HIV treatment interruptions are associated with heightened biomarkers of inflammation, coagulopathy and T-cell activation despite viral suppression

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Disclosures

- None

Background

- Immune activation/inflammation predicts non-AIDS morbidity/mortality in treated HIV
- Among virologically suppressed, average adherence to antiretroviral therapy (ART) is inversely associated with biomarkers of immune activation/inflammation (Castillo-Mancilla, JAIDS 2017)
- However, association with sustained treatment interruptions is unknown

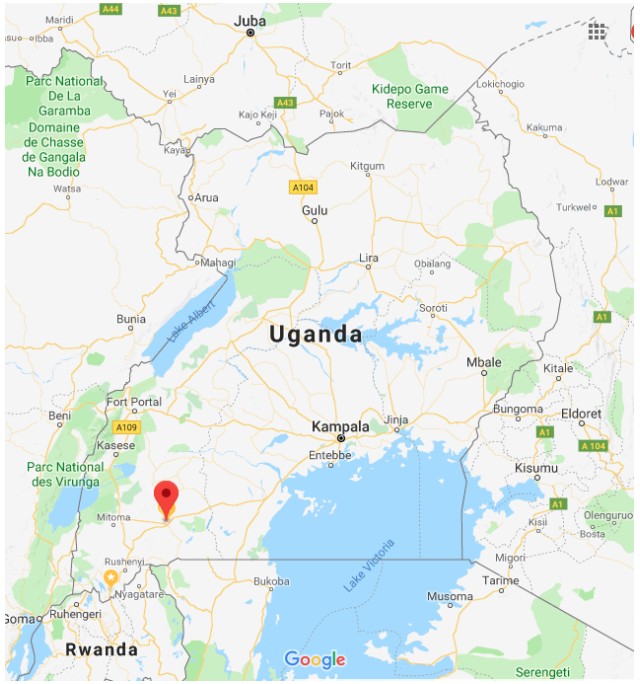
Research questions

- Are sustained treatment interruptions also associated with heightened levels of biomarkers activation/inflammation?

- Does this relationship remain after controlling for percentage adherence?

Uganda AIDS Rural Treatment Outcomes Study (UARTO)

- Longitudinal observational cohort study among adults living with HIV and initiating ART
- 772 participants enrolled between 2005-2012
- Baseline and quarterly follow-up
  - Socio-demographic data
  - ART regimen data
  - Electronic ART adherence (MEMS)
  - Blood drawn for plasma and cell isolation



Biomarkers

- Inflammation
  - Interleukin-6 (IL-6)
  - Kynurenine/tryptophan (K/T) ratio
  - Soluble (s) CD14
  - Soluble (s) CD163
- T-cell activation
  - HLA-DR+/CD38+
- Coagulopahty
  - D-dimer

Analysis

- **Primary:** For each biomarker, we fit a multivariable linear regression assessing effect of treatment interruptions on the log-transformed level of the biomarker
- **Secondary:** Primary model adjusted for percentage adherence

