Mean Duration of Recent Infection: Frequent Testing Adjustment

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Overview

The R tool implements a method for adjusting the Mean Duration of Recent Infection (MDRI) in the following setting:

- The algorithm for identifying 'recent' infection requires that, in addition to other criteria, viral load is above some cut-off (e.g. 1000 copies per ml).
- There is non-negligible occurrence of viral suppression (defined as a viral load below the cut-off above) from treatment, occurring within time T after detectable infection (where the MDRI is defined as the average time 'recent' within T after detectable infection).

The tool was developed for purposes of the analysis presented in

> **Reshma Kassanjee, Alex Welte, Kennedy Otwombe, Maya Jaffer, Minja Milovanovic, Khuthadzo Hlongwane, Adrian Puren, Naomi Hill, Venice Mbowane, Kristin Dunkle, Rachel Jewkes, Glenda Gray, Fareed Abdullah, and Jenny Coetzee. Persistently high HIV incidence among female sex workers in South Africa found by multiple methods applied to cross-sectional survey data. 2021.**

though encompasses greater flexibility than required in the analysis above, and can be directly used or further adapted for other analyses. Input parameters should be relevant to the setting.

The general framework for incidence estimation, which provides the formal definition of the MDRI, is outlined in

> **Reshma Kassanjee, Thomas A McWalter, Till Bärnighausen, Alex Welte. A new general biomarker-based incidence estimator Epidemiology 2012. 23(5):721-728. doi: 10.1097/EDE.0b013e3182576c07.**

Methods

Framework

Please refer to the articles listed above for background information. Note that 'infection' refers to detectable infection as per the diagnostic algorithm used in the incidence study.

- In the absence of viral suppression from treatment within T after infection, $P_R(t)$ is the probability of returning a 'recent' result (and being alive) at time t after infection, and the 'unadjusted' MDRI is
$$\Omega_T = \int_{t=0}^{t=T} P_R(t)\, dt.$$

- Introducing the possibility of viral suppression from treatment within T after infection, we define $P'_R(t)$ as the probability of returning a 'recent' result at time t after infection, constructed as
$$P'_R(t) = P_R(t) \cdot (1 - P_{VS}(t))$$
where $P_{VS}(t)$ is the probability of being virally suppressed due to treatment at time t after infection, among those alive at time t. The 'adjusted' MDRI is thus
$$\Omega'_T = \int_{t=0}^{t=T} P'_R(t)\, dt.$$

- As a special case for constructing $P_{VS}(t)$, define V as the time after infection that a person becomes virally suppressed (and, if $V < T$, remains virally suppressed until T), and the probability density function for V as $f_V(.)$. For ease of interpretation, we also assume negligible mortality within T after infection. This implies that, for a given realization $V = v$,

$$P'_R(t) = \begin{cases} P_R(t) & if\ t < v \\ 0 & if\ t \geq v \end{cases}$$

and therefore

$$\int_{t=0}^{t=T} P'_R(t)\,dt = \int_{t=0}^{t=\min(v,T)} P_R(t)\,dt.$$

- The adjusted MDRI can therefore be expressed as

$$\Omega'_T = \int_v \left(\int_{t=0}^{t=\min(v,T)} P_R(t)\,dt \right) f_V(v)dv$$

or, splitting the support of V,

$$\Omega'_T = \int_{v=0}^{v=T} \left(\int_{t=0}^{t=v} P_R(t)\,dt \right) f_V(v)dv + P(V > T) \cdot \Omega_T$$

where $P(V > T)$ includes the probability that a person does not become virally suppressed (ever).

Implementation and `tool inputs`

Note that the same unit of time should be used throughout, and that T is specified as **`bigt`**.

- In this tool, the adjusted MDRI Ω'_T is estimated by Monte Carlo integration, based on $N =$ **`nsim`** random draws of V $(v_1, v_2, \ldots, v_N)$:

$$\Omega'_T \approx \frac{1}{N}\left(\sum_{v_i<T} \int_{t=0}^{t=v_i} P_R(t)\,dt + \sum_{v_i \geq T} \Omega_T \right)$$

for sufficiently large N, and where a person i who does not become virally suppressed is included in the set $v_i \geq T$. To assess convergence of the approximation to the value of the integral, a plot of the MDRI approximation after every **`plotsim`** draws of V is produced.

