High Rate of HCV Reinfection Among Recently Injecting Drug Users: Results from the TraP Hep C Program – A Prospective Nationwide, Population-Based Study

Johannesson JM, Olafsson S, Tyrfingsson T, Runarsdottir V, Bergmann OM, Hansdottir I, Björnsson ES, Johannsson B, Sigurdardottir B, Fridriksdottir RH, Löve A, Hellard M, Löve TJ, Gudnason T, Heimisdottir M, Gottfredsson M

Disclosure of interest

- Gilead Sciences provides DAAs for the Trap Hep C program in support of an epidemiological study. Fridriksdottir, Runarsdottir, Olafsson and Gottfredsson have received consultancy fee from Gilead Sciences.

Background

- Hepatitis C is caused by the **hepatitis C virus (HCV)**
  - Affects an estimated 70 million people globally
  - Leading cause of **cirrhosis** and **hepatocellular carcinoma**
- Most prominent mode of transmission is **injection drug use (IDU)** among **people who inject drugs (PWID)**
- **Direct-acting antivirals (DAAs)** are safe and effective
- WHO in 2016 set goal of eliminating HCV as a major health threat by 2030
  - **65% reduction in HCV-related deaths** and **80% reduction in HCV incidence**
- SVR does **not** confer protection to reinfection: major threat to elimination

Background

- **Treatment as Prevention for Hepatitis C in Iceland (TraP Hep C)** was launched in January 2016
    - Maximize **diagnosis** and **treatment access (DAAs)** for hepatitis C
    - **Harm reduction** scaled up, including **needle-syringe programs**
    - Establish **follow-up** and **further linkage to care**
- Onset of program:
    - **Estimated 760 individuals with HCV infection** (75 undiagnosed)
    - **Confirmed 682 individuals with HCV infection**
- After 36 months (183 new HCV infections diagnosed):
    - 824 (**95.3%**) diagnosed infections linked to care
    - 795 (**96.5%**) treatment initiations after linkage to care
    - 717 (**90.2%**) cures achieved after treatment initiation

Aims

- Determine **reinfection rate** of HCV among patients that successfully completed treatment within the TraP Hep C cohort
- Elucidate **risk factors for reinfection**

Methods

- Prospective cohort study
- Study cohort consisted of all HCV-cured patients with an estimated SVR between **January 11th 2016 and November 20th 2018**
- Follow-up until **November 20th 2019**
- Iceland as a setting:
    - Estimated population ~357,000, **majority in capital region**
    - Estimated HCV viremic **population prevalence 0.3%**
    - National health insurance
    - Single reference virology laboratory serving the whole country
    - Central registry of reportable infectious diseases (including HCV)

Methods

- All results from HCV RNA measurements performed in the country during the study period were obtained and connected to patient data
- Patient-specific variables gathered at treatment initiation:
  - **Recent IDU**: IDU within the last 6 months from time of baseline interview
  - **Preferred injected drug**: stimulant or non-stimulant
- **Genotyping** performed for all suspected reinfections
  - Deep sequencing and phylogenetic analysis to distinguish from virological relapse

Methods

- **Two** separate cohorts
    - **SVR cohort**: Cure defined as **confirmed SVR at 12 weeks post-treatment or more**
    - **Non-SVR cohort**: Cure defined as **undetectable HCV RNA during or after treatment**
- Observation time measured in **person years (PYs):**
    - SVR cohort: from **SVR** to most recent HCV RNA measurement or first measurement with detectable HCV RNA
    - Non-SVR cohort: from **end of DAA treatment** to most recent HCV RNA measurement or first measurement with detectable HCV RNA
- **Reinfection**: presence of detectable HCV RNA following cure without signs of virological relapse
    - **Time to reinfection**: observation time among those with confirmed reinfection

Methods

- **Reinfection rate (RIR) calculated per 100 PYs**
  - **Theoretical minimum RIR** with assumption of every cured patient having remained negative until November 20th 2019
- Survival analysis performed with reinfection as outcome of interest
- Multivariate Cox proportional hazards models used to identify predictor variables for reinfection
  - **Traditional model**: no account for recurrent events
  - **Andersen Gill model**: correlations among recurrent events induced by measured covariates
  - **Frailty model**: frailty term accounts for heterogeneity due to unmeasured variables
- Statistical analysis performed in **R with R Studio**

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Results – SVR cohort

- **617 treatments of 597 patients**
  - 68.5% male, 31.5% female
  - Average age 44.5 years
- **44 reinfections in 42 patients**
  - 78.6% male, 21.4% female
- Follow-up: 484.8 PYs
  - Median observation time: 594.5 days
- Median time to diagnosis of reinfection: 252 days
- 85% with history of IDU and 33% with recent IDU
  - Stimulants preferred injected drug among 85%
- **RIR: 9.1/100 PYs (95% CI 6.5 – 11.6)**
  - Theoretical minimum RIR: 3.0/100 PYs (95% CI 2.2 – 3.9)

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Results – Non-SVR cohort

- **640 treatments of 614 patients**
    - 67.9% male, 32.1% female
    - Average age 44.3 years
- **52 reinfections in 50 patients**
    - 74% male, 26% female
- Follow-up: 693.0 PYs
    - Median observation time: 230 days
- Median time to diagnosis of reinfection: 328.5 days
- 84.8% with history of IDU and 34.4% with recent IDU
    - Stimulants preferred injected drug among 85.5%
- **RIR: 7.5/100 PYs (95% CI 5.5 – 9.5)**
    - Theoretical minimum RIR: 3.1/100 PYs (95% CI 2.2 – 3.9)

