Existing HCV Treatment Failure Data and On-going Studies

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SURVEILLANCE OF HEPATITIS C ANTIVIRAL RESISTANCE, EPIDEMIOLOGY AND METHODOLOGIES

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Who?

What?

How?

Who?

Country	Institute/Principal Investigators
Australia	**The Kirby Institute** Tanya Applegate & Jason Grebely **School of Medical Sciences , UNSW.** Andrew Lloyd, Rowena Bull **The Westmead Institute** Mark Douglas
Canada	**BC-Centre for Excellence in HIV/AIDS** Anita Howe/Richard Harrigan **BC-Centre for Disease Control** Mel Krajden ***Can HepC*** Jordan Feld
France	**Hopital Henri Mondor** Universite Paris Est Jean-Michel Pawlotsky
Netherlands	**Utrecht Medical Center** HepCare Charles Boucher, Stephanie Popping
Italy	**University of Rome Tor Vergata** Francesca Ceccherini-Silberstein Valeria Cento
Spain	**HU San Cecilio Granada** GEHEP-004 Cohort Federico Garcia & Ana Belén Pérez
Sweden	**Uppsala University** Johan Lennerstrand
USA	**HCV TARGET** David Nelson/Joy Peter/Gary Wong **The Forum** Veronica Miller/Malene Coburne **Bristol Myers Squibb** Fiona McPhee
UK	**Stop Hep C** Ellie Barnes & David Bonsal

What?

Objective 1: **To collect HCV sequences, conduct resistance analysis of virologic failures, define prevalence of known RASs and identify novel RASs among all HCV genotypes.**

Objective 2: To evaluate the impact of baseline polymorphisms in HCV on treatment outcomes of IFN-free DAA containing regimens.

Objective 3: To report the *in vitro* drug susceptibility of mutations selected by approved direct-acting antivirals, and correlate biological cut-offs and clinical outcomes.

Objective 4: To describe the prevalence of genetic polymorphisms in HCV genotypes 4-6 and their distribution in different geographic regions.

Objective 5: To share technologies and know-how for resistance evaluation

Objective 6: **To evaluate clinical and behavioural factors (e.g. ongoing injecting drug use) associated with the development of RASs.**

RESISTANCE PROFILES FOR EACH APPROVED DAA AND DRUG CLASS STRATIFIED BY HCV GENOTYPES AND SUBTYPES WILL BE ASSESSED TO:

1. Identify specific RASs or RAS patterns selected by each approved DAA or drug class;
2. Compare the prevalence of mutations in NS3, NS5A, and NS5B between DAA-treated and untreated patient populations;
3. Identify treatment-emergent RASs versus persistent baseline RASs in virologic failures with paired baseline and virological failure sequences;
4. Correlate RASs and RAS patterns with demographic and clinical characteristics;
5. Estimate the persistence of RASs over time
6. Evaluate the impact of resistance guided therapy on SVR;
7. Compare the frequency of RASs detected by Sanger population sequencing versus ultra deep-sequencing with different sequencing cut-offs.
8. Evaluate the rescue treatment outcomes in DAA-failures

How?

Anonymized HCV sequences and their associated clinical and behavioural information from laboratories and clinics worldwide

Key Inclusion Criteria:

① chronic HCV infection,

② naïve or experienced to PEG-IFN or DAA,

③ age >18 years and with at least one HCV genotypic resistance test available on NS3 and/or NS5A and/or NS5B

④ Pre/post-OLT and decompensated cirrhosis, or HIV/HBV co-infections are not criteria for exclusion.

How?

Anonymized HCV sequences and their associated clinical and behavioural information from laboratories and clinics worldwide

Key Exclusion Criteria:

① Age <18 years.

② HCV-infected subjects with only HCV antibody without sequence data.

③ Subjects with incomplete treatment information or outcome data will be excluded from Objectives 1 and 2

④ Can be included in Objective 4 for the epidemiology studies.

How?

Data sets:

Demographic information (at initiation of therapy):

age, gender, ethnicity, BMI, country of birth, and clinical and behavioural factors (history of injecting drug use or opioid substitution therapy, and socio-economical information may be collected depending on the availability of data)

Virology data:

HCV viral load, genotype, HCV amino acid and/or nucleotide sequences; other viral coinfections

Treatment data:

treatment regimen and duration corresponding prior treatment history and response, and other relevant medications; SVR, non-response, viral breakthrough, relapse, drop-out, and reinfection

How?

Data sets:

Host genetics data:

IFNL3 (IL28B) polymorphisms

Biochemistry:

ALT, AST, bilirubin, haemoglobin, albumin, creatinine, INR, phosphate, urea, platelets, CD4 count, C-reactive protein, HBV and/or HIV co-infection status.

Liver function data:

liver fibrosis assessment, Child-Turcotte-Pugh class, MELD score, past orthotopic liver transplant, variceal bleeding, encephalopathy, ascites, hepatocellular carcinoma

Extra-hepatic comorbidities:

renal diseases, cardiovascular diseases, and cancers

So far

Sample Size and Statistical Plan:

- **First Data Merger:**
  - Approximately 7000 sequences (3 genes)
  - Collected between 2011 – 2016
  - Canada (n = 600VF+300BL), Australia (n = 500VF+380BL), Sweden (n = 500), Netherland (n = xxx), France (n = 400), Italy (n = 300VF+1500BL), Spain (n = 300VF+600BL) and the United States (n = 50VF+500 BL).
- **Statistical differences in the demographics, clinical characteristics and resistance profiles will be assessed by using Chi Square test or Fisher's exact test (for categorical variables) and Mann-Whitney test (for continuous variables) or Logistic Regression Models, as appropriate.**

MEMBERSHIP AND COLLABORATION STRUCTURE

Open to any researcher who is interested to bring in data, scientific expertise and/or financial support

Project Coordinator:

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DATA OWNERSHIP AND USAGE

- Contributing collaborators possess full ownership of their own data, which is within the control of the collaborators and subjected to and governed by privacy law applicable to the collaborators
- Contributing collaborators may use their own data for research or other collaborations
- All data obtained as part of the Collaboration will be available for specific analyses to any researcher following review and approval by the Coordination Committee
- All publications arising from the use of data from the Collaboration shall list individual study collaborators as co-authors and acknowledge SHARED