Delayed Initiation of Antiretroviral Therapy is Not Associated With Increases in Virologic Failure

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Introduction

Viral load is the most important marker of initial and sustained response to antiretroviral therapy (ART). Virologic suppression reduces mortality and HIV disease progression.

Randomized clinical trial data has demonstrated that early ART initiation (CD4 count ≤350 cells/mm^3) confers a mortality advantage. It is important to understand whether this finding is in any way related to differences in rates of virologic suppression.

Purpose

1. To determine using randomized clinical trial data whether delaying ART until CD4 count ≤200 cells/mm^3 or subjects develop of an AIDS defining condition will affect virologic outcomes at 2 years.
2. To identify predictors of virologic failure using multivariate logistic regression modelling

Methods

- Prospective study of HIV-infected ART-naïve non-pregnant adults conducted at the GHESKIO Center in Port-au-Prince, Haiti.
- 816 subjects were randomized to early (CD4 count ≤350 cells/mm^3) or delayed ART initiation (CD4 count ≤200 cells/mm^3 or development of an AIDS defining condition) between August 2005 and June 2008.
- A validated 9-item food security questionnaire was administered at ART initiation.
- Following ART initiation all subjects were seen in follow-up at 1, 2, 3, 6, 12, 18 and 24 months. During these visits ART adherence was assessed using 3 day recall and any report of a missed dose was considered suboptimal adherence.
- All analyses were performed using stata 13 software (StataCorps, TX).

Figure 1: **Screening, randomization and follow-up**

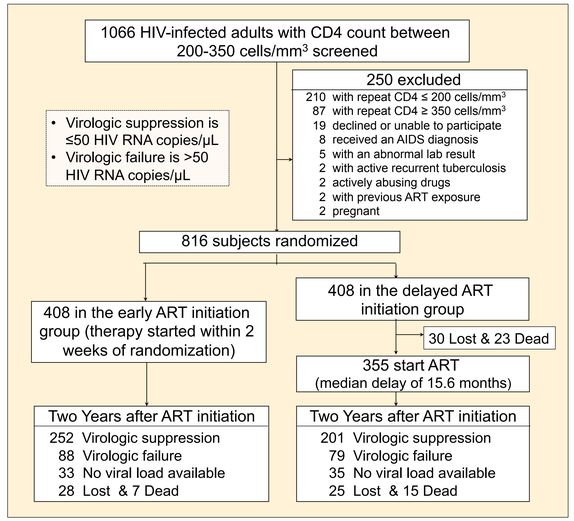


Table 1: **Baseline Characteristics at ART initiation**

	Early ART initiation (N=408)	Delayed ART initiation (N=355)	p-value
Median age (IQR)	39 (33-46)	41 (34-47)	0.207
Female	241 (59.1%)	198 (55.8%)	0.359
Marital status			0.494
Married	79 (19.4%)	63 (17.8%)	
Unmarried/ widowed	329 (80.6%)	292 (82.2%)	
Literate	276 (67.5%)	256 (72.1%)	0.181
Annual income <US $100	259 (63.5%)	219 (61.7%)	0.610
HIV Clinical Stage			**<0.001**
Stage I	137 (33.6%)	64 (18.0%)	
Stage II	193 (47.3%)	171 (48.2%)	
Stage III	78 (19.1%)	113 (31.8%)	
Stage IV	0 (0.00%)	7 (1.97%)	
Median CD4 count (IQR)	274 (241.5-309)	221 (170-280)	**<0.001**
Median viral load (IQR)	110,000 (34,000-275,000)	78,000 (29,000-210,000)	0.73
Active tuberculosis	28 (6.9%)	17 (4.8%)	0.225

IQR denotes interquartile range

Table 2: **Predictors of Virologic Failure (>50 HIV RNA copies/µL) Two Years After ART Initiation**

	Univariate	Multivariate Model 1	Multivariate Model 2
	Odds Ratio (95% CI, p-value)	**Odds Ratio (95% CI, p-value)**	**Odds Ratio (95% CI, p-value)**
Early ART initiation group	0.89 (0.62-1.27; 0.515)	0.97 (0.66-1.41; 0.867)	*Excluded*
Age at ART initiation	0.97 (0.96-0.99; **0.008**)	0.98 (0.96-0.99; **0.031**)	0.98 (0.96-0.99; **0.014**)
Female	1.14 (0.79-1.63; 0.48)	*Excluded*	*Excluded*
Marital status			
Married	1 (reference)	1 (reference)	*Excluded*
Unmarried/ widowed	1.79 (1.09-2.97; **0.022**)	1.60 (0.95-2.70; 0.077)	*Excluded*
Literate	0.88 (0.60-1.29; 0.508)	*Excluded*	*Excluded*
Annual income <US$100	1.57 (1.07-2.29; **0.020**)	1.55 (1.05-2.30; **0.029**)	1.56 (1.06-2.31; **0.026**)
Food Security Score			
0 to 3	1 (reference)	*Excluded*	*Excluded*
4 to 6	1.46 (0.73-2.91; 0.283)	*Excluded*	*Excluded*
5 to 9	1.49 (0.97-2.29; 0.072)	*Excluded*	*Excluded*
HIV Clinical stage at ART initiation			
Stage I	1 (reference)	*Excluded*	*Excluded*
Stage II	1.08 (0.70-1.65; 0.739)	*Excluded*	*Excluded*
Stage III or IV	1.07 (0.65-1.76; 0.782)	*Excluded*	*Excluded*
Tuberculosis at ART initiation	2.25 (1.12-4.55; **0.023**)	1.84 (0.87-3.90; 0.111)	*Excluded*
Suboptimal ART adherence	1.91 (1.33-2.74; **<0.001**)	1.79 (1.23-2.61; **0.002**)	1.81 (1.25-2.63, **0.002**)
Number of visits	0.77 (0.66-0.89; **0.001**)	0.69 (0.57-0.84; **<0.001**)	0.68 (0.57-0.82; **<0.001**)

Results

- Baseline characteristics in the early and delayed ART initiation groups were similar at randomization (data not shown).
- 355 subjects (87%) in the delayed group started therapy with a median delay of 15.6 months.
- At ART initiation, the delayed group had lower CD4 counts and more advanced HIV (p-value <0.001).
- After starting therapy, virologic outcomes at 2 years in the early and delayed groups are similar.
- Predictors of virologic failure are younger age (p-value 0.014), annual income <US $100 (p-value 0.026), missed visits (p-value <0.001) and sub-optimal adherence (p-value 0.002).

Conclusions

Delaying ART initiation resulted in significant pre-ART attrition, interim progression of HIV disease and greater food insecurity. In spite of this, virologic outcomes did not differ when compared to the early ART initiation group.

Besides age, all of the identified predictors of virologic failure (annual income <US $100, missed visits and suboptimal ART adherence) are potentially modifiable.

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