Modelling the possibilities of Cure and Eradication

Prof. dr. Maria Prins
Public Health Service (GGD) & Academic Medical Center (AMC) Amsterdam

1st European Roundtable on Hepatitis Cure and Eradication, September 9-10, 2015
Modelling the possibilities of Cure and Eradication: What are the gaps and challenges?

I. Ongoing transmission in key risk groups in Europe
   Maria Prins

II. Hepatitis C Treatment as prevention: What is needed for elimination in Europe?
   Natasha Martin, University of California, San Diego, USA

III. Challenges in the real world
     Maria Prins
HCV key populations in Europe

- People who inject drugs
- Migrants from HCV endemic countries
- Men having sex with men
Prevalence of anti-HCV in people who inject drugs

Globally 10 million anti-HCV positive
Midpoint anti-HCV prevalence: 67%

Nelson et al, Lancet 2011
Anti-HCV prevalence among people who inject drugs < 2 years in the EU, 2006-2011
Incidence of HCV infection in people who inject drugs

Median 13 cases/100 py (IQR 8.7-28)

Wiessing et al, PLOS One 2014
Trends in HCV incidence in people who inject drugs

Meta-analysis: Lengthening in time to HCV infection since onset of injecting


Individual studies: Evidence for declining trends in HCV incidence in high income countries

Methadone bus of the Public Health Service of Amsterdam

Dam Square, Amsterdam, The Netherlands 1989

photo ANP
Annual number of needles exchanged in Amsterdam 1984-2013
Effect of harm reduction participation on HIV and HCV incidence: Amsterdam Cohort Study among PWID

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
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<th>HCV</th>
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<tbody>
<tr>
<td></td>
<td>IRR 95% CI</td>
<td>p value</td>
<td>IRR 95% CI</td>
<td>p value</td>
<td></td>
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</tr>
<tr>
<td>No harm reduction</td>
<td>1 &lt;0.001</td>
<td></td>
<td>1 &lt;0.001</td>
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<tr>
<td>Incomplete harm reduction</td>
<td>0.87 (0.50-1.52)</td>
<td>1.17 (0.59-2.31)</td>
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<tr>
<td>Full harm reduction</td>
<td>0.43 (0.21-0.87)</td>
<td>0.36 (0.13-1.03)</td>
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<tr>
<td>-Limited dependence</td>
<td>0.046 (0.006-0.35)</td>
<td>0.044 (0.006-0.35)</td>
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<tr>
<td>-No dependence</td>
<td>0.20 (0.078-0.50)</td>
<td>0.13 (0.044-0.40)</td>
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</tbody>
</table>

Adjusted for injection duration, HIV status steady partner (for HIV only)

Van den Berg et al, Addiction 2007
Main trends in HIV and HCV incidence among Amsterdam DU were reproduced assuming no harm reduction effects.

Assuming harm reduction measures had led to a strong decrease in risk behaviour over time improved the model.
Evaluation of combined harm reduction measures for people who inject drugs

Mounting evidence from observational studies that high coverage of comprehensive harm reduction programmes can reduce HCV incidence

HCV, migrants and migration patterns

Increasing migration flows from middle or high HCV prevalence countries to low prevalence countries might increase HCV prevalence in the general population / incidence in risk groups

Europe
- Old migration groups from the Mediterranean countries
- Migration from sub-Saharan Africa, Eastern Europe and Latin America
- Recent large migrant flows from the Middle East and Africa
- 2013: 1.4 million EU immigrants of non-member countries
HCV and non-western migrants (limited data)

- Prevalence general population in migration country < prevalence in migrants < prevalence general population in the country of origin
- Migrants account for about 5%-40% of HCV prevalent cases in high income countries
- Transmission likely took place in country of origin with no further transmission in migration countries
- Migration diversifies HCV genotype distribution
- Large proportion still undiagnosed

Hepatitis C virus incidence in HIV-positive men having sex with men in relation to calendar time

Hagan et al, AIDS 2015
HCV incidence among MSM with documented dates of HIV seroconversion: CASCADE in Eurocoord study

van Santen et al, CASCADE meeting 2015
Incidence initial infection in HIV-infected MSM vs. incidence reinfection following primary HCV infection

Incidence initial infection in HIV-infected MSM

- pooled estimate: 1.3/100 py in 2012  
  Hagan et al, AIDS 2015

HCV re-infection incidence in HIV-infected MSM

- Netherlands: 15.2 per 100 py (95% CI 8.0-26.5)  
  Lambers et al, AIDS 2011
- UK: 7.8/100 py (95% CI 5.8-10.5)  
  Martin et al, AIDS 2013

