Poster 565

Cumulative Viral Load Predicts All-cause and AIDS-related Mortality After Initiation of ART

Michael Mugavero*, Andrew Westfall, M. John Gill, Michael Saag, Sophie Abgrall, Gerd Fatkenheuer, Peter Reiss, Suzanne Ingle, Margaret May, Jonathan Sterne on behalf of the Antiretroviral Therapy Cohort Collaboration (ART-CC)

Correspondence: mmugavero@uab.edu

Abstract

Background: The prognostic value of cross-sectional viral load (VL) measures for clinical events following ART initiation is well established but the best way to quantify their association with clinical events and death over time is unclear.

Methodology: Treatment-naïve patients starting ART between January 2000 and December 2009 in one of 17 cohorts participating in the ART Cohort Collaboration (ART-CC) were included. Time-updated viremia copy-years (VCY) following ART initiation ("baseline"). VCY estimates the cumulative plasma viral burden based on the area under the VL curve and was calculated daily for each patient. We assumed a lower limit of detection of 500 copies/ml: values <500 were set to 250 for calculation of VCY). Procedures for standardized coding of deaths were adapted from the CoDe protocol. We used Cox models to estimate associations (hazard ratio [HR], 95% CI) of baseline and time-updated viral load, and time-updated VCY, with all-cause, AIDS-related, and non-AIDS-related mortality. All models were adjusted for baseline age, sex, transmission risk group and cohort, and time-updated CD4 count.

Results: Among 33563 patients (mean age 39 years, male 71%, mean baseline CD4 217 cells/μL), a mean 13 viral load measures were available during mean 3.2 years following ART initiation. 1341 patients died, including 503 AIDS-related deaths, 614 non-AIDS-related deaths, and 224 unclassifiable/unknown deaths. All viral load measures predicted all-cause mortality, but time-updated VCY remained strongly predictive when adjusted for the other viral load measures. Similar patterns, with stronger associations, were observed for AIDS-related mortality. Associations with non-AIDS mortality were modest, with little evidence that any of the three VL measures independently predicts non-AIDS mortality.

Table. Hazard ratios (95% CI) for associations of viral load measures with all-cause mortality, after adjusting for other prognostic factors

	Person-years	Deaths	HR (95% CI) for all-cause mortality: Adjusted for other prognostic factors	HR (95% CI) for all-cause mortality: Additionally adjusted for other VL measures*	HR (95% CI) for AIDS-related mortality: Adjusted for other prognostic factors	HR (95% CI) for AIDS-related mortality: Additionally adjusted for other VL measures*
Baseline VL (copies/mL)						
<100,000	51093	506	1	1	1	1
>=100,000	59632	835	1.23 (1.09-1.37)	1.09 (0.95-1.25)	1.21 (1.00-1.46)	0.95 (0.75-1.20)
Time-updated VL (copies/mL)						
<500	83461	738	1	1	1	1
500-9,999	7868	148	1.50 (1.25-1.81)	1.37 (1.13-1.66)	1.58 (1.17-2.14)	1.34 (0.98-1.83)
10,000-100,000	8277	178	1.25 (1.04-1.50)	1.15 (0.95-1.39)	1.37 (1.03-1.82)	1.14 (0.84-1.54)
>100,000	7317	277	1.45 (1.22-1.73)	1.13 (0.92-1.37)	1.53 (1.18-1.98)	0.99 (0.73-1.35)
Time-updated viremia (VC) (copy-years/ml)						
<10,000	47417	494	1	1	1	1
10,000-100,000	49456	611	1.23 (1.08-1.39)	1.14 (0.98-1.33)	1.40 (1.13-1.74)	1.45 (1.12-1.89)
100,000-250,000	8368	196	1.75 (1.45-2.11)	1.56 (1.24-1.96)	2.08 (1.51-2.86)	2.18 (1.46-3.26)
>350,000	1683	96	2.00 (1.52-2.63)	1.74 (1.27-2.39)	3.40 (2.23-5.20)	3.64 (2.17-6.10)

* other VL measures are the other two viral load measures listed in the table

Conclusions: Cumulative plasma viral burden following ART initiation better predicts all-cause and AIDS-related mortality than most recent VL, independent of time-updated CD4 count. None of the VL measures considered was clearly associated with non-AIDS mortality.

