Effects of direct active antivirals on kidney function in patients with HIV-HCV co-infection

Target trial emulation

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CFAR symposium on statistics and data science, June 6th 2023

Road map

1. HCV and DAA
2. Effect of DAA treatment on kidney function
3. Methodological issues
4. Target trial emulation
5. Results
6. Discussion

Road map

Chronic hepatitis C infection

- Hepatitis C Virus (HCV) infection affects approximately 2.4 million people in the U.S. and 71 million people in the world
- Chronic HCV infection causes cirrhosis, liver cancer, liver transplantation, and death
- Extra-hepatic manifestations (metabolic alterations, kidney damage, cancer, cardiovascular disease, and diabetes)

Direct acting antiviral (DAA) treatment

- Widely available in the U.S. and Europe since 2015
- Very effective: 95% of treated patients achieved sustained virological suppression (cure)
- Short treatment course (8 to 12 weeks), no toxicities
- Current WHO and US guidelines recommend DAA treatment in all individuals with HCV infection

Road map

Effect of DAA treatment on kidney function

- Individuals with HIV-HCV co-infection are at high risk of kidney disease and have fast kidney function decline
- **Question**: Does receiving DAA improve kidney function in patients with chronic kidney disease?
- **Causal effect**: contrast in changes in kidney function under two treatment strategies: DAA for all versus no DAA
- **Measure of kidney function**: estimated glomerular filtration rate (eGFR) - the higher the better

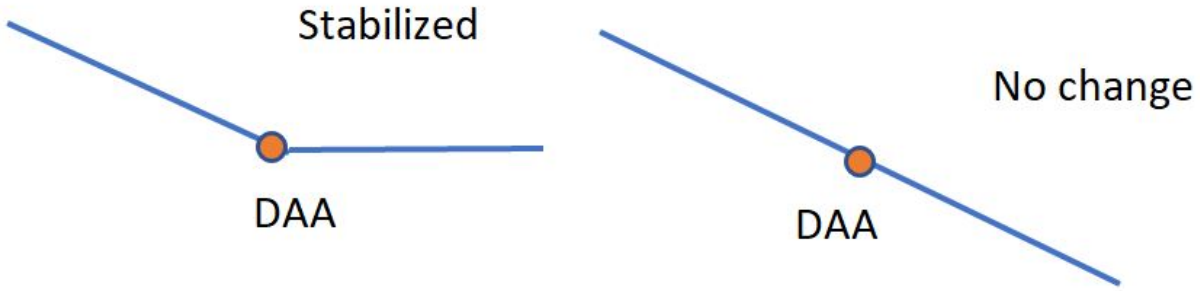
HepCAUSAL Collaboration

- An international collaboration of 12 cohorts of HIV-HCV co-infection from the Europe, Canada and the U.S.
- Data collected in routine clinical practice mostly HIV and/or infectious disease clinics
- Settings with universal access to healthcare and no barriers to DAA treatments
- Complex data including: demographics, clinical diagnoses, procedures, visits, vitals, medications, virological and serological tests, blood panels, death, loss to follow-up, pregnancy, smoking, alcohol drinking, drug use

Effect of DAA treatment on kidney function

Previous observational studies

- Before and after DAA comparisons
- Estimate and compare the mean or the slope of eGFR before and after DAA
- Reminder: high eGFR is good for you



- **Problem**: in observational studies DAA is not randomized and this approach does not estimate a causal effect