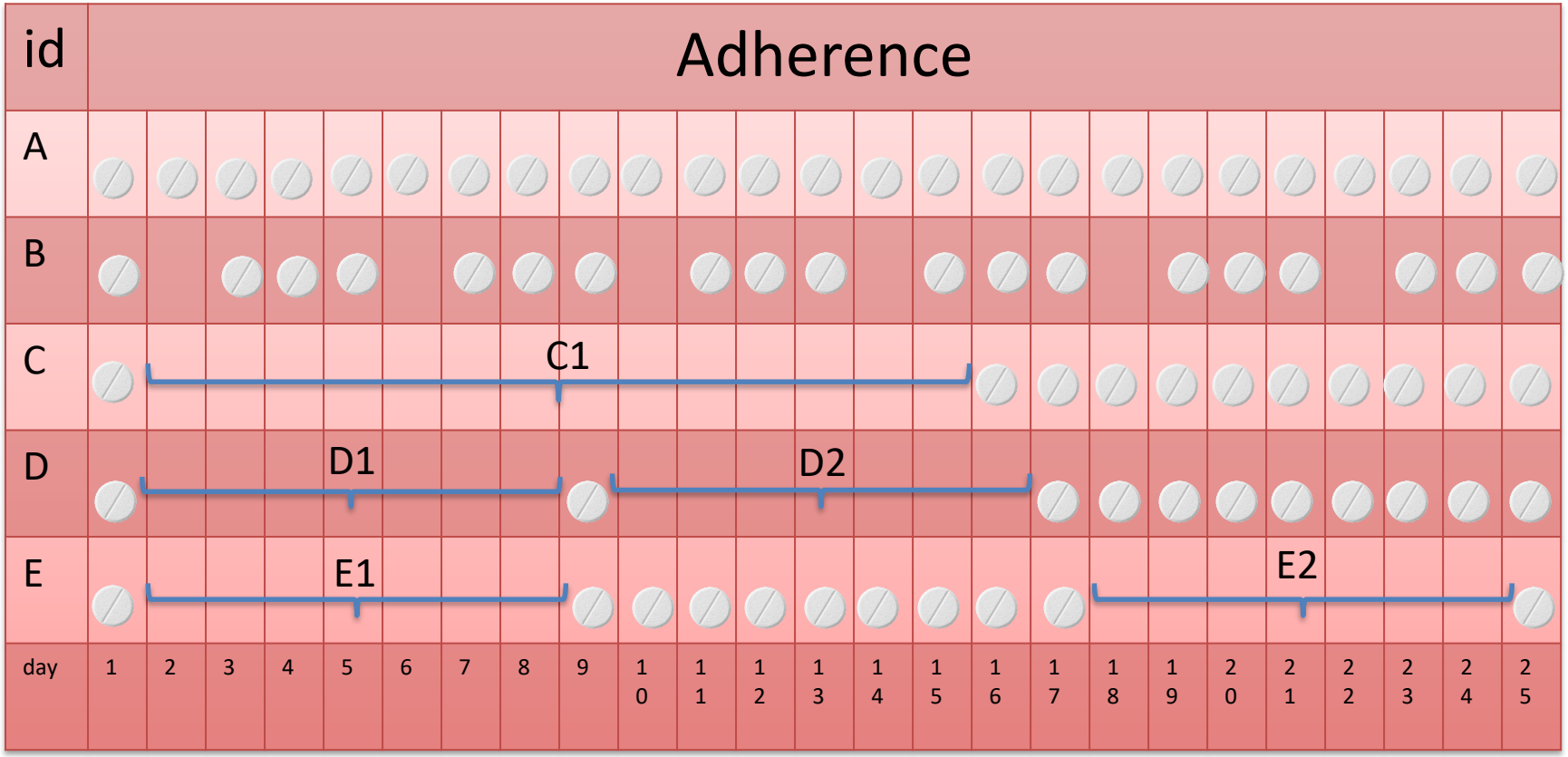
Eligibility criteria for analysis

- Restricted to first 6 months of follow-up after ART initiation
- Biomarker levels available at baseline and after 6 (+/- 1) months on ART
- Virologically suppressed (VL<400 copies/ml) at the 6-month visit
- ART adherence data available for 3+ months in the 6-month period

Main predictor: Treatment interruptions

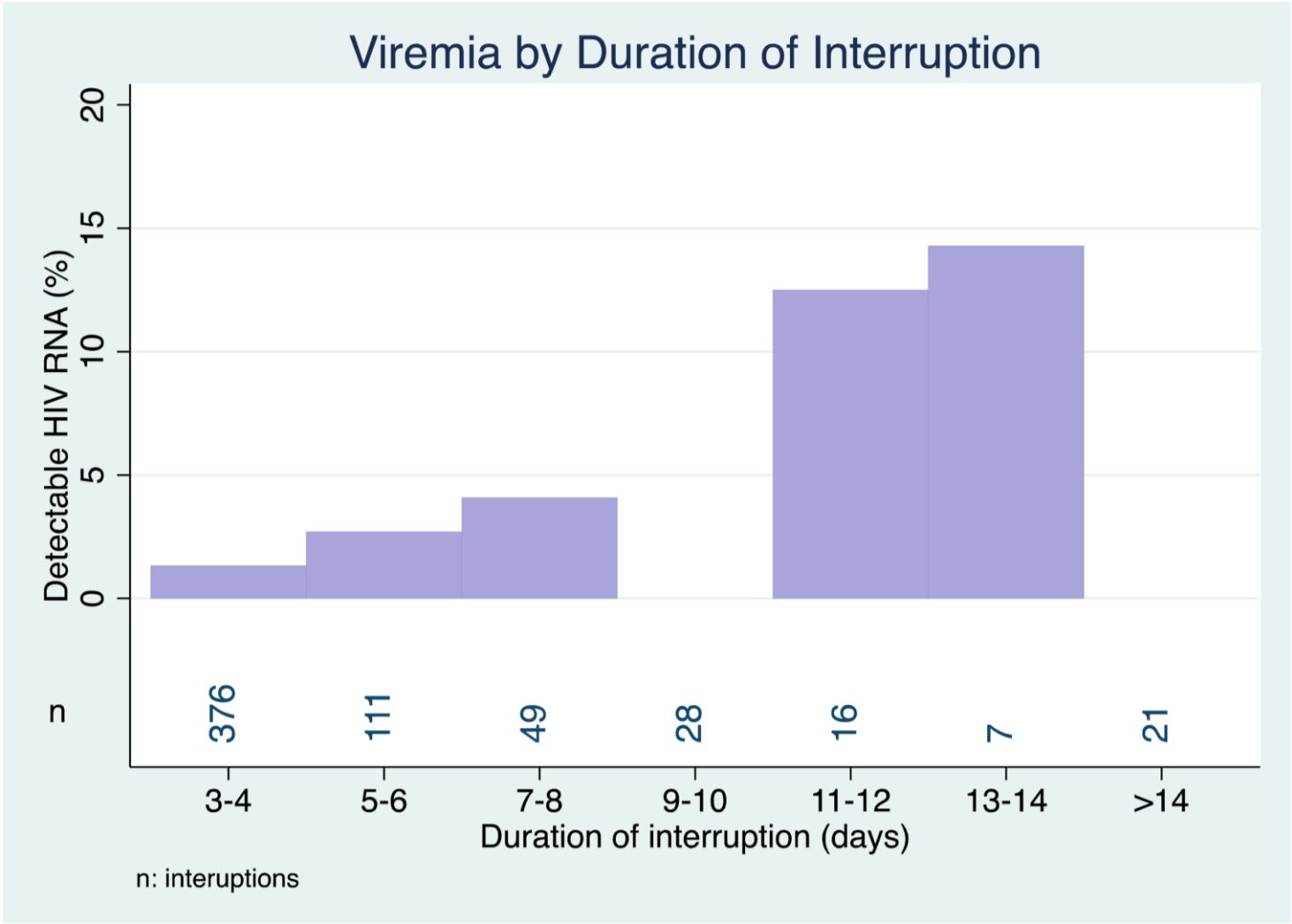
- Potential approaches to computing treatment interruptions
  - 1) Frequency of interruptions lasting X or more days
    - Assumes that interruptions are equal in their relationship with treatment outcomes
  - 2) Proportion of days when running average adherence was less than 10% or 20% etc