Background

- Prognostic value of cross-sectional viral load measures for clinical events following ART initiation is well established
- Recent evidence indicates enhanced prognostic value of cumulative measures of viral load burden[1,2]
- We evaluated the prognostic value of viremia copy-years (VCY), an estimate of cumulative viral load, for all-cause and cause-specific mortality following ART initiation among ART-CC patients while controlling for cross-sectional viral load measures and other covariates

Methods

- ART-CC combines data from ARV naïve patients from 21 cohort studies in Europe and North America
  - 17 Cohorts contributed to this analysis
- Eligibility criteria for this study
  - ART initiation b/t January 2000 and December 2009
- Principal independent variables
  - Cross-sectional viral load measures: baseline prior to ART start, 6-mos on ART, time-updated (most recent)
  - Viremia copy-years: a time-varying measure of cumulative viral load estimated by trapezoidal rule[1,2]
- Outcome measures
  - All-cause, AIDS-related & non-AIDS-related mortality
  - Standardized coding of deaths using adapted CoDe protocol,[3] with adjudication by ART-CC committee
- Statistical analysis
  - Standard survival methods used for all analyses
  - Separate models for each viral load measure for all-cause and cause-specific mortality
  - Combined models including all viral load measures (cross-sectional and VCY) for mortality outcomes
  - Primary models with categorical classification of viral load measures and covariates
  - Sensitivity analyses: continuous viral load measures and survival clock starting 6 mos post-ART initiation
  - Multivariable Cox models adjusted for age, sex, risk factor (IDU, heterosexual, MSM), entry CD4 count, time-updated CD4 count (most recent) and cohort

Results

Table 1. Characteristics of 33,563 ART-CC patients following ART initiation (2000-09) and observed for 106,924 person-years follow-up

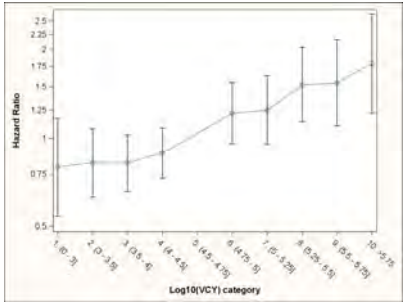
Characteristic	Mean ± SD, N (%), or Person-years
Age (years)	39 ± 10
Male	23,803 (71)
Female	9760 (29)
Men who have sex with men (MSM)	11,576 (34)
Heterosexual sex	15383 (46)
Intravenous drug use	3775 (11)
Other or Unknown	2829 (8)
Baseline CD4 count	217 ± 175
Baseline plasma HIV viral load <100,000c/mL	16,499 (49)
Baseline plasma HIV viral load >100,000 c/mL	17,064 (51)
Plasma HIV viral load 6-months post-ART initiation	
<500 c/mL	23,924 (82)
500-9,999 c/mL	1,951 (7)
10,000-100,000 c/mL	2,127 (7)
>100,000 c/mL	1,175 (4)
Time-updated viral load (most recent)	
<500 c/mL	85,462
500-9,999 c/mL	7,868
10,000-100,000 c/mL	8,277
>100,000 c/mL	5,317
Viremia copy-years	
<10,000 copies*years/mL	47,417
10,000-100,000 copies*years/mL	49,456
100,000-350,000 copies*years/mL	8,368
>350,000 copies*years/mL	1,683
Deaths	
All-cause	1,341 (4)
AIDS-related	503 (1.5)
Non-AIDS related	614 (1.8)
Unknown	224 (0.7)

Table 2. Cox Proportional Hazards models evaluating all-cause, AIDS-related and non-AIDS-related mortality according to cross-sectional and cumulative viral load classifications

	All-cause mortality		AIDS-related deaths		Non-AIDS-related deaths	
Characteristic	Cox models for separate viral load measures HR (95% CI)	Cox models for combined viral load measures HR (95%CI)	Cox models for separate viral load measures HR (95% CI)	Cox models for combined viral load measures HR (95%CI)	Cox models for separate viral load measures HR (95% CI)	Cox models for combined viral load measures HR (95%CI)
Baseline plasma viral load						
<100,000 c/mL	Ref	Ref	Ref	Ref	Ref	Ref
>100,000 c/mL	1.23 (1.09-1.37)	1.08 (0.95-1.25)	1.21 (1.00-1.46)	0.95 (0.75-1.20)	1.27 (1.08-1.51)	1.23 (1.00-1.51)
Time-updated viral load						
<500 c/mL	Ref	Ref	Ref	Ref	Ref	Ref
500-9,999 c/mL	1.50 (1.25-1.81)	1.37 (1.13-1.66)	1.58 (1.17-2.14)	1.34 (0.98-1.83)	1.53 (1.17-2.01)	1.49 (1.12-1.96)
10,000-100,000 c/mL	1.25 (1.04-1.50)	1.15 (0.95-1.39)	1.37 (1.03-1.82)	1.14 (0.84-1.54)	1.09 (0.81-1.45)	1.09 (0.81-1.48)
>100,000 c/mL	1.45 (1.22-1.73)	1.12 (0.92-1.37)	1.53 (1.18-1.98)	0.99 (0.73-1.35)	1.36 (1.02-1.82)	1.20 (0.86-1.66)
HR per category	1.13 (1.07-1.19)	1.04 (0.97-1.11)	1.14 (1.05-1.25)	1.00 (0.90-1.10)	1.10 (1.00-1.20)	1.06 (0.96-1.17)
Viremia copy-years						
<10,000 copies*years/mL	Ref	Ref	Ref	Ref	Ref	Ref
10,000-100,000 copies*years/mL	1.23 (1.08-1.39)	1.14 (0.98-1.33)	1.40 (1.13-1.74)	1.45 (1.12-1.89)	1.14 (0.95-1.37)	0.99 (0.82-1.23)
100,000-350,000 copies*years/mL	1.75 (1.45-2.11)	1.56 (1.24-1.96)	2.08 (1.51-2.86)	2.18 (1.46-3.26)	1.41 (1.07-1.87)	1.15 (0.83-1.60)
>350,000 copies*years/mL	2.00 (1.52-2.63)	1.74 (1.27-2.39)	3.40 (2.23-5.20)	3.64 (2.17-6.10)	1.42 (0.91-2.21)	1.09 (0.67-1.80)
HR per category	1.28 (1.19-1.38)	1.22 (1.10-1.34)	1.47 (1.30-1.68)	1.52 (1.29-1.80)	1.15 (1.03-1.29)	1.05 (0.91-1.21)