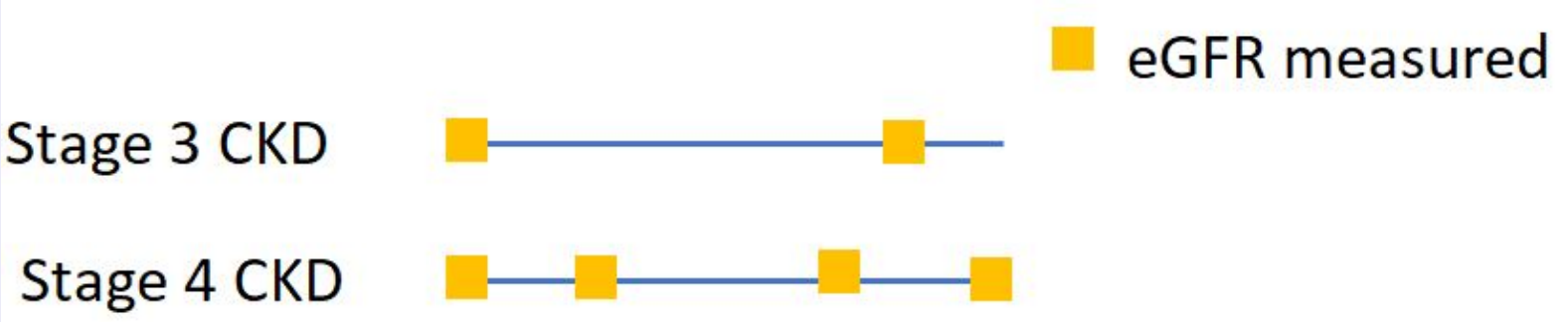
Road map

Informative presence/visit process

Irregular visits and timing of eGFR measurements

- In clinical trials participants are seen at scheduled study visits

- In 'real life' patients with poor kidney function will be measured monitored more often



Definition of time origin

Couldn't we just compare change in eGFR in patients who received DAA and those who never received DAA?

- For instance, split the sample into DAA users and never DAA users and use propensity score adjustment or matching

Problem: This approach DOES NOT estimate the average treatment effect

- No obvious index date/time origin for patients who never receive DAA
- Selection bias: People with longer follow-up will have more chance to start DAA but are also more likely not to die and to use health care more often treatment

Time-varying treatment and confounding

Time-varying treatment and confounding

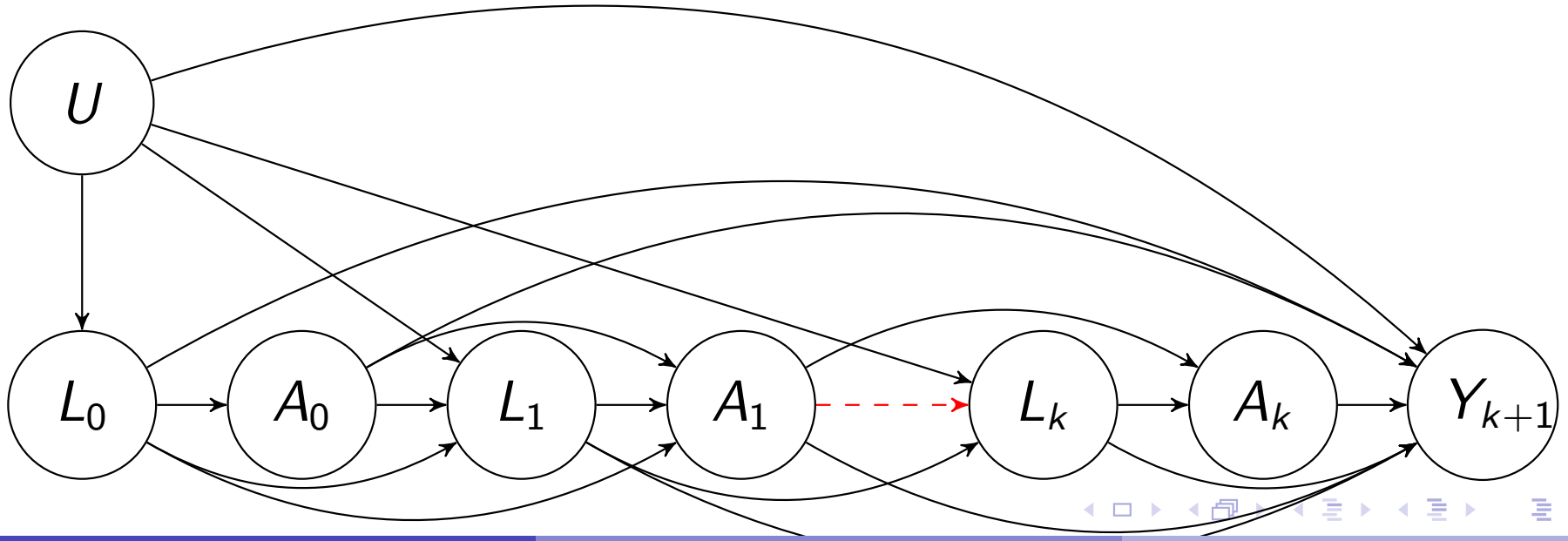
Notation:

U=Kidney function (unknown)

$\bar{L}_k$=$(L_0, L_1, ..., L_k)$ History of markers for kidney disease

$\bar{A}_k$=$(A_0, A_1, ..., A_k)$ History of DAA treatment status

Y_{k-1}=GFR at time $k-1$



Road map

The Target Trial

- The (hypothetical) randomized trial that we would like to conduct to answer a causal question
  - To estimate the effect of DAA on kidney function
- A causal analysis of observational data can be viewed as an attempt to emulate some target trial