But are interruptions really equal in their relationship with treatment outcomes?



Eg. Is the relationship between D2 and viral suppression similar to that between E2 and viral suppression?

But are interruptions really equal in their relationship with treatment outcomes?



Haberer, JAIDS 2015

Main predictor: Treatment interruptions

- We chose running average approach since it considers more information about the interruptions
- We computed treatment interruptions as the proportion of days when the running average (+/- 4 days) adherence was less than 10%

Other predictor variables

- Baseline of respective biomarker
- Age
- Gender
- Baseline viral load (log)
- Alcohol (AUDIT-C)
- Depression
- Percentage adherence
  - Included in only secondary model
  - (Total MEMS bottle openings*100)/total prescribed doses

Results: Participant characteristics

- Of 282 eligible participants,
  - Female: 70%
  - Median age: 35 years(IQR: 29, 39)
  - Median pre-ART CD4 count: 135 cells/mm^3
  - Median pre-ART log viral load: 5.1

Results: Multivariable regression

	Primary models: Treatment Interruption Effect		**Secondary models:** Treatment Interruption Adjusted for Average Adherence	
Biomarker	**Effect (95% CI)**	**P**	**Effect (95% CI)**	**P**
IL-6	12.4% (3.0, 22.7)	0.009	4.4% (-8.5, 18.9)	0.52
K/T ratio	4.3% (0.6, 8.0)	0.022	6.8% (0.4, 13.6)	0.037
sCD14	3.2% (1.5, 4.9%)	p<0.001	4.7% (1.5, 8.1)	0.004
sCD163	4.7% (1.8, 7.6)	0.001	8.2% (3.4, 13.2)	0.001
HLA-DR+/CD8+	2.6% (0.4, 4.9)	0.023	1.4% (-2.5, 5.4)	0.50
D-dimer	9.8% (1.5, 18.7)	0.020	3.1% (-10.5, 18.6)	0.67

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Results: Effect of percentage adherence

- Percentage adherence no longer significantly associated with biomarkers after adjusting for treatment interruptions

Strengths and Limitations

- Strengths
  - Objectively measured adherence
  - Running average reflects impact of adherence interruptions better than count data
- Limitations
  - Running average not intuitive
  - Potential error in adherence measurement
  - Results applicable to first 6 months as dynamics of adherence beyond 6 months may differ

Conclusions

- Within first 6 months of ART initiation, sustained treatment interruptions are associated with increased levels of biomarkers of immune activation/inflammation
  - Relationship persists for K/T ratio, sCD163 and sCD14 after controlling for percentage adherence
- No evidence seen for an association between percentage adherence and levels of biomarkers after controlling for treatment interruptions

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- Study staff
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Questions, Comments?