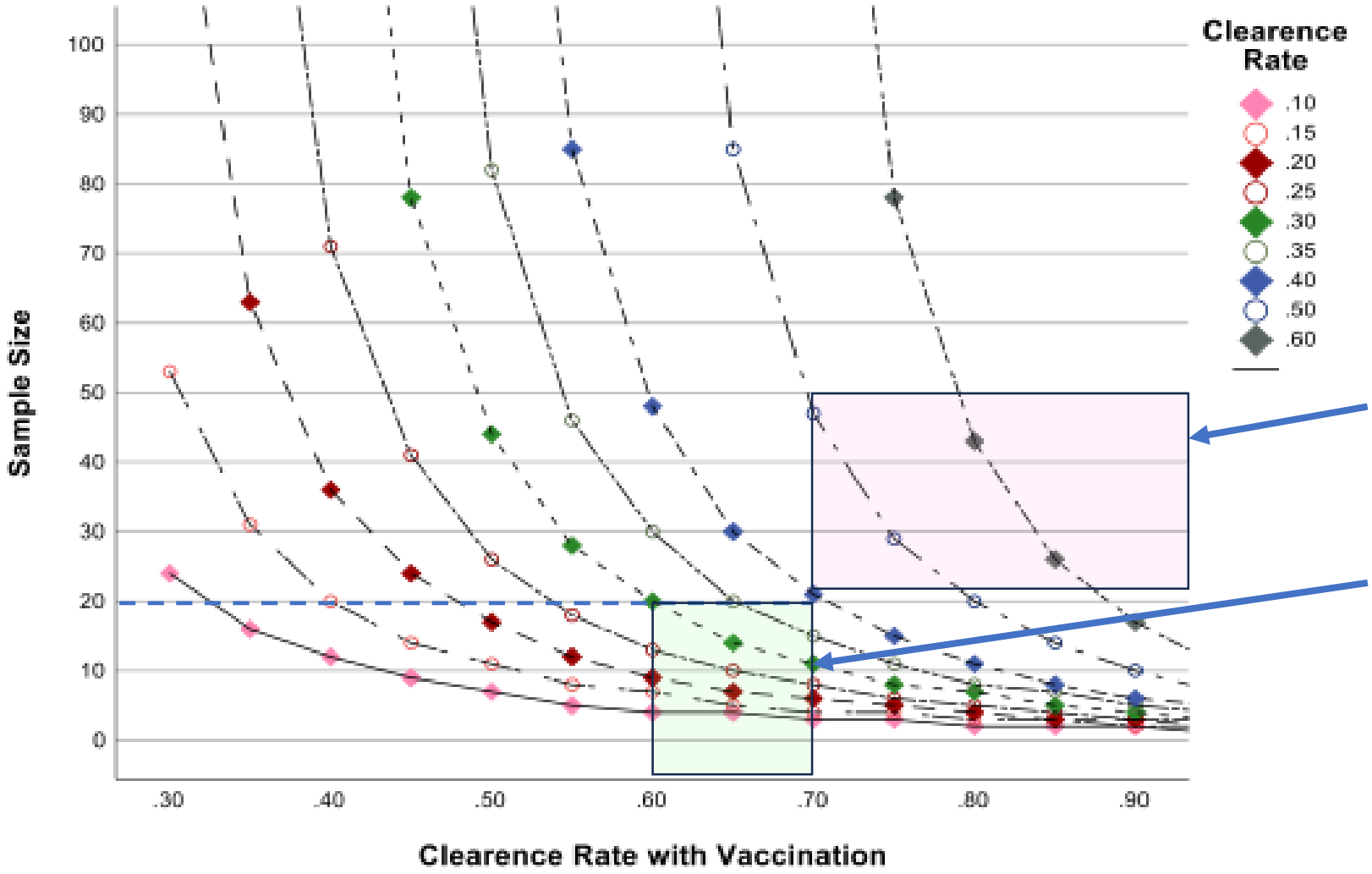
# Sample size considerations – Vaccine Cohorts




Each colour – spontaneous clearance rate

Sample size required for 80% power

Larger sample sizes required if spont clearance rate 50% or greater

With spont clearance of 20-30% 10-20 participants per inocoulm to show vaccine effectiveness of 60-70%

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# Summary

- Development of a successful HCV CHIM requires a step-wise approach to establish the inocula and determine the spontaneous clearance rate(s)
- Clearance at 6m balances the chance of missing late clearance with the potential risk and practicalities of longer infection
- Initial CHIM studies will be performed in young, healthy populations with subsequent evaluation in at-risk populations esp PWID
- Risk mitigation strategies at all stages
- This is one HCV CHIM approach - final protocol details will require regulatory input/guidance

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