vitalant℠
Research Institute

Using Recent Infection Testing Algorithms in Background HIV Incidence Estimation

Eduard Grebe

Vitalant Research Institute, San Francisco, CA
SACEMA, Stellenbosch University, Stellenbosch, South Africa
Eduard Grebe Consulting, Cape Town, South Africa

29.07.2022

Disclosures

I have been paid for consulting services to Sedia Biosciences Corporation and Gilead Sciences.

Background

- Recent Infection Testing Algorithms (RITAs) have been extensively used to estimate HIV incidence cross-sectionally in population-based surveys
  - *their use in PrEP trials to establish 'counterfactual' background HIV incidence rates in lieu of a placebo arm is a novel use without established best practices*

- The use of RITAs in HIV incidence estimation raise numerous technical and methodological issues that impact
  - **accuracy** of incidence estimates (bias)
  - **precision** of incidence estimates
- Changing epidemiological realities, including earlier diagnosis and ART initiation present specific challenges

These issues can be particularly acute in key populations studies, regional/subnational studies and clinical trials

Key considerations to avoid bias in cross-sectional incidence estimates

- Minimising selection bias
  - *do aspects of the protocol, such as screening out individuals who previously tested HIV-positive impact the representivity of the study population?*

- Minimising bias in the key properties of the recency test, i.e.
  - mean duration of recent infection (MDRI) – the average duration of the 'recent' state after HIV infection, while infected for less than a specified time cutoff (T)
  - false-recent rate (FRR) – the proportion of individuals infected for longer than T who nevertheless appear recently infected

- **Epidemiological context impacts both MDRI and FRR, meaning that these parameters are not universal and constant properties of an assay or RITA**
- *Bias in MDRI and FRR estimates result in bias in incidence estimates; the MDRI and FRR themselves impact the precision of incidence estimates*

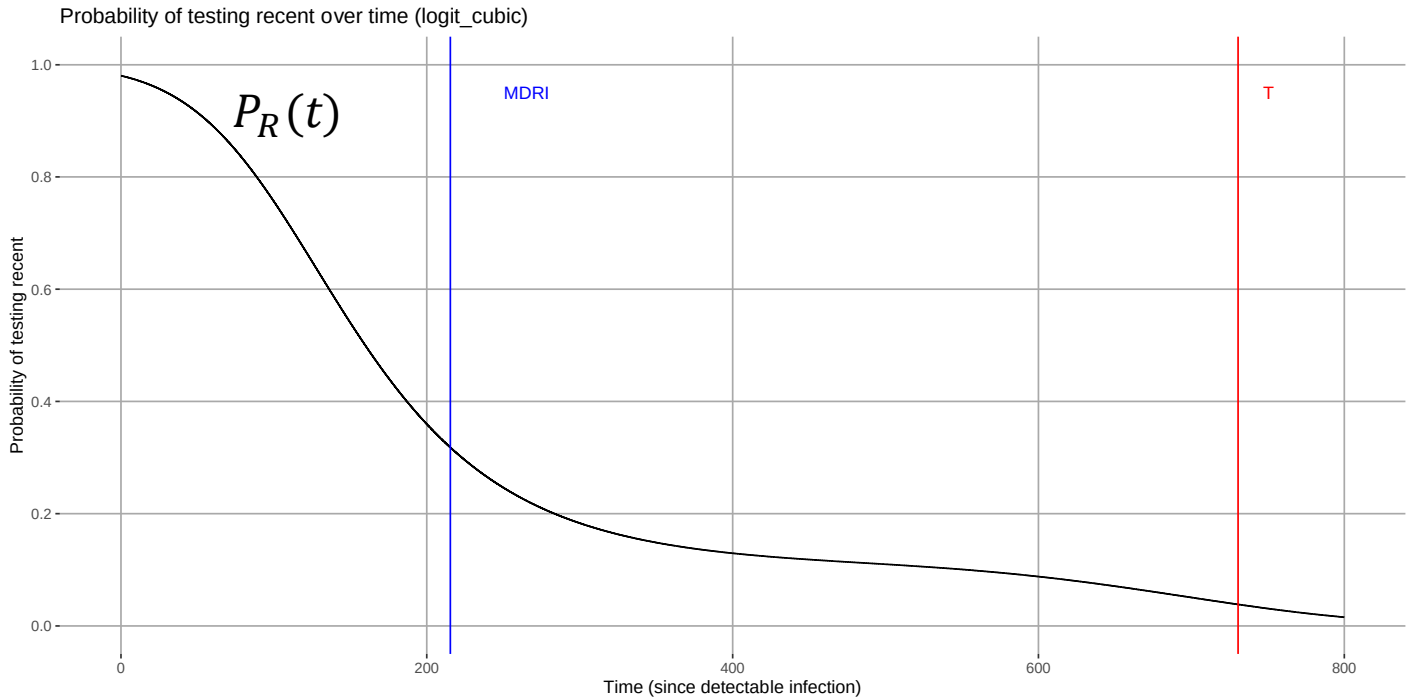
Impact of epidemiological context on the MDRI for a RITA

