DISCLOSURES

I have received unrestricted research grants from Gilead and honoraria from Merck, AbbVie, and Gilead.
WHO “ELIMINATION AS A PUBLIC HEALTH THREAT”

• Goal: Eliminate viral hepatitis as a public health threat by 2030

• “Elimination as a public health threat”: achievement of measurable global targets in relation to infection and burden of a disease. Continued intervention required.
ACHIEVING HBV AND HCV ELIMINATION: IMPORTANCE OF MODELING

• Countries need advice on how to achieve these targets with limited resources (& evaluate impact afterwards)

• Modeling critical to providing this information
<table>
<thead>
<tr>
<th>Model type</th>
<th>Includes transmission?</th>
<th>Can inform WHO mortality target?</th>
<th>Can inform WHO incidence target?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static disease burden model</td>
<td>NO. Usually assume no or fixed incidence</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Dynamic transmission model</td>
<td>YES. Incidence related to prevalence and interventions</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>
• Incidence related to prevalence, level of interventions, and risk behavior -> can predict incidence
• As treatment increases, prevalence AND incidence decrease accordingly.
PHASES AND USES OF TRANSMISSION MODELING DURING ELIMINATION EFFORTS

**Pre-intervention**
- **Understanding the epidemic:**
  - Key drivers/risk groups?
  - What is future burden?

- **Intervention planning:**
  - What level of scale-up/targeting is needed to eliminate?
  - What is the budgetary impact?
  - What is the most cost-effective strategy with limited resources?
  - What key data need to be collected to measure an effect?
  - Where do key uncertainties lie?

**During**
- **Interim evaluation:**
  - Are we on track?
  - What do we need to change?

**Post-intervention**
- **Interpretation:**
  - Disentangling likely impact of intervention

- **Extrapolation:**
  - Long-term impact
OUTLINE

• HBV elimination modeling
  • Global

• HCV elimination modeling
  • Country level (US, Pakistan)
  • People who inject drugs (PWID)
  • HIV-infected men who have sex with men (HIV+ MSM)
OUTLINE

• HBV elimination modeling
  • Global

• HCV elimination modeling
  • Country level (US, Pakistan)
  • People who inject drugs (PWID)
  • HIV-infected men who have sex with men (HIV+ MSM)
WHAT IS REQUIRED TO REACH HBV ELIMINATION TARGETS GLOBALLY?

- Infant vaccination already resulting in decline in new infections
- To reach WHO targets, need:
  - 90% infants vaccinated
  - 80% neonates with birth dose vaccination
  - 80% eAg+ mothers provided peripartum antivirals
  - Population wide testing and 80% eligible treated

GLOBAL COSTS OF HBV ELIMINATION

SUBSTANTIAL HETEROGENEITY IN TIME TO ELIMINATION BY REGION

Each country will require tailored, setting specific approach to achieving targets.
OUTLINE

• HBV elimination modeling
  • Global

• HCV elimination modeling
  • Country level (US, Pakistan)
  • People who inject drugs (PWID)
  • HIV-infected men who have sex with men (HIV+ MSM)
FOR HCV ELIMINATION, LIKELY NEED TO TARGET DIFFERENT GROUPS FOR EACH ELIMINATION TARGET

Incidence target: PWID (likely young)

Mortality target: Advanced fibrosis/cirrhosis, baby boomers (U.S.), former PWID

Optimal targeting/level of intervention to reach both targets?
• Scaled-up treatment can significantly reduce HCV mortality

• Limited impact on HCV incidence unless increased screening measures implemented, particularly among PWID (given epidemic concentration)
PAKISTAN: MODELING TO UNDERSTAND A GENERALIZED HCV EPIDEMIC

- Large population/epidemic changes predicted by 2030:
  - Population increase by one-third to ~250 million
  - Chronic HCV prevalence increase from 3.9% to 5.1%

- Consequently, estimated in 2030:
  - 12.6m chronic infections (up from 7.5m in 2016)
  - 1.1m incident infections/yr

- Transmission highly disseminated

Aaron Lim, Peter Vickerman, Natasha Martin et al (under review)
PAKISTAN: MODELING SCALE-UP AND TARGETING REQUIRED TO ACHIEVE HCV ELIMINATION TARGETS

