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When to start antiretroviral therapy in HIV positive persons aged over 50 years

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Background

- The TEMPRANO and START randomized controlled trials have shown that early initiation of combined antiretroviral therapy (ART) reduces the risk of serious AIDS and non-AIDS events in HIV-positive individuals
- Since the individuals included in the RCT were relatively young and the number of deaths was low, it is unknown whether early initiation reduces mortality in older HIV-positive individuals
- Earlier ART initiation may decrease mortality associated with non-AIDS comorbidities for which older individuals are at increased risk
- Some of these benefits might be offset by 'polypharmacy', i.e. taking a large number of different medicines, that can make adherence to ART more difficult and can increase the risk of side effects and drug interactions

Objective

To estimate the risk of all-cause, AIDS-related and non-AIDS related mortality under several ART initiation strategies in individuals aged 50-70 years in high-income countries, and to compare these risks with those in younger individuals

Methods

Study population

- The HIV-CAUSAL Collaboration is a consortium of prospective cohort studies from 8 countries in Europe and the Americas
- All cohorts record routinely collected data in clinical practice
- We included individuals who met the following inclusion criteria:
  - aged between 50 and 70 years at enrollment
  - enrolled in the cohort after January 1, 2000
  - at least one CD4 count and one HIV-RNA measured within 3 months of each other
  - ART-naïve and AIDS-free
- Follow-up started at baseline, defined as the date when all criteria were met, and ended at earliest date of death, 12 months after the most recent laboratory measurement, or cohort-specific administrative censoring
- To interpret these results, the same analyses were conducted on individuals in age groups 18-34 and 35-49 years at enrolment.

Table 1. Characteristics of the included individuals

At baseline	Included patients, N	12088
	Males, %	85%
	HIV diagnosis after 2004, %	65%
	Median [IQR] age, years	55 [52,60]
	Median [IQR] CD4 count, cells/mm^3	314 [160,490]
At ART initiation	ART initiators, N (%)	9996 (83%)
	Median [IQR] CD4 count , cells/mm	258 [164,350]
	CD4≥500 cells/mm^3 at ART initiation	1128 (11%)
Outcomes	Deaths (all-cause), N	1333
	Death (non-AIDS related), N	498
	Death (AIDS related), N	394

ART initiation strategies

We compared three ART initiation strategies:

1. Immediate universal treatment – ART initiation within 3 months of baseline, regardless of the CD4 count
2. ART initiation within 3 months of a CD4 count <**500** cells/mm^3 or an AIDS diagnosis
3. ART initiation within 3 months of a CD4 count <**350** cells/mm^3 or an AIDS diagnosis

Outcomes

- All cause mortality
- AIDS-related mortality
- Non-AIDS related mortality

For each outcome at 7 years we computed:

- Absolute risk (ie, cumulative incidence)
- Risk difference
- Difference in restricted mean survival time

Statistical analyses

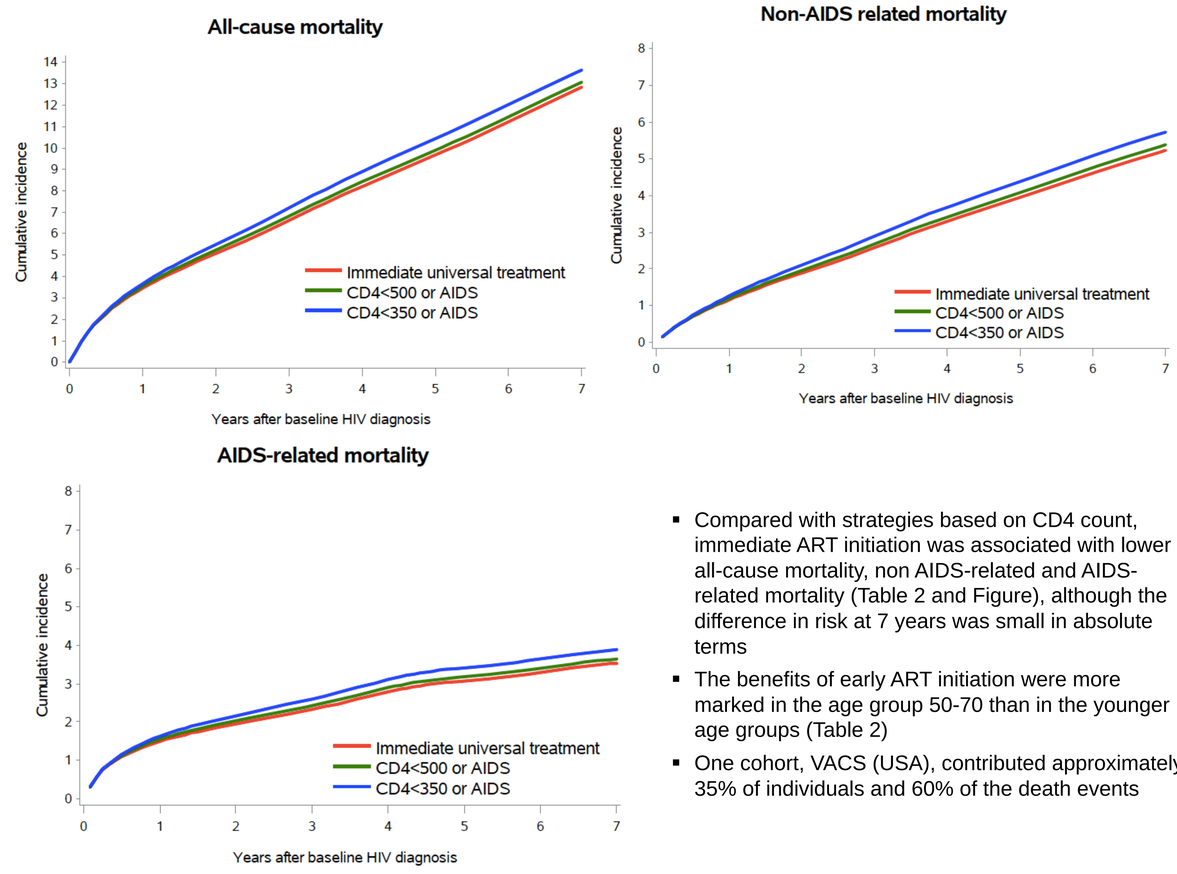
- We used the parametric g-formula, an extension of standardization, to adjust our estimates for the following measured baseline and time-varying confounders:
  - Baseline confounders: sex, transmission group, geographical origin, cohort, CD4 count, HIV-RNA, calendar period at baseline
  - Time-varying confounders affected by previous treatment: CD4 cell count, HIV-RNA and AIDS
- The g-formula assumptions are : i) no residual confounding and ii) correct model specification