- The dynamics of immune markers can depend on HIV subtype, meaning that the mix of subtypes in the population of interest should be taken into account
  - *one approach is to take a weighted average of subtype-specific MDRI estimates*

- Increasingly early diagnosis and treatment initiation impacts MDRI
  - diagnosis and/or treatment offers a second 'route' out of the 'recent' state
  - *e.g., a RITA that includes viral load will classify all virally suppressed individuals as long-term, even if the infection is only a few months old, but treatment was initiated early*
  - this phenomenon may be especially pronounced in key populations targeted with frequent testing interventions

Estimating MDRI

fit the probability of recent infection as a function of time since infection using data from seroconverter cohorts (in the absence of ART)



this reflects the biological properties of the recency test

vitalant Research Institute

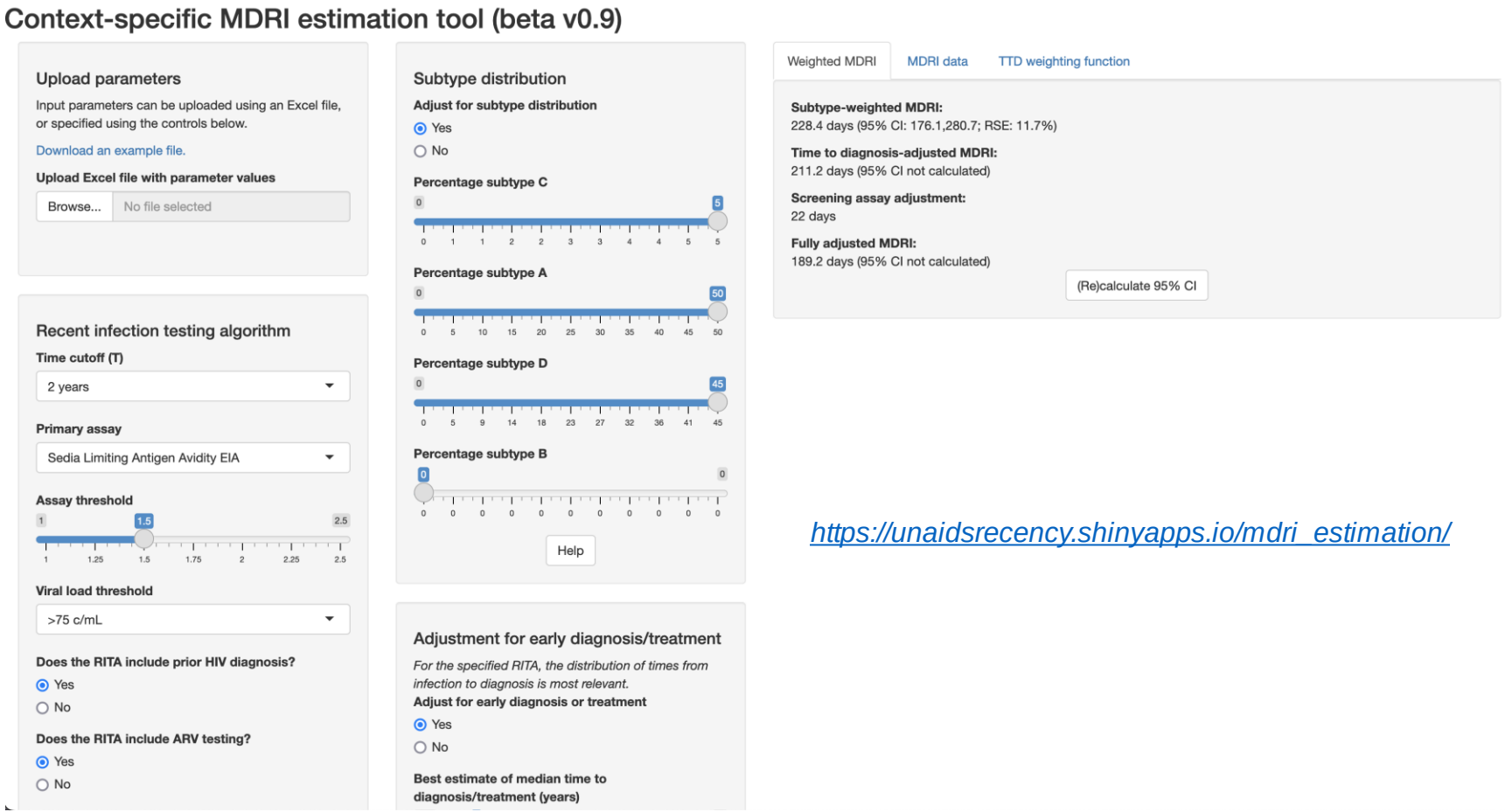
Adjusting MDRI for early diagnosis and treatment

- Weight the $P_R(t)$ curve by a survival function representing 'survival' in the undiagnosed/untreated state
  - *depending on the RITA, diagnosis or treatment initiation may be most relevant*