- >850k treatments/yr needed if untargeted
- Fewer if target cirrhotic and PWID
- Slightly fewer needed if reducing PWID risk (transmission disseminated)
- Need to reduce ALL risks to substantially reduce treatment numbers

Aaron Lim, Peter Vickerman, Natasha Martin et al (under review)
OUTLINE

• HBV elimination modeling
  • Global

• HCV elimination modeling
  • Country level (US, Pakistan)
  • People who inject drugs (PWID)
  • HIV-infected men who have sex with men (HIV+ MSM)
CAN TREATMENT ALONE ELIMINATE HCV AMONG PWID? MODELING IN MELBOURNE, AUSTRALIA

HCV chronic prevalence (%) among PWID

- Data
- No scale-up from baseline (5 per 1000 PWID annually)
- Scale-up to 10 per 1000 PWID annually
- Scale-up to 20 per 1000 PWID annually
- Scale-up to 40 per 1000 PWID annually
- Scale-up to 80 per 1000 PWID annually

IFN-free DAAs

MODELING COMBINATION PREVENTION FOR ELIMINATION AMONG PWID

40% chronic HCV prevalence among PWID

10-yr impact on incidence

- White area: >90% reduction within 10 years
- Elimination not achievable with harm reduction alone
- Requires combination approach

HCV treatments per 1000 PWID annually

Coverage of combination harm reduction (%)
HCV ELIMINATION AMONG PWID IN US: COMPARING URBAN AND RURAL SETTINGS

- High incidence (>10 per 100pyrs) in all 3 settings
- Lowest stable incidence in San Francisco (~12/100py)
- Moderate stable incidence in Perry County, KY (~20/100py)
- Increasing and much higher in Scott County, IN (>40/100py)
HCV ELIMINATION AMONG PWID IN US: REQUIRED SCALE-UP SETTING-SPECIFIC

- Without harm reduction scale-up
  - <15%/yr treated in SF & KY
  - Double treatment rate in Scott County, IN as incidence higher and increasing

- With harm reduction scale-up (50% coverage each)
  - Halves treatment rate in Hazard County, KY and Scott County, IN
  - Less impact in SF due to higher baseline coverage of syringe exchange
RETREATMENT IS REQUIRED TO ACHIEVE ELIMINATION IN SCOTT COUNTY, INDIANA

IF NO RETREATMENT OF REINFECTIONS:

- HCV epidemic can rebound due to reinfection
- Harm reduction can maintain impact
- BUT cannot reach WHO target

Fraser H et al, Addiction 2017
ACHIEVING SCALE-UP AMONG PWID TO REACH ELIMINATION TARGETS

• HCV treatment recommended for all persons with chronic HCV infection (WHO, IAS-USA, EASL guidelines) including PWID

• But budgetary issues remain... so continued discussions on:
  • concerns of reinfection/retreatment among PWID
  • prioritization of therapy
MEDICAID REIMBURSEMENT CRITERIA: BASED ON FIBROSIS STAGE

MEDICAID REIMBURSEMENT CRITERIA: REQUIRED ABSTINENCE FROM DRUG/ALCOHOL
HCV elimination will not be achieved if treatment:
- Denied to those at risk of transmitting
- Prioritized to those who are unlikely to transmit

Does this strategy of restriction / de-prioritization of PWID make economic sense?

Among 269 HCV antibody positive PWID recruited from 2016-2017. Preliminary unpublished data, courtesy of S. Mehta
DAA THERAPY FOR PWID IS COST-EFFECTIVE

- DAAs cost-effective for PWID in UK, Australia, Netherlands\(^1\)-\(^3\)
- More cost-effective in low prevalence settings, as greater prevention benefit
- Early DAA treatment for PWID cost-effective compared to delay to cirrhosis\(^1\)

Early treatment vs delay to cirrhosis

- Incremental cost-effectiveness ratio (£/QALY gained) of early DAAs

\(\£1 = \text{USD }\$1.30\)

- 20% chronic prevalence among PWID
- 40% chronic prevalence among PWID
- 60% chronic prevalence among PWID

UK willingness-to-pay threshold

1. Martin NK et al. J Hepatol 2016
MORE COST-EFFECTIVE TO PRIORITIZE EARLY TREATMENT FOR PWID INSTEAD OF BY STAGE IN 20/40% PREV SETTINGS

Economic modeling supports treatment for and prioritization of PWID – essential for achieving elimination targets