Table 2. Seven year risk of all-cause mortality by ART initiation strategy and age group

	7-year risk, (95% CI)	Risk difference (95% CI)	Difference in restricted mean survival, months (95% CI)
Age ≥ 50 years (N=12,088)			
Immediate universal initiation	12.8 (12.3, 13.8)	0 (Ref.)	0 (Ref.)
<500 cells/mm^3 or AIDS	13.1 (12.6, 14.1)	0.24 (0.16,0.36)	-0.16 (-0.21,-0.12)
<350 cells/mm^3 or AIDS	13.7 (13.3, 14.6)	0.82 (0.54,1.04)	-0.47 (-0.56,-0.36)
Age 35-49 years N=38,187			
Immediate universal initiation	4.9 (4.7, 5.2)	0 (Ref.)	0 (Ref.)
<500 cells/mm^3 or AIDS	5.0 (4.8, 5.2)	0.05 (0.00,0.08)	-0.03 (-0.05,-0.01)
<350 cells/mm^3 or AIDS	5.1 (4.9, 5.4)	0.21 (0.06,0.26)	-0.11 (-0.15,-0.05)
Age 18-34 years (N=40,138)			
Immediate universal initiation	2.0 (1.8,2.2)	0 (Ref.)	0 (Ref.)
<500 cells/mm^3 or AIDS	2.0 (1.8,2.1)	-0.05 (-0.09,0.00)	0.03 (0.00,0.05)
<350 cells/mm^3 or AIDS	1.9 (1.8,2.2)	-0.07 (-0.15,0.04)	0.05 (-0.01,0.09)

Results

Table 2. Plots of cumulative incidence of mortality in individuals with age 50-70 years at baseline



- Compared with strategies based on CD4 count, immediate ART initiation was associated with lower all-cause mortality, non AIDS-related and AIDS-related mortality (Table 2 and Figure), although the difference in risk at 7 years was small in absolute terms
- The benefits of early ART initiation were more marked in the age group 50-70 than in the younger age groups (Table 2)
- One cohort, VACS (USA), contributed approximately 35% of individuals and 60% of the death events

Interpretation

- We found that compared with CD4 count based ART initiation strategies, immediate initiation is associated with lower risk of all-cause mortality, non AIDS related mortality and AIDS-related mortality in AIDS free individuals with age 50-70 years. This suggests that overall early initiation is beneficial in increasing survival in older HIV positive patients.
- Although small in magnitude, the absolute survival benefit of early initiation is greater for older individuals than for younger age groups. This suggests that early ART initiation should be prioritized in older patients.
- The overall 5-year risk of mortality in the START trial was 0.5% and 0.9% for immediate initiation and initiation with CD4<350 or AIDS, respectively. This study complements the results of START by providing the estimates of mortality risk in patients with age 50-70 years at 5 years (9.7% and 10.4%, respectively) and at 7 years (12.8% and 13.7%, respectively).

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