Value of viremia copy years in deciding optimal timing of ART initiation in adults with HIV

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ABSTRACT

Background: Time updated VL levels and CD4 counts are routinely used to monitor HIV positive adults but fail to capture cumulative HIV exposure. Viremia copy years (VCY) is such a measure and has been shown to be predictive of AIDS/death, although it is unclear of its use in deciding when to start ART. We aimed to assess the impact of initiating vs. deferring ART on risk of AIDS/death by levels of VCY both independent of and within two CD4 strata, <350 and ≥350 cells/mm^3.

Methodology: Using CASCADE data on HIV seroconverters, we created a series of nested cohorts corresponding to consecutive months starting month 5 post seroconversion (SC) for individuals ≥16 years at SC after 1997, had ≥1 VL measured 4-12 months post SC, were ART naïve and AIDS free prior to end of baseline month. Time to AIDS/death was compared in those initiating vs. deferring ART in the baseline month using Cox models adjusted for time independent factors: country, sex, risk group, SC year; and time dependent factors prior to the baseline month: age, time since last VL, and current CD4, VCY and VL (excluding the first 4 months post SC) and mean number of previous CD4/VL measurements/year. Robust variance was used to adjust for individuals contributing ≥1 baseline visit. We repeated analyses using CD4 strata <500 and ≥500 cells/mm^3.

Results: Of 6497 individuals contributing ≥1 baseline month, 3089 (48%) initiated ART and 293 (5%) acquired AIDS/died. Median (IQR) CD4 at ART initiation was 322 (249, 419) cells/mm3. Pooling CD4 strata, hazard ratios (HR) of AIDS/death associated with initiating vs. deferring ART reduced as VCY increased, suggesting a stronger benefit of ART in those with higher VCY. Trends by VCY were different when stratifying by CD4; in patients with CD4<350 cells/mm^3, there was an overall reduction in the HR of AIDS/death in all VCY groups (all HR < 1) with no evidence that this benefit varied by VCY (p=0.78). At CD4 ≥ 350 there was a trend for increasing benefit of initiation with increasing VCY, with the largest benefit seen in the VCY ≥ 100,000 c/mL group (HR, 95% CI= 0.56, 0.35-0.90); no evidence of benefit if VCY was < 20,000 c/mL. Results were qualitatively similar for CD4 strata ≥ 500 cells/mm^3.

Conclusions: Although we cannot rule out the possibility of unmeasured confounding, it appears that limiting the cumulative HIV burden to < 100,000 VCY in individuals with CD4 ≥ 350 cells/mm^3 through ART reduces the hazard of clinical outcomes by 44%.

Table: Estimated HR (95% CI) for the benefit of initiating vs. deferring ART by VCY strata

VCY Strata	CD4<350	het p	CD4≥350	het p	Pooling CD4	het p
VCY < 10,000	0.55 (0.19, 1.60)	0.78	1.49 (0.79, 2.81)	0.16	1.27 (0.74, 2.17)	0.001
VCY [10,000-20,000)	0.63 (0.27, 1.47)		1.18 (0.55, 2.57)		1.10 (0.62, 1.95)	
VCY [20,000-50,000)	0.35 (0.15, 0.80)		0.65 (0.34, 1.22)		0.51 (0.31, 0.85)	
VCY [50,000-100,000)	0.29 (0.11, 0.79)		0.81 (0.43, 1.51)		0.49 (0.29, 0.85)	
VCY ≥100,000	0.39 (0.27, 0.59)		0.56 (0.35, 0.90)		0.37 (0.27, 0.50)	

INTRODUCTION

Time updated viral load is one factor used to tailor first line ART regimes, gauge antiretroviral therapy (ART) failure and assess the risk of HIV transmission, but updated viral loads fail to capture individuals' cumulative exposure to HIV replication. Viremia copy years (VCY) is a cumulative measure of viral burden where 1000 viremia copy years/mL is the equivalent of having a viral load of 1000 copies/mL for an entire year. VCY is a prognostic marker of disease progression in adults on and off ART independent of time updated CD4 and viral load measurements. This suggests that cumulative HIV burden increases the risk of developing clinical events through mechanisms other than immunodeficiency. Given that on-going viral replication is associated with disease progression, it is important to determine whether ART initiation prior to the accrual of viremia copy-years (even at high CD4 levels) would improve clinical outcomes.

METHODS

Using 2011 CASCADE data of individuals with well estimated dates of HIV seroconversion, we created a sequence of 'trials' in which individuals were classified as initiating or deferring ART. We restricted our study to adults (≥ 16 years old) in European cohorts seroconverting >1996 with at least one HIV RNA measured between 4 and 12 months post seroconversion. We created a series of nested cohorts corresponding to consecutive months starting at 5 months post seroconversion, where each month represented a new 'trial'. Individuals were eligible for entry in each 'trial' until they started ART, acquired AIDS, died, or there was a lapse of >1 year without a laboratory measurement, and were followed–up until they were lost to follow-up, acquired AIDS or died. VCY were calculated using the trapezoid rule. Pooling across 'trials', we used Cox models to estimate hazard ratios (HR) for time from 'trial' entry to AIDS/death for those initiating vs. deferring ART by levels of VCY pooling CD4 cell count strata and separating CD4 cell count strata; < 350 vs. ≥ 350 cells/mm^3. We adjusted for country of care, sex, HIV transmission risk group, seroconversion year, age, time since last HIV-RNA measurement, current CD4, current VCY, current HIV RNA and mean number of previous laboratory measurements per year. Time dependent factors were considered if they occurred prior to the 'trial' baseline month to ensure they were measured before the decision to initiate or defer ART in the current 'trial'. Most individuals contributed to more than one 'trial', so we used a robust variance estimator to account for within-person correlation. In a sensitivity analysis, we repeated the above analysis using CD4 strata <500 and ≥500 cells/mm^3.