*£20,000 willingness to pay.
OUTLINE

• HBV elimination modeling
  • Global

• HCV elimination modeling
  • Country level (US, Pakistan)
  • People who inject drugs (PWID)
  • HIV-infected men who have sex with men (HIV+ MSM)
<table>
<thead>
<tr>
<th>Population size</th>
<th>Small compared with PWID (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine integration of HCV case-finding and treatment</td>
<td>Good in many developed country settings</td>
</tr>
<tr>
<td>Next-generation DAA SVR</td>
<td>High</td>
</tr>
<tr>
<td>Evidence for other HCV prevention interventions</td>
<td>Poor</td>
</tr>
<tr>
<td>HCV treatment uptake</td>
<td>Good (~50% treatment experienced in Berlin(^1) &amp; UK(^2))</td>
</tr>
<tr>
<td>HCV incidence</td>
<td>Low (1-2% per 100py(^3))</td>
</tr>
<tr>
<td>Reinfecction rate</td>
<td>Higher (5-10x) than primary incidence(^4)</td>
</tr>
<tr>
<td>Global network</td>
<td>Highly connected network in Europe.</td>
</tr>
</tbody>
</table>

HCV ELIMINATION AMONG HIV+ MSM IN THE UK

- Difficult to reduce low incidence by 90% (to <0.14%) by 2030
  - Treatment rates required much higher than among PWID populations
- Elimination requires 100% treatment after diagnosis plus:
  - Enhanced testing or
  - Behavior risk reduction

Preliminary work based on Martin NK et al. CID 2016
AMONG HIV+ MSM IN BERLIN: A SETTING WITH INCREASING INCIDENCE AND HIGH TREATMENT RATES

- Even more difficult to eliminate in a setting with increasing incidence with existing high testing/treatment.
- Elimination likely requires both universal treatment and behavior risk reduction.

Martin NK and Ingiliz P et al, preliminary work
REAL WORLD EVIDENCE: ON TRACK FOR ELIMINATION AMONG HIV+ MSM IN THE NETHERLANDS?

Pre-scale up model: at most ~20% reduction in 2 years…BUT:

Observed: halving in acute HCV incidence 2014-2016 with widespread scale-up

Boerekamp A et al. CROI 2017 abstract 137LB
Hullegie SJ et al. CROI 2015 abstract 536

Need modeling disentangling the likely impact of treatment scale-up on observed incidence declines
DISCUSSION: MODELING USES AND LIMITATIONS
CONCLUSIONS FROM ELIMINATION MODELING

• Transmission modeling highlights importance of considering local epidemic characteristics when developing HBV and HCV elimination strategies

• Among PWID, modest levels of HCV treatment and harm reduction can achieve elimination in variety of settings
  • Requires sustained efforts & retreatment of reinfections
  • Economic modeling supports treatment for and prioritization of PWID – essential for achieving elimination targets

• Among HIV+ MSM, likely requires high levels of screening and treatment, plus behavioral risk interventions
MODELING LIMITATIONS AND DIRECTIONS

• Models highly reliant on good data:
  • Large population based surveys gold standard but not good for concentrated epidemics
  • Need routine surveillance tracking prevalence/incidence in high risk—repeat testing, acute HCV testing
  • Need good size estimates of population at risk

• Modeling alone insufficient evidence for HCV TasP
  • Need real-world empirical data with population incidence/prevalence (not just SVR or reinfection)
  • Yet, modeling should be embedded within these trials
ACKNOWLEDGEMENTS

Health Protection Scotland: Sharon Hutchinson, David Goldberg, Esther Aspinall
Queen Mary’s London: Graham Foster
University College London: Alicia Thornton, Caroline Sabin, Huw Price
Public Health England: Valerie Delpech
Imperial College London: Mark Nelson, Graham Cooke, Emma Thomson
Burnet Institute: Margaret Hellard
University of New South Wales: Greg Dore, Jason Grebely, Andrew Lloyd
CDC: Jon Zibbell, John Ward
Center for Infectology Berlin: Patrick Ingiliz

FUNDERS: US Center for Disease Control, Gilead Sciences, National Institute for Drug Abuse R01 DA037773-01A1, UCSD Center for AIDS Research (P30 AI036214), UK EPSRC, UK National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at University of Bristol. The views expressed are those of the authors and not necessarily those of the UK NHS, UK NIHR, UK Department of Health.