Hernan and Robins (2016)

Step 1 - Specify Target Trial protocol

- Eligibility criteria
- Treatment strategies
- Treatment assignment
- Outcomes
- Start/End follow-up
- Causal contrast
- Analysis plan

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
• Eligibility criteria	• Eligibility criteria
• Treatment strategies	• Treatment strategies
• Treatment assignment	• Treatment assignment
• Outcomes	• Outcomes
• Start/End follow-up	• Start/End follow-up
• Causal contrast	• Causal contrast
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Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol

Eligibility Criteria

- Adults with HIV-HCV co-infection, DAA naive, on HIV medications
- Measure of liver disease: FIB-4 measurement
- Chronic kidney disease: 2 eGFR<60

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Eligibility Criteria	
• Adults with HIV-HCV co-infection, DAA naive, on HIV medications • Measure of liver disease: FIB-4 measurement • Chronic kidney disease: 2 eGFR<60	• **Same**

Step 1 - Specify Target Trial protocol

Interventions

- DAA: start DAA soon after baseline
- No DAA: never start DAA
- For all: eGFR measured at 36 months

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Interventions	**Interventions**
• DAA: start DAA soon after baseline	• Immediate DAA: start DAA within **6 months** of baseline
• No DAA: never start DAA	• **Same**
• For all: eGFR measured at 36 months	• For all: eGFR measured at **36** -/+**3** months

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Treatment assignment • Randomly assign participants to either strategy • Participants and study staff aware of the assigned strategy	

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Treatment assignment	**Treatment assignment**
• Randomly assign participants to either strategy	• **Randomization not possible** – identify confounders to adjust for in statistical analyses
• Participants and study staff aware of the assigned strategy	• Same

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Outcome	
• Change in eGFR between baseline and the 36-month visit: $\text{eGFR}_{36} - eGFR_0$	• Same
• Average treatment effect: difference in mean eGFR change between DAA groups	• Same

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Follow-up	**Follow-up**
• Start: randomization	• Start: **earliest date** all inclusion criteria are met
• End: earliest date of end of the study, 12 months with no new eGFR measurement or death	• Same

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Causal Contrast	**Causal Contrast**
• Intention to treat: effect of being assigned to DAA vs no DAA treatment strategy	• **Impossible to estimate**
• Per-protocol: effect of DAA vs no DAA if everybody had followed treatment assignment, had eGFR measured at 36 months and no loss to follow-up	• Per-protocol

Step 1 - Specify Target Trial protocol	Step 2 - Emulate Target Trial protocol
Statistical Analyses	**Statistical Analyses**
Per-protocol analysis	Per-protocol Analysis
• Adjustment for pre and post baseline prognostic factors that predict DAA initiation, loss to follow-up, eGFR visit process and kidney function	• Same
• G-methods (g-formula, inverse probability weighting, doubly robust estimators)	• Same

G-formula as a weighted average

$$\mathbb{E}(Y^g_{k+1}) =$$

$$\sum_{\bar{l}} \mathbb{E}(Y_{k+1}|\bar{A} = \bar{a}^g, \bar{L} = \bar{l}, C_{k+1} = 0) \times \prod_{j=0}^{k} f(l_j|\bar{a}^g_{j-1}, \bar{l}_{j-1}, C_j = 0)$$

- Stratum-specific mean conditional on treatment history and on measured confounder history observable under g and no censoring
- Weights are the 'chance' of having a confounding history under g and no censoring

Robins (1986)