Variable	Reinfections	Person years	Reinfections/100 person years (95% confidence interval)
Gender			
Male	38	462.3	8.2 (5.7 - 10.7)
Female	14	230.7	6.1 (3.0 - 9.1)
Recent IDU by self-report			
Recent IDU	39	260.6	15 (10.6 - 19.3)
No recent IDU	12	357.8	3.4 (1.5 - 5.2)
OST	6	84.7	7.1 (1.6 - 12.6)
Use of non-injectable drugs			
Cannabis	9	100.4	9 (3.4 - 14.5)
Opiates	3	27.8	10.8 (-0.7 - 22.3)
Stimulants	10	56.9	17.6 (7.7 - 27.5)
Sedatives	7	38.5	18.2 (6.0 - 30.4)
Coinfection with HIV			
HIV-positive	7	60.5	11.6 (3.5 - 19.6)
HIV-negative	45	626.1	7.2 (5.2 - 9.2)
Age group			
Age 20-39 years	34	277.1	12.3 (8.4 - 16.1)
Age 40-59 years	16	318.8	5 (2.6 - 7.4)
Age 60 years and above	2	97.1	2.1 (-0.8 - 4.9)
Living situation at treatment initiation			
Halfway house	7	66.9	10.5 (3.1 - 17.8)
Homeless/streets	9	48.3	18.7 (7.7 - 29.6)
Own property/rental/relatives	24	514.8	4.7 (2.8 - 6.5)
Penitentiary	11	45.5	24.2 (11.7 - 36.6)

Results – SVR cohort

- Traditional Cox proportional hazards model:
  - Age group (5-year groups): **HR 0.76, 95% CI 0.64 - 0.89**
  - Recent IDU: **HR 2.59, 95% CI 1.16 - 5.80**
- Andersen Gill model:
  - Age group: **HR 0.76, 95% CI 0.67 - 0.87**
  - Recent IDU: **HR 2.59, 95% CI 1.04 - 6.45**
- Similar results in frailty model

Results – Non-SVR cohort

- Traditional Cox proportional hazards model:
    - Age group: **HR 0.77, 95% CI 0.66 - 0.91**
    - Recent IDU: **HR 3.08, 95% CI 1.35 - 6.99**
- Andersen Gill model:
    - Age group: **HR 0.79, 95% CI 0.67 - 0.92**
    - Recent IDU: **HR 3.09, 95% CI 1.36 - 7.03**
- Similar results in frailty model
- Subanalyses within group with recent IDU
    - **Younger age group** significantly associated with increased reinfection risk
    - Preference for either stimulant or non-stimulant injected drugs **not significantly associated** with reinfection risk
    - Number of injection days in the preceding month **not significantly associated** wit risk

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Discussion

- Reinfection rate after treatment in Iceland is **high**
- Reinfection rate is particularly high among **young marginalized individuals with recent IDU and those who have unstable housing**
- Multivariate analyses reveal increased risk of reinfection among **younger age groups and those with recent IDU**

Discussion

- **No risk association** with preferred injected drug or rate of injections
    - Use of stimulants and mixed use (stimulants + opiates) particularly common in Iceland
- Overestimate of RIR due to more sampling from high-risk patients?
- Further emphasis on high-risk populations is necessary to maintain and further reduce HCV prevalence and transmission, and reach elimination goals
- This can best be done by:
    - **Prevention efforts**
    - **Maintaining inclusive multidisciplinary care**
    - **Educating patients**
    - **Frequent testing**
    - **Continued follow-up of high-risk groups**
    - **Prompt treatment of reinfections**

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Questions?

	Female	%	Male	%
Number of individuals	197	NA	417	NA
Finished treatments	206	NA	434	NA
Mean age (years)	42.9	NA	45	NA
History of addiction*	126	64.0%	380	91.1%
History of IDU*	156	79.2%	367	88.0%
History of previous non-DAA treatment*	28	14.2%	49	11.8%
HIV-infection*	13	6.6%	26	6.2%
Recent IDU	64	31.1%	156	35.9%
OST	17	8.3%	43	9.9%
Use of non-injected drugs	36	17.5%	103	23.7%
Cannabis	21	10.2%	72	16.6%
Opiates	10	4.9%	13	3.0%
Stimulants	16	7.8%	38	8.8%
Sedatives	13	6.3%	17	3.9%
Living situation at treatment initiation				
Own property/rental/relatives	166	80.6%	319	73.5%
Halfway house	23	11.2%	38	8.8%
Homeless/streets	10	4.9%	30	6.9%
Penetentiary	4	1.9%	37	8.5%
Other living arrangements	3	1.5%	10	2.3%
Preferred intravenous drug				
Methylphenidate	61	39.1%	98	26.7%
Other stimulants	70	44.9%	218	59.4%
Opiates	19	12.2%	47	12.8%
Other	6	3.8%	4	1.1%
Cirrhosis	7	3.4%	38	8.8%
Genotype				
3a	124	60.2%	243	56.0%
1a	63	30.6%	164	37.8%
1b	16	7.8%	17	3.9%
Other	3	1.5%	10	2.3%