RESULTS

6497 individuals contributed ≥1 baseline 'trial'; 3089 (48%) initiated ART and 293 (5%) acquired AIDS/died. Individuals who initiated ART typically had much lower CD4 cell counts and higher RNA values than those who deferred ART.

Table 1: Characteristics for individuals who initiated or deferred ART by levels of viremia copy years

	VCY < 10k		VCY 10-20k		VCY 20-50k		VCY 50-100k		VCY ≥100k	
	Initiated ART	**Deferred ART**	**Initiated ART**	**Deferred ART**	**Initiated ART**	**Deferred ART**	**Initiated ART**	**Deferred ART**	**Initiated ART**	**Deferred ART**
Sub-cohort observations N	373	35,962	265	16,378	592	28,046	515	22,142	1,345	32,982
Follow-up, median (IQR) person years	2.8 (1.2, 6.1)	3.0 (1.4, 5.4)	2.9 (1.2, 5.5)	3.0 (1.4, 5.2)	2.9 (1.2, 5.9)	2.9 (1.4, 5.0)	2.6 (1.1, 4.9)	2.7 (1.3, 4.8)	2.7 (1.3, 4.8)	2.7 (1.2, 4.6)
Male N (%)	196 (53%)	27,742 (77%)	198 (75%)	13,695 (84%)	463 (78%)	24,148 (86%)	441 (86%)	19,423 (88%)	1,214 (90%)	30,264 (92%)
MSW N (%)	188 (51%)	10,727 (30%)	90 (34%)	3,651 (22%)	178 (30%)	5,484 (20%)	125 (24%)	4,069 (18%)	247 (18%)	5,182 (16%)
Seroconversion age	30 (25, 37)	33 (27, 39)	33 (27, 40)	33 (28, 40)	33 (28, 41)	33 (27, 39)	33 (27, 41)	33 (28, 40)	35 (29, 42)	34 (28, 40)
CD4 median (IQR)	370 (269, 550)	630 (480, 822)	350 (268, 446)	545 (428, 705)	337 (259, 447)	517 (410, 661)	330 (259, 419)	489 (386, 624)	300 (231, 375)	460 (362, 583)
HIV-RNA median (IQR)	3.7 (2.9, 4.1)	3.4 (2.7, 3.9)	4.2 (3.8, 4.6)	4.1 (3.7, 4.4)	4.6 (4.0, 4.9)	4.3 (3.9, 4.6)	4.8 (4.2, 5.1)	4.5 (4.2, 4.8)	5.1 (4.6, 5.5)	4.9 (4.5, 5.2)

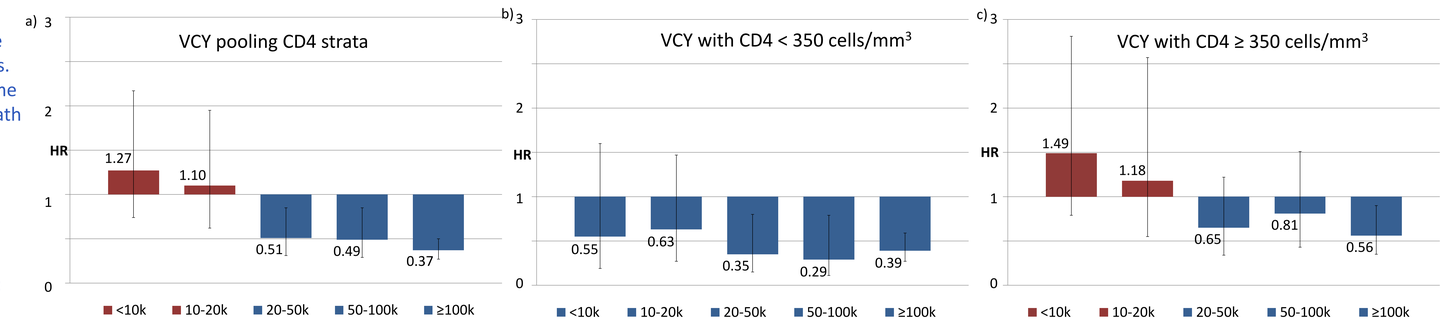


Figure 1: Adjusted hazard ratios for the effect of initiation vs. deferring ART on time from SC to AIDS/death by a) viremia copy years pooling CD4 stratum, b) viremia copy years with CD4<350 cells/mm^3 and c) viremia copy years with CD4≥350 cells/mm^3

Pooling CD4 strata, hazard ratios for the effect of initiating ART on time from seroconversion to AIDS/death decreased as VCY year increased, with a 63% reduced risk of AIDS/death for those initiating ART when VCY exceeded 100,000. At CD4<350 cells/mm^3, there was an overall reduction in the risk of AIDS/death in all VCY groups (all HR < 1) for those initiating vs. deferring ART with no evidence that this benefit varied by VCY (p=0.78). At CD4 ≥ 350 there was a trend for increasing benefit of initiation vs. deferral with increasing VCY, with the largest benefit seen in the VCY ≥ 100,000 c/mL group (HR, 95% CI= 0.56, 0.35-0.90, p(heterogeneity) = 0.16). Results were qualitatively similar for CD4 strata ≥ 500 cells/mm^3.

CONCLUSION

Although we cannot rule out the possibility of unmeasured confounding, it appears that limiting the cumulative HIV burden to < 100,000 VCY in individuals with CD4 ≥ 350 cells/mm3 through ART reduces the hazard of clinical outcomes by 44% (10%-65%).

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SEVENTH FRAMEWORK PROGRAMME