Comparisons: be aware of the differences in study populations
Factors associated with hepatitis C virus seroconversion in studies of HIV-positive MSM, with attributable risk measures

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Behaviour</th>
<th>Adjusted measure of association (95% confidence interval)</th>
<th>AR%</th>
<th>pr (exposure) in controls</th>
<th>PAR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fierer et al. [48]</td>
<td>Receptive anal intercourse without a condom, with ejaculation</td>
<td>23 (2.2–243.8)</td>
<td>95.7%</td>
<td>23.0%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Schmidt et al. [4]</td>
<td>Rectal trauma with bleeding</td>
<td>6.2 (1.2–32.8)</td>
<td>83.9%</td>
<td>4.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>Frequent receptive fisting without gloves (or gloves shared)</td>
<td>5.7 (1.5–21.7)</td>
<td>82.5%</td>
<td>6.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Wandeler et al. [28]</td>
<td>Inconsistent condom use</td>
<td>2.1 (1.3–3.3)</td>
<td>52.4%</td>
<td>51.0%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Fierer et al. [48]</td>
<td>Sex while high on methamphetamine</td>
<td>28.6 (1.8–443.0)</td>
<td>96.5%</td>
<td>4.0%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Schmidt et al. [4]</td>
<td>Use of nasally administered drugs (coca, amphetamine, ketamine and so on)</td>
<td>3.25 (1.1–9.9)</td>
<td>69.2%</td>
<td>52.2%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>

PAR%, population attributable risk percentage.

Hagan et al, AIDS 2015
Factors associated with acute HCV among HIV-infected men who have sex with men: MOSAIC study, the Netherlands

**SEXUAL BEHAVIOR**
- receptive UAI
- sharing sex toys
- unprotected fisting

**SEX-RELATED VARIABLES**
- no. of casual sex partners (per doubling*)
- anal rinsing
- rectal bleeding
- meeting casual sex partner(s) at sex party

**DRUG USE BEFORE / DURING SEX**
- injected drugs
- NADs used, straws shared

**CLINICAL CHARACTERISTICS**
- CD4 cell count (per cubic root lower***)
- ulcerative STI

![Graph showing adjusted odds ratio for various factors.](image-url)
Conclusions HCV transmission in Europe

- People who inject drugs
  - High prevalence
  - Combined comprehensive harm reduction programmes with high coverage can reduce HCV transmission
  - Declining trends in incidence in various EU countries, but in general not to very low levels

- Migrants (limited data)
  - Migrants account for a substantial proportion of HCV prevalent cases
  - Transmission likely took place in the country of origin with no further transmission in migration countries

- Men having sex with men
  - Increasing/stabilizing trends in HCV incidence; high reinfection rate
  - Largely limited to HIV positive MSM
    - HIV PrEP uptake might change this
  - Data support sexual transmission, international network and role of drugs during sex

Volk et al CID 2015
Halting transmission

- Prevention measures not sufficient to halt spread
- No vaccine yet
- Modelling studies: HCV treatment might reduce transmission
Treatment Potential

Best strategies for global HCV eradication

Liesl M. Hagan and Raymond F. Schinazi
Center for AIDS Research, Emory University School of Medicine and Veterans Affairs Medical Center, Decatur, Georgia 30033, USA

Hepatitis C could be virtually eliminated by 2030, experts believe

Geoff Watts
Definitions

- Elimination: reduction to zero of the incidence of a specified disease/infection in a defined geographic area as a result of deliberate efforts. Continued intervention measures are required during outbreaks.

- Eradication: permanent reduction to zero of the worldwide incidence of disease/infection as a result of deliberate efforts. Eradication implies a permanent reduction to zero incidence without any outbreaks that need intervention.

*Dowdle WR. The principles of disease elimination and eradication.*

*Bulletin of the World Health Organization 1998*
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HCV TREATMENT AS PREVENTION AMONG HIGH RISK POPULATIONS (PEOPLE WHO INJECT DRUGS AND MEN WHO HAVE SEX WITH MEN): WHAT IS NEEDED FOR ELIMINATION IN EUROPE?