Parametric g-formula

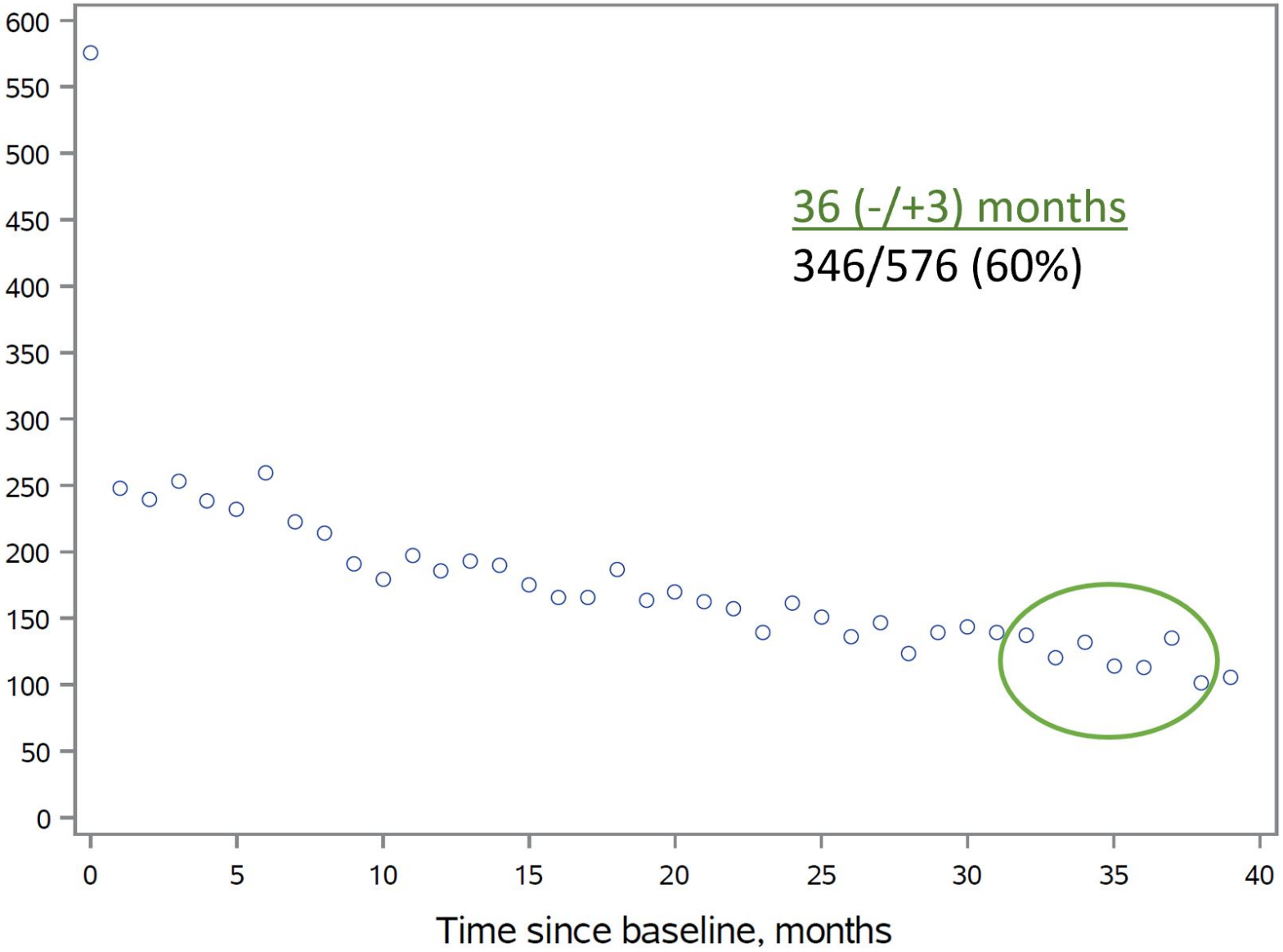
- Also called g-computation formula or non iterative conditional estimation (NICE) g-formula
- A method to estimate the g-formula consisting of
  - Parametric model estimation
  - Monte Carlo simulation

Confounders

- Defined **a priori**
- Baseline confounders
  - Age, sex, cohort, HIV transmission group, eGFR, advanced fibrosis/cirrhosis, CD4 cell count, HIV-RNA, smoking history, history of heavy drinking
- Time-varying confounders (updated at each time k)
  - eGFR, HIV-RNA, switching to an HIV treatment that affects kidney function, ever received DAA
  - For eGFR and HIV-RNA Values are carried forward until a new measurement become available
  - Binary indicators for the measurements of eGFR and HIV-RNA k

