Persons with advanced liver disease are under-represented in clinical trials

- Limited numbers of patients with cirrhosis were included in BOC and TVR registration trials, and tolerability to triple therapy in cirrhotics in practice has been poor.
- Persons with decompensated cirrhosis are technically ineligible for interferon-based therapies.
- Interferon free treatments that are safe and efficacious in persons with advanced liver disease are desperately needed.
- There is a hesitation to study DAA in persons with advanced liver disease, however these are the patients in greatest need of treatment.

Ongoing INF-free Trials Allowing or Exclusively Studying Persons with Advanced Liver Disease

DAA Combination	Patient Population	N	NCT#	Status
Daclatasvir + simeprevir ± RBV	Allows 1/3 F3 or F4 without decompensation	180	01628692	Ongoing, not recruiting
Sofosbuvir + simeprevir ± RBV	Allows half with F3 or F4 no decompensation	168	01466790	Ongoing, not recruiting
Sofosbuvir + RBV	Pre-transplant CP ≤ 7	50	10559844	Enrollment complete
ABT450/r + ABT333 + ABT267 + RBV (TURQUOISE-II)	All cirrhotics CP ≤ 6	300	01704755	Recruiting
Sofosbuvir + RBV	All cirrhotics including decompensation CP < 10, HVPG > 6	50	01687257	Recruiting
Sofosbuvir + RBV	Post-transplant recurrence, 6 mo-12 yr post-transplant, excludes decompensation	40	01687270	Recruiting

www.clinicaltrials.gov

How can we safely use DAA in Persons with Advanced Liver Disease?

- Need to determine the optimal drug doses and combinations

- Achieved through a comprehensive understanding of the pharmacokinetics and physiologic features of advanced liver disease which may influence DAA pharmacokinetics

Features of Advanced Liver Disease which may Alter DAA PK

1. Hepatic enzyme expression and/or function
2. Membrane transporter expression and/or function
3. Protein Binding
4. Phosphorylation enzyme expression and/or function
5. Portal-Systemic Shunting

Questions

- Results of DAA PK hepatic impairment trials highlight the need for mechanistic explanations for PK results
  - If we understand why the PK is altered this will guide what we do next…..
- Role for physiologic-based pharmacokinetic modeling?
  - Johnson TV, et al. Clin PK 2010;49(3):189-206.
- Role for therapeutic drug monitoring?
  - Plasma correlate with hepatocyte concentrations?
- Other ideas for pharmacology research needs in this patient population?