Association of pregnancy post-ART initiation with retention in care, AIDS, death and immune recovery

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Introduction

- HIV-infection is a major cause of maternal mortality in sub-Saharan Africa.
- We hypothesized that pregnancy after antiretroviral therapy (ART) initiation may impact health outcomes among HIV-infected women.
- The objectives of this study are to estimate the risk of becoming loss to follow-up (LTFU), AIDS progress or dying and determine whether pregnancy has an impact on the long-term CD4 cells gain among women becoming pregnant post-ART initiation in West-Africa.

Methods

This retrospective cohort analysis was conducted within the IeDEA West Africa collaboration. (http://www.iedea-hiv.org)

- All HIV-infected women aged <50 years, starting ART for their own health at 13 clinical sites in 9 West-African countries over a 10-year period were eligible.

Survival model:

- All women starting ART while pregnant or with an AIDS diagnosis were excluded. The effect of pregnancy (time dependent variable) on LTFU, progression to AIDS and death 48 months after ART initiation was estimated by adjusted Cox regression models.

Linear mixed model:

- The mean gain of CD4 cells in the first 24 months following ART initiation was estimated in multivariable linear mixed model accounting for countries heterogeneity and regardless of AIDS status at ART initiation.

Survival analysis

- Accounted for 12,851 HIV-infected women on ART, of which 864 (6.7%) reported at least one pregnancy at M48 post-ART initiation **(table 1)**.
- Among women with pregnancy (n=864) and no pregnancy (n=11,987), 15.2% and 12.7% progressed to AIDS or death and 8.3% and 24.8% were LTFU at M48, respectively.

Table 1. Baseline characteristics of eligible women for survival analysis (n=12,851). IeDEA West-African Collaboration.

Variables	Pregnant women (n=1,102)	Not pregnant women (n=11,749)	Total (n=12,851)	p-value
Median age in years (IQR*)	29.5 (26.5;32.8)	33.4 (28.8;39.2)	32.9 (28.5;38.6)	<0.0001**
Median CD4 count in cells/µl (IQR)	199 (122;307)	189 (105;285)	190 (106;287)	0.0011**
CD4 count in categories (%):				0.0116£
<50 cells/µl	78 (7.1)	1,003 (8.5)	1,081 (8.4)	
50-99 cells/µl	81 (7.4)	1,010 (8.6)	1,091 (8.5)	
100-199 cells/µl	263 (23.9)	2,574 (21.9)	2,837 (22.1)	
200-349 cells/µl	268 (24.3)	2,717 (23.1)	2,985 (23.2)	
>349 cells/µl	153 (13.9)	1,275 (10.9)	1,428 (11.1)	
Missing	259 (23.5)	3,170 (27.0)	3,429 (26.7)	
Median hemoglobin in g/dl (IQR)	10.5 (9.4;11.5)	10.5 (9.2;11.6)	10.5 (9.2;11.6)	0.2416**
Hemoglobin in categories (%):				0.0046£
<7.5 g/dl	30 (2.7)	419 (3.6)	449 (3.5)	
7.5-10 g/dl	210 (19.1)	2,071 (17.6)	1,311 (10.2)	
10-12 g/dl	343 (31.1)	2,742 (23.3)	3,085 (24.0)	
≥12 g/dl	117 (10.6)	1,194 (10.2)	2,281 (17.8)	
Missing	402 (36.5)	5,323 (45.3)	5,725 (44.6)	
First ART regimen (%)				<0.0001£
2NRTIs†+ nevirapine	910 (82.6)	8,241 (70.1)	9,151 (71.2)	
2NRTIs+efavirenz	101 (9.2)	2,477 (21.1)	2,578 (20.1)	
2NRTIs+PI†	61 (5.5)	726 (6.2)	787 (6.1)	
3NRTIs	13 (1.2)	170 (1.5)	183 (1.4)	
Others	17 (1.5)	135 (1.2)	152 (1.2)	
Deaths 5 years after ART (%)	16 (1.5)	273 (2.3)	289 (2.3)	0.0620£