Road map

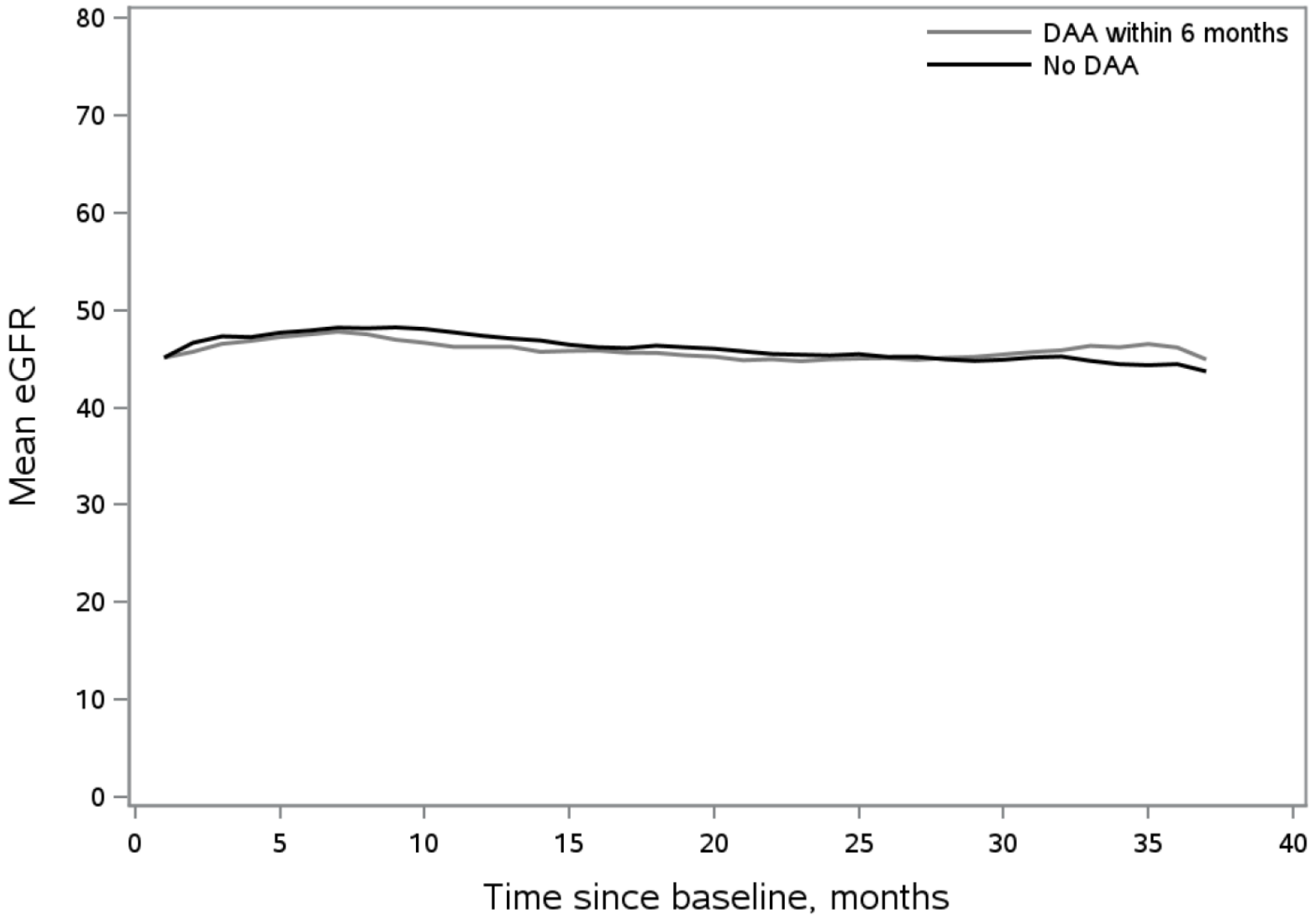
Number of individuals with eGFR measurement



G-formula estimates of change in eGFR at 36 months

DAA	-0.47 (-3.47, 0.30)
Never DAA	-1.70 (-4.40, 0.61)
DAA vs never DAA	1.23 (-2.86, 3.12)

Estimated eGFR trends under DAA interventions



Road map

Conclusions

- No evidence of an effect of receiving DAA vs not receiving DAA on kidney function in individuals HIV-HCV co-infection with chronic kidney disease in HepCAUSAL
- The target trial approach helps us define the research question and address the complexities in the data
- Subject-specific expertise is key for a successful trial emulation and interpretation of the data

Limitations

Our estimates rely on many assumptions

- Positivity
- No unmeasured confounding
  - All common causes (at baseline and time-varying) between DAA initiation and kidney function were included in our models
- Correct model specification

HepCAUSAL Collaboration

Coordinating center: Sara Lodi, Miguel Hernan, Sophia Rein, Roger Logan, Mathieu Chalouni, Daniela Van Santen - CausaLAB at Harvard TH Chan School of Public Health

Funding: NIHAID R37 AI102634

Participating cohorts:

- Europe: AMACS (Greece), ATHENA (Netherlands), Aquitaine (France),AHIVCOS (Austria), CoRIS (Spain), ICONA (Italy), PISCIS, Swiss HIV Cohort Study (Switzerland)
- Canada: South Alberta HIV Cohort, Canadian Co-infection Cohort
- U.S.: Boston Medical Center, Veteran Aging Cohort Study (VACS)

Thank you!!!!