Viremia copy years and its impact on risk of clinical progression according to shape

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Background

- Viremia copy-years (VCY), a measure of cumulative HIV burden approximated by the area under the patient’s viral load (VL) curve (AVULC), was shown to predict mortality independently of VL and current CD4 count in antiretroviral treatment (ART) experienced patients.
- For a given AUVLC, its shape (e.g. the rectangular with a height of 10,000 copies/ml and base 1 year as opposed to, say, that of a 1,000 copies/ml maintained for 10 years) may provide different indications in terms of patients’ future prognosis.

Aims

- To quantify the possible bias associated with estimating the association between current VY and the risk of morbidity/mortality using standard regression techniques as opposed to a marginal structural (MSM) model with inverse probability weighting (IPW)
- To evaluate whether the association between VY and the risk of morbidity/mortality may vary according to the shape of the AUVLC

Methods

Inclusion Criteria

Individuals in the Icona Foundation Study were included if they started combined ART (i.e., combination of 2 nucleoside reverse transcriptase inhibitors plus a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor) between 1995 and 2006 and had available CD4 count at enrollment, time-varying VL, and time-varying ART history.

Exposure

VL (log scale) was calculated using the trapezoidal rule on the VL log scale using the last VL value carried forward (Figure 1). Participants were classified according to the proportion of AUVLC over the maximum rectangular with base the length of VL follow-up and height the person’s ever observed VL peak under cART. Roughly, a proportion of 100% identifies patients with stable VL trajectory at peak while low percentages people with dips and spikes in VL. The quartiles of this percentage distribution were used to create four distinct exposure groups (A, B, C, D; Figure 2). The association with pre-cART and the 24-week VL value was also evaluated.

Outcomes

i) AIDS or death due to any cause
ii) Severe non-AIDS (SNAE) or death due to any cause

Results

Figure 1. Use of trapezoidal rule to calculate the AUVLC

Figure 2. AUVLC shapes over the first 3 years of ART according to quartile of percentage distribution (one representative person per group)

Table 1. Characteristics of study population at starting cART by type of regimen

Table 2. AUVLC shape CVD diagnosis, n(%) AID diagnosis, n(%) Gender, n(%) Female Male CVD diagnosis, n(%) AID diagnosis, n(%) Gender, n(%) 0 18 36 54 72 90 108 126 144 162 0 18 36 54 72 90 108 126 144 162 0 18 36 54 72 90 108 126 144 162 0 18 36 54 72 90 108 126 144 162

Table 2. HR from fitting standard Cox regression analysis vs. a MSM with IPW

Limitations

- The potential impact of using the last VL carried forward to estimate individuals’ AUVLC is unknown
- It might be argued that VY is not a well-defined ‘intervention’ and therefore a causal link cannot be established
- The use of MSM with IPW does not remove the issue of bias due to unmeasured confounding

Conclusions

- In people receiving ART, VY appears to be a significant predictor of future clinical progression particularly in people showing fairly stable VL trajectories
- Strategies to maximize the chance of viral suppression should be considered for patients with suboptimal viral response even in people with stable low-level detectable viremia