Improved Longitudinal Adherence to ART in Virally Suppressed PWH Reduces Development of Serious Non-AIDS Events

657

Roland van Rensburg[1], Mercy Rop[1], Daniel Mashishi[1], Innocent Maposa[1], Katherine Tassiopoulos[2], Kunling Wu[2], Jose Castillo-Mancilla[3], **Netanya Utay**[4], Kristine Erlandson[3], Eric Decloedt[1]

[1]Stellenbosch University, Cape Town, South Africa, [2]Harvard T. H. Chan School of Public Health, Boston, MA, United States, [3]University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [4]University of Texas Southwestern Medical Center, Dallas, TX, United States

BACKGROUND

- **Serious non-AIDS events (SNAEs)** are steadily increasing, in particular cardiovascular disease (CVD) and death.
- People with HIV (PWH) on antiretroviral therapy (ART) develop SNAEs earlier and with fewer traditional risk factors compared to their counterparts without HIV, **despite viral suppression**.
- Suboptimal adherence in the setting of viral suppression has been associated with increased inflammation, immune activation, coagulopathy, progression of coronary disease, and death.
- Risk models using cardiovascular biomarkers showed that **improved ART adherence beyond what is needed for viral suppression reduces SNAE risk**.

Primary aim: To determine the time-varying effect of self-reported ART adherence and HIV RNA levels on SNAE incidence (CVD and death) in PWH who are virally suppressed at baseline.

METHODS

- Analysis of de-identified data of participants from the prospective observational **Advancing Clinical Therapeutics Globally (ACTG) A5001 and A5322 studies.**
- Baseline was defined as the time at first viral suppression to <200 copies/mL after treatment initiation. Transient viral blips were allowed.
- Adherence was assessed using the periodically administered **ACTG self-report questionnaire:**
  - Percentage adherence was calculated as the proportion of prescribed doses taken over the preceding four days for each visit.
- Data were analyzed **using inverse probability of censoring weights (IPCW) modelling** to address potential bias from dependent censoring and estimate the effect of time-varying ART adherence on time to first SNAE.
- Multivariable associations were investigated for the development of 1) first SNAE, and 2) all SNAEs over the duration of follow-up.

In suppressed PWH, each 10% increase in ART adherence decreased the hazard of serious non-AIDS events by 9%

RESULTS

- We included **2,940** unique participants (**Table 1**) over 24 years (1998 to 2022), with a median follow-up of 6.2 years (IQR 3.1–10.5).
- Median HIV RNA was **<50 copies/mL** (IQR <40 to <50) for the duration of follow-up.
- **260 SNAE events occurred**: 126 deaths, and 134 non-fatal CVD-related events.
- Derived mean self-reported ART adherence was 97.1% (95% CI 96.9–97.2) captured over 2.2 reports per year (IQR 1.8–3.0).

Table 1: Selected baseline characteristics

Age (years), median (IQR)	39.4 (32.0 – 46.6)
Sex (male), n (%)	2,422 (82%)
Race/Ethnicity, n (%)	
White non-Hispanic	1,347 (46%)
Black non-Hispanic	857 (29%)
Hispanic (Regardless of race)	648 (22%)
Other/Missing	88 (3%)
Body Mass Index (kg/m²), median (IQR)	25.3 (22.6 – 28.5)
ART class (backbone regimen), n (%)	
Non-nucleoside reverse transcriptase inhibitors	1,243 (42.3%)
Protease inhibitors	1,218 (41.4%)
Integrase strand transfer inhibitors	349 (11.8%)
Other	130 (4.4%)
Comorbidities (yes), n (%)	1,618 (55%)
Smoking status (current), n (%)	948 (32%)

- **Adherence level was significantly associated with both first SNAE and all SNAEs** over the duration of follow-up (**Figure 1**).
  - **The primary outcome showed a reduction in the hazard of first SNAE of 9% for each 10% increase in adherence** (aHR 0.991, 95% CI 0.983-0.999).
- The inverse association remained when restricting the analysis to those remaining <50 copies/mL over the full follow-up period.

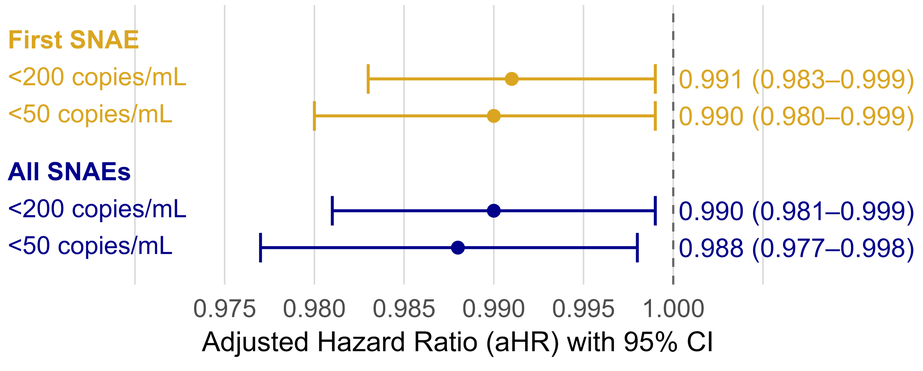


Figure 1: Adjusted hazard (aHR) ratios with 95% confidence intervals (CI) for SNAE development. The dashed vertical line represents the null value. Horizontal bars indicate 95% CIs, and points represent adjusted point estimates. aHR<1 indicates reduced risk of SNAEs.

- In the multivariable regression analysis, **age** and **HIV RNA level** showed a significant positive association with first SNAE development:
  - Age – aHR 1.020 (95% CI 1.003-1.038) for each year increase.
  - HIV RNA – aHR 3.886 (95% CI 3.049-4.953) for each $\log_{10}$ copies/mL increase.
- **Non-current smoking was protective**, compared to current smokers:
  - Never smoked – aHR 0.308 (95% CI 0.216-0.440)
  - Former smoker – aHR 0.406 (95% CI 0.283-0.581)

CONCLUSIONS

- **Higher ART adherence reduces SNAE risk even in virally suppressed PWH.**
- Globally, optimal **ART adherence remains challenging**, and enhanced efforts are needed for continued adherence support despite achieving viral suppression to improve long-term health outcomes.

ADDITIONAL KEY INFORMATION

Secondary analysis:

- **Highest viremia and baseline protease inhibitor use** were not independently associated with the risk of first and all SNAE development, but adherence and smoking history remained predictors.

AUTHOR CONTACT INFORMATION:

Roland van Rensburg
rvr@sun.ac.za

Acknowledgements:
The ACTG provided the data.
Merga Belina performed some of the initial statistical work.

PLAIN LANGUAGE SUMMARY:
Taking ART more regularly helps to prevent cardiovascular disease and death, even when virally suppressed.