Natasha Martin, DPhil
Associate Professor
Division of Global Public Health, University of California San Diego

Hannah Woodall, Matthew Hickman,
Peter Vickerman
School of Social and Community Medicine, University of Bristol
Modelling HCV elimination among people who inject drugs (PWID) in Europe
Despite evidence that PWID achieve similar SVR rates as non/ex-PWID\textsuperscript{1–3}

And despite small-scale studies reporting low re-infection rates among PWID\textsuperscript{1,4,5}

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TERMINOLOGY REMINDER: ERADICATION VS ELIMINATION VS CONTROL

• **Eradication**: Permanent reduction to zero of the worldwide incidence of infection. Intervention measures no longer needed. Only one success: Smallpox

• **Elimination**: Reduction to zero of incidence in a defined geographical area as a result of deliberate efforts. Continued intervention measures required.

• **Control**: Reduction in the incidence, prevalence, morbidity or mortality of an infectious disease to a locally acceptable levels. Continued intervention measures required.
EVALUATING HCV TREATMENT AS PREVENTION: A DYNAMIC HCV TRANSMISSION MODEL IS NECESSARY

ADDITIONAL MODEL HETEROGENEITY

- Additionally stratify by risk and opiate substitution therapy (OST)
- Flow/turnover between states (based on data)
- Proportional mixing in base-case

EDINBURGH, SCOTLAND: ELIMINATION ACHIEVABLE WITH DAA SCALE-UP GIVEN LOW PREVALENCE

SEVEN UK CITIES: DAA SCALE-UP TO RATES CURRENTLY ACHIEVED RESULTS IN ELIMINATION IN LOWER PREVALENCE SETTINGS

HCV chronic prevalence among PWID (%)

- Baseline in 2014
- 2024, no scale-up, ITT SVR with PEG-IFN + RBV
- 2024, scale-up to 26/1000 annually with IFN-free DAAs (all genotypes) in 2016

Martin NK, et al. Journal Viral Hepatitis 2014
FRANCE: HIGH LEVELS OF EXISTING TREATMENT MAY BE SUFFICIENT FOR ELIMINATION?

- 0 - Current treatment standards
- 1 - Incoming DAAs regimens
- 2 - Incoming DAAs regimens & Improved testing
- 3 - Incoming DAAs regimens & Improved linkage to care
- 4 - Incoming DAAs regimens & Improved testing and linkage to care
- 5 - Incoming DAAs regimens & Improved adherence
- 6 - Incoming DAAs regimens & Treatment from F0
- 7 - Incoming DAAs regimens & Improved testing, linkage to care and adherence

Cousien A, et al  
EASL 2014 Oral abstract
CZECH REPUBLIC: ELIMINATION (INCIDENCE <1%) ACHIEVABLE BY 2025 WITH SCALE-UP GIVEN LOW PREVALENCE/INCIDENCE

- Requires 26 treatments per 1000 PWID (95% CI 18 – 39)
- Roughly DOUBLE (95%CI 1.5-3 fold) current treatment rates (12 treatments per 1000 PWID)

Woodall H, Vickerman P, Martin NK, Hickman M et al. (in preparation)
STOCKHOLM, SWEDEN: NOT POSSIBLE TO ACHIEVE ELIMINATION (INCIDENCE <1%) WITH TREATMENT ONLY BY 2025 DUE TO HIGH PREVALENCE/INCIDENCE

Not possible to reduce incidence to 1% even if every chronically infected individual is treated from 2015 each year.

Woodall H, Vickerman P, Martin NK, Hickman M et al. (in preparation)
COMBINATION PREVENTION (HARM REDUCTION+DAAs) COULD ACHIEVE ELIMINATION AMONG PWID EVEN IN HIGH PREVALENCE SETTINGS

60% chronic HCV prevalence among PWID

• White: >80% reduction in prevalence within 10 years

• Large (>40%) reductions require treatment
CONCLUSIONS: HCV TREATMENT AS PREVENTION AMONG PWID

- Existing levels of HCV treatment, even in the DAA era, are likely to have minimal impact on reducing HCV incidence to <1% except possibly in France

- Scale-up of HCV treatment could substantially result in elimination in many settings

- Combination prevention important in all settings, but especially in very high prevalence settings (>80% HCV Ab+/ >60% chronic HCV)
HCV treatment as prevention among HIV-infected MSM in Europe
DYNAMIC MODEL OF HCV AMONG HIV-DIAGNOSED MSM

Also stratify by treatment naïve, IFN experienced, DAA experienced and low/high risk
HIV and non-HIV death occurs from all states
MODEL CALIBRATION/PARAMETERIZATION TO UK