- The time from infection to viral suppression is the sum of two durations

$$V = V_{i2t} + V_{t2v}$$

where
  - V_{i2t} is the time from infection to testing for HIV, and
  - V_{t2v} is the time from testing to viral suppression from treatment.

To sample values of V, the following processes are assumed.

The time from infection to testing (V_{i2t}) is generated by one of five processes:

	Probability	Distribution of V_{i2t}
1. Infrequent testing	**`p.i`**	It is assumed that *after* some fixed test-free time after infection (**`delaytotest.i`**), the time until testing follows an exponential distribution with an average time to testing of **`delta.mean.i`** (i.e. a rate parameter of 1/ `delta.mean.i`), e.g., 1 year.
2. Regular testing	**`p.r`**	V_{i2t} follows a uniform distribution with support 0 to **`delta.fixed.r`** (based on an inter-test interval of `delta.fixed.r`, independent of infection), e.g., 3 months.
3. Frequent testing	**`p.f`**	V_{i2t} follows a uniform distribution with support 0 to some maximum time X, where X is first drawn from

		a uniform distribution with support `delta.min.f` to `delta.max.f` (based on an inter-test interval that varies, and is independent of infection), e.g., 2 to 4 months.
4. Never tests	`p.n`	No testing occurs (and therefore viral suppression from treatment does not occur).
5. Same-day testing	`p.s`	$V_{i2t} = 0$

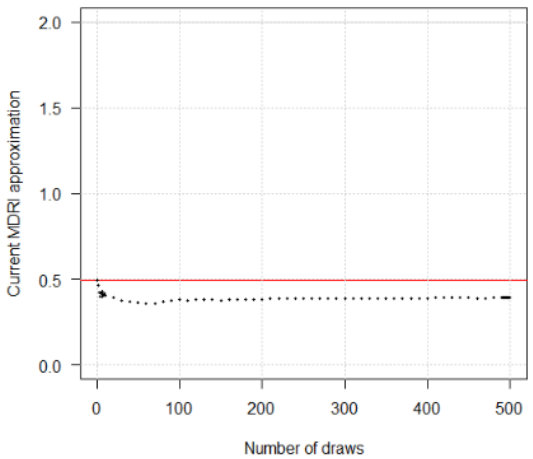
The time from testing to viral suppression (V_{t2v}) is generated by one of two processes:

	Probability	**Distribution of V_{t2v}**
1. Fixed time	`p.vs.fixed`	$V_{t2v} =$ `vs.fixed`
2. Variable time	`p.vs.var`	V_{t2v} is drawn from a Weibull distribution parameterised such that the proportion `vs.p1` of individuals are virally suppressed by time `vs.x1` after testing and proportion `vs.p2` by time `vs.x2`.

- $P_R(t)$ is assumed to have the shape of Weibull cumulative distribution function, specified by a shape and a scale parameter[1]. The shape parameter `mdri.shape` is directly input, and the scale parameter is calculated so that the total area under the curve $P_R(t)$ is `mdri.unadj`, which is equal to Ω_T in the special case that $P_R(t) = 0 \; \forall \; t > T$.

Example

```
out1 <- f.est.adjmdri(bigt = 2 # units of years throughout
                      , mdri.unadj = 183/365.25
                      , mdri.shape = 1
                      , p.vs.fixed = 0
                      , vs.fixed = 3/12
                      , p.vs.var = 1
                      , vs.x1 = 2.5/12, vs.p1 = 0.5
                      , vs.x2 = 6/12, vs.p2 = 0.98
                      , p.i = 0.45
                      , delaytotest.i = 0/12
                      , delta.mean.i = 1
                      , p.r = 0.2
                      , delta.fixed.r = 3/12
                      , p.f = 0
                      , delta.min.f = 3/12
                      , delta.max.f = 6/12
                      , p.n = 0.35
                      , p.s = 0
                      , nsim = 500
                      , plotsim = 10)
```




```
out1$mdri.unadj.rev*365.25 # Unadjusted MDRI = 180 days
out1$mdri.adj*365.25 # Adjusted MDRI = 146 days
out1$mdrired.perc # Percentage reduction (unadjusted to adjusted MDRI) = 19%
```

[1] I.e. $P_R(t) = 1 - exp\left(-\left(\frac{t}{b}\right)^k\right)$ for $t > 0$ where b is the scale parameter and k is the shape parameter.