$$\Omega_T = \int_0^T P_R(t)\ dt$$ ← 'biological' MDRI

$$\Omega'_T = \int_0^T S_u(t)\ P_R(t)\ dt$$ ← 'effective' MDRI

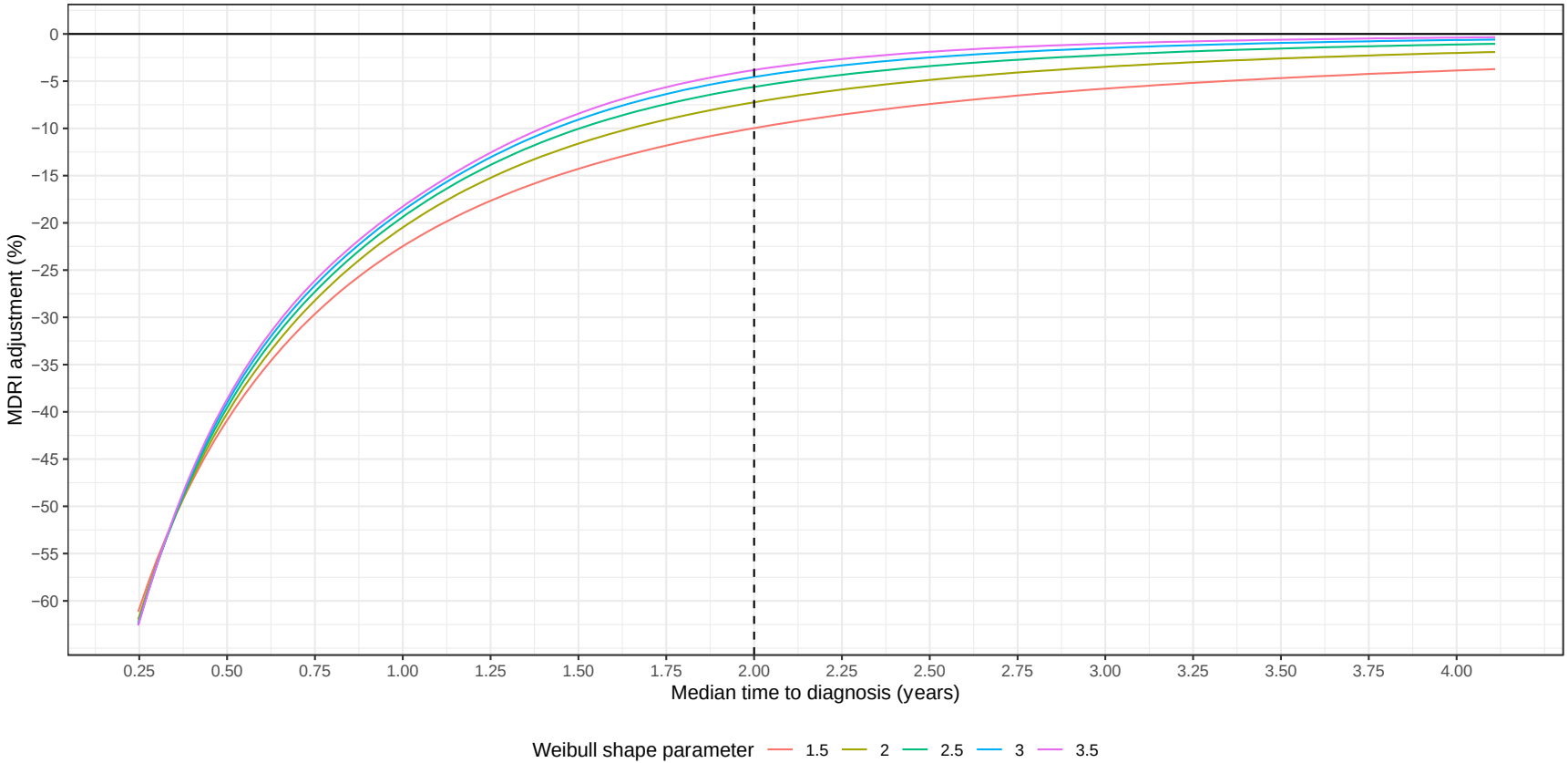
User-friendly tool for MDRI estimation



https://unaidsrecency.shinyapps.io/mdri_estimation/

vitalant Research Institute

Impact of early diagnosis/treatment on ‘effective MDRI’



vitalant Research Institute

Impact of epidemiological context on the FRR for a RITA

- Most recency assays produce falsely recent results in a very high proportion of long-infected individuals on treatment and in ‘elite controllers’
  - *this generally necessitates the inclusion of a viral load threshold and/or ARV detection in a RITA*

- The FRR of a RITA is therefore inherently context-dependent, and his sensitive especially to
  - treatment coverage in the population
  - the distribution of times-since-infection in the untreated population infected for longer than T

Conclusions

- Appropriate MDRI and FRR estimates are crucial for accurate cross-sectional incidence estimation
  - *both in population surveys and in PrEP trials where background HIV incidence serves as the counterfactual*
  - *increasingly, accounting for early diagnosis and treatment is important for avoiding bias in MDRI estimates and consequently incidence estimates*

- Optimisation of RITAs, i.e., maximising MDRI and minimising FRR is critical to ensure optimal precision of incidence estimates
  - *important for the feasibility of PrEP trials by maximising the power and keeping sample size requirements manageable*

Thank you

vitalant℠ Research Institute