- Model calibrated to:
  - HIV diagnoses\(^1\) (increasing)
  - HCV prevalence (Ab+ or RNA+) among HIV+ MSM 2004-2011\(^2\) (~10% increasing)
  - HCV primary incidence among HIV+ MSM 2004-2011\(^2\) (~1%, stable)
  - HCV reinfection incidence among HIV+ MSM\(^3\) (~8 per 100py)

- Model parameterized by:
  - HIV survival\(^4\) (increasing over time, 20-40 years from diagnosis)
  - HCV testing rates\(^2\) (increasing over time, to 88%/yr in 2015)
  - HCV treatment rates\(^2\) (46%/22% within 1 year of acute/chronic diagnosis, respectively, 7%/yr thereafter)
  - HCV treatment success rates (80%/30% acute/chronic with IFN/RBV, assume 90% DAAs)

1. Public Health England data
2. UK CHIC cohort data- Martin NK et al (submitted)
3. Martin TCS et al. AIDS 2012
MODELLING HCV AMONG HIV+ MSM IN UK: CALIBRATION TO UK CHIC DATA

HCV prevalence (Ab+ or RNA+) among HIV diagnosed MSM (%)

HCV primary incidence among HIV diagnosed MSM (per 100py)

Martin NK, et al (submitted)
HCV CHRONIC (RNA+) PREVALENCE AMONG HIV+ MSM IN UK: MODELLING INTERVENTION SCENARIOS

Martin NK, et al (submitted)
HCV PRIMARY INCIDENCE AMONG HIV+ MSM IN UK: MODELLING INTERVENTION SCENARIOS

Martin NK, et al (submitted)
HIGHER TREATMENT RATES ONLY TEMPORARILY LEAD TO HIGHER TREATMENT NUMBERS IN THE UK

Martin NK, et al (submitted)
HCV AMONG HIV+ MSM IN SWITZERLAND: ELIMINATION REQUIRES BEHAVIOUR CHANGE

Figure 1. HCV incidence observed in the SHCS (green dots and error bars) and corresponding model estimates (continuous blue line; shaded: 95% confidence intervals)

Figure 3. Projected HCV incidence in HIV-infected MSM with combined interventions to reduce high-risk sexual behaviour and to increase treatment uptake and/or efficacy

- A. Further increase in high-risk sexual behaviour
- B. Stabilisation of high-risk sexual behaviour
- C. Substantial reduction in high-risk sexual behaviour

Salazar L et al. CROI 2015
CONCLUSIONS: HCV TREATMENT AS PREVENTION AMONG MSM IN EUROPE

• Expanding epidemic of HCV among HIV+ MSM in UK and Switzerland
• Continued expansion or at best stabilization with current levels of treatment
• Substantial reductions in incidence/prevalence with achievable scale-up, especially with behaviour change

• Limitations:
  • neglect network effects and migration/travel; need better epidemiological and behavioural data
## TREATMENT AS PREVENTION AMONG PWID VS HIV+ MSM

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<tr>
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<th>HCV+ PWID</th>
<th>HIV+/HCV+ MSM</th>
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</thead>
<tbody>
<tr>
<td>Population size</td>
<td>Large (~10 million)</td>
<td>Small compared with PWID (thousands)</td>
</tr>
<tr>
<td>HCV prevalence</td>
<td>Heterogeneous, but can be high (&gt;60%)</td>
<td>Relatively low (~10%)</td>
</tr>
<tr>
<td>Routine testing and HCV treatment integrated with other treatment settings</td>
<td>Poor/evolving</td>
<td>Good in many developed country settings (~50% treatment experienced in Berlin(^1)&amp; UK(^2))</td>
</tr>
<tr>
<td>Next-generation DAA SVR for chronic infection</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Evidence for other prevention/behaviour change interventions</td>
<td>Good (opiate substitution therapy, needle/syringe programmes)</td>
<td>Poor</td>
</tr>
<tr>
<td>International transmission network</td>
<td>Probably minimal in most settings</td>
<td>High</td>
</tr>
<tr>
<td>Reinfection rate</td>
<td>Appears lower than primary incidence</td>
<td>Appears higher (5-10x) than primary incidence</td>
</tr>
</tbody>
</table>

2. Martin NK et al (submitted)
ACKNOWLEDGEMENTS

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University College London: Prof Caroline Sabin, Dr Alice Thornton, Dr Huw Price

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Treatment of HCV infections as prevention
1. Do treated individuals and those at HCV risk mix?