Cox proportional hazards models for separate and combined viral load measures controlling for age, sex, risk transmission group, baseline and time-varying CD4 count, and cohort
Hazard ratios (HR) reported per $\log_{10}$ viral load for baseline plasma viral load and time-varying viral load (most recent), and as $\log_{10}$ copy*years for viremia copy-years.

Figure. Hazards of all-cause mortality according to viremia copy-years (VCY) deciles controlling for cross-sectional viral load measures and covariates



Conclusions

- When evaluated independently of one another, and along with covariates, baseline and time-updated viral load, and viremia copy-years were associated with all-cause, AIDS-related and non-AIDS related mortality
- When viral load measures were evaluated together, with covariates, viremia copy-years retained prognostic value for all-cause and AIDS-related mortality, but not for non-AIDS deaths, and baseline and time-updated viral load had marked attenuation of hazard ratios
- Cumulative viral load measures such as viremia copy-years may have independent and enhanced prognostic value for mortality relative to cross-sectional measures

Citations

1 Cole et al. *Am J Epidemiology* 2010;171:198-205 (PMCID:PMC2878100)
2 Mugavero et al. *Clin Infect Dis* 2011;53:927-35 (PMCID:PMC3189165)
3 Gill MJ et al. *Clin Infect Dis* 2010;50:1387-96 (PMCID: PMC3157754)

ART-CC Contributing Cohorts

UAB 1917 Clinic Cohort, **Aquitaine**, **ATHENA** (AIDS Therapy Evaluation Project Netherlands), **BCCfE-HIV** (British Columbia Centre for Excellence in HIV/AIDS), **CHORUS**, **EuroSIDA**, **Frankfurt**: Klinikum der JW Goethe-Universität Frankfurt), **FHDH** (French Hospital Database on HIV), **ICONA** (Italian Cohort of Antiretroviral-Naive Patients), **Köln/Bonn**: Departments of Internal Medicine at University of Cologne and Bonn, Germany, **PISCIS** (Proyecto para la informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA), **Royal Free**: Ian Charleson Centre at the Royal Free Hospital London, UK, **South Alberta**: Southern Alberta Clinic, Canada, **Swiss HIV Cohort Study**, **VACS**: Observational cohort study of HIV-positive and matched HIV-negative veterans based on the Veterans Health Administration, USA, **Vancouver**: St. Paul's Hospital in Vancouver, Canada, **Washington**: University of Washington Harborview Medical Center, USA

ART-CC Steering Committee

Jordi Casabona (PISCIS), Geneviève Chêne (Aquitaine), Dominique Costagliola (FHDH), François Dabis (Aquitaine), Antonella D'Arminio Monforte (ICONA), Frank de Wolf (ATHENA), Matthias Egger (SHCS), Gerd Fatkenheuer (Köln/Bonn), John Gill (South Alberta Clinic), Robert Hogg (BCCfE-HIV), Amy Justice (VACS), Mari Kitahata (Washington), Bruno Ledergerber (SHCS), Amanda Mocroft (EuroSIDA), Andrew Phillips (EuroSIDA), Peter Reiss (ATHENA), Michael Saag (UAB 1917 Clinic Cohort), Caroline Sabin (Royal Free), Schlomo Staszewski (Frankfurt), Ian Weller

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