**Treated Population** <> **Transmission Population**

- Longer lasting infection
- Middle-aged
- Limited risk behaviour
- Diagnosed

- Recently or non-infected
- Young
- High levels of risk behaviour
- Undiagnosed
2. Can we reach the undiagnosed key risk population and motivate them to test?

More than 1 MILLION PEOPLE DIE each year from disease caused by hepatitis B & C.

Most of those infected don’t know they have it, INCREASING THE RISK of developing severe liver disease and transmitting the virus to others.

World Health Organization

© World Health Organization 2014
Proportion (%) of HCV-infected people who inject drugs undiagnosed

Median 49% (IQR 38-64)

Wiessing et al, PLOS One 2014
Motivating people to get tested and treated

Reasons for non-testing among individuals informed and with a test advice
- Belief that personal risk is low
- Absence of symptoms
- Low perceived urgency for testing
- Fear for consequences of positive test results
- Discouraging social environment

Zuure et al, BMC Public Health 2011

Stigma as barrier to HCV care and treatment

Treloar et al, Clin Infect Dis 2013
3. Is screening (cost)effective?

Systematic review: characteristics & outcomes of HCV screening programs targeted at risk groups hidden in the general population

- 67 screening programs worldwide, of whom 24 non-integrated, identified 25,700 HCV-infected individuals
- Higher prevalence in programs
  - In countries with intermediate-high HCV prevalence
  - In psychiatric clinics
  - That used a pre-screening selection based on HCV risk factors

Zuure et al, BMC Public Health 2014

Dried blood screening in non-clinical settings has to potential to increase screening

McAllister J Clin Virol 2014
Cost-effective screening

Review of literature: HBV and HCV screening in the general population and subgroups: 29 publication included

Main findings

- HCV screening of people who inject drugs: cost-effective
- HCV screening of pregnant women and STI clinic attendees: probably not cost-effective.
- US HCV baby-boom generation screening: cost-effective
- For other programs including HCV screening of migrants, prisoners and MSM, the evidence found was insufficient to draw conclusions

Hahné et al, BMC Infect Dis 2013

Cost-effective ≠ Cost-saving ≠ Cheap
4. Can we optimize linkage to care and treatment delivery?

Key population and patient barriers
- Knowledge
- Risk perception
- Lifestyle, etc.

Provider barriers
- Knowledge
- Attitude towards key risk populations, etc.

Structural barriers
- Policy
- Suboptimal service delivery and capacity
- Financial resources, license and costs of therapy, etc.
Proportion (%) of HCV-infected people who inject drugs entering treatment, observational studies, non-clinical setting

Median 9.5% (IQR 3.5-15)

Wiessing et al, PLOS One 2014
Treatment uptake in diagnosed patients

Systematic review: 25 studies in Europe (individual level data)

Mean rate of no treatment in HCV RNA positive patients: 57%

- highest in Romania (89%), lower though still high in other European countries
  
  Papatheodoridis, Liv Int 2014

Programs that use existing infrastructure for key risk population health are most successful
  
  Brugman Clin Infect. Dis 2013,

Meta-analysis:

- Targeted testing interventions (i.e. targeting individuals or groups at increased risk) are effective in diagnosing cases and increasing treatment uptake (RR 1.7).

- Strategies involving practitioner-based interventions most favourable outcomes (RR 3.5)

  Aspinall Eur J Epidemiol 2015
5. Who should we cure first?

Hepatitis C Virus treatment as prevention in people who inject drugs (PWID)

Reinfections among key risk populations occur: pooled risk in PWID: 2.4/100py

Aspinall Clin Inf Dis 2013

Modelling study: to which group treatment is best targeted

- When more than half of all exchanged syringes in a population of PWID are contaminated by HCV, it is most efficient to treat low-risk PWID first.
  - Corresponding threshold of HCV-RNA-prevalence among PWID: 32%
- Below this threshold, it is most efficient to treat high-risk PWID first

Conclusions and discussion

- Elimination of HCV infection might be feasible in the long term under optimal conditions, but eradication will be hard. Control is most realistic.

- Models help to find optimal strategies and inform decision making to achieve control and eventually elimination of HCV infection

- Models might be wrong: urgent need to test ‘treatment as prevention strategies’ in the real world

- Strong societal en political commitment is required
Thanks
Colleagues
Organizers
Audience