After adjustment on baseline CD4 count; age, Body Mass Index and hemoglobin at ART initiation; initial ART regimen; calendar year at ART start and country, pregnancy reduced the risk of AIDS or death (aHR=0.61; 95%CI: 0.40-0.92) and the risk of becoming LTFU at M48 (aHR=0.71; 95%CI: 0.55-0.92). **(Table 2)**

Table 2. Effect of pregnancy (time dependent variable) on loss to follow-up, AIDS progression and death at 48 months after ART initiation, estimated by adjusted Cox regression model (N=12,851)

Outcomes	Adjusted Hazard Ratio†	CI 95%	p-value
Model 1: Restricted risk period *			
AIDS or death	0.75	[0.48;1.17]	0.1990
Lost to follow-up	0.72	[0.54;0.96]	0.0245
Both	0.81	[0.63;1.03]	0.0875
Model 2: Unrestricted risk period **			
AIDS or death	0.61	[0.40;0.92]	0.0193
Lost to follow-up	0.71	[0.55;0.92]	0.0088
Both	0.72	[0.57;0.90]	0.0040

* Restricted risk period: risk period starts at pregnancy reporting date and goes until 15 months after pregnancy detection.
** Unrestricted risk period: risk period starts at pregnancy reporting date and goes endpoint date (e.g. maximum 48 months after ART initiation).

Linear mixed model

- Overall 20,408 HIV-infected women accounted for the second analysis, among them 1,561 (6.2%) reported at least one pregnancy at M24 post-ART. **(table 3)**

Table 3. Baseline characteristics of eligible women for linear mixed models (n=20,408)

Variables	Pregnant women (n=1,615)	Not pregnant women (n=18,793)	Total (n=20,408)	p-value
Median age in years (IQR*)	29.5 (26.3;32.7)	33.4 (28.8;39.4)	33.0 (28.5;38.8)	<0.0001**
Median CD4 count in cells/µl (IQR)	189 (105;282)	169 (82;264)	170 (84;266)	<0.0001**
Clinical stage (%):				<0.0001£
A,B/I,II	1,146 (71.0)	11,920 (63.4)	13,066 (64.0)	
C/III,IV	302 (18.7)	4,597 (24.5)	4,899 (24.0)	
missing	167 (10.3)	2,276 (12.1)	2,443 (12.0)	
Median hemoglobin in g/dl (IQR)	10.2 (9.0;11.4)	10.1 (8.8;11.3)	10.1 (8.9;11.3)	0.0073**
First ART regimen (%)				<0.0001£
2NRTIs†+nevirapine	1,207 (74.7)	12,019 (64.0)	13,226 (64.8)	
2NRTIs+efavirenz	266 (16.5)	5,097 (27.1)	5,363 (26.3)	
2NRTIs+PI†	97 (6.0)	1,225 (6.5)	1,322 (6.5)	
3NRTIs	14 (0.9)	218 (1.2)	232 (1.1)	
Others	31 (1.9)	234 (1.3)	265 (1.3)	

- The mean gain of CD4 cells between ART initiation and M24 was significantly higher among women who experienced a pregnancy in the first six months following ART initiation, compared to those with no pregnancy **(Table 4)**.

Table 4. Post-ART pregnancy and CD4 count cells gain in the first 24 months following ART initiation estimated by adjusted* linear mixed models (n=20,408).

	Mean CD4 count slope between ART initiation and M6 (cells/µl gained per month)		Mean CD4 count slope between M6 and M24 (cells/µl gained per month)		Mean CD4 count gain between ART initiation and M24 (cells/µl)*	
	Adjusted estimate** (95%CI)	p-value	Adjusted estimate** (95%CI)	p-value	Adjusted estimate** 95%CI)	p-value
No pregnancy	+29.9 (26.6;33.3)	Ref	+5.6 (2.5;8.7)	Ref	+280 (227;333)	Ref
Pregnancy in the first 6 months after ART initiation	+35.5 (31.6;39.4)	<0.0001	+5.7 (2.5;8.8)	0.7839	+315 (260;370)	<0.0001
Pregnancy beyond 6 months after ART initiation	-	-	+5.7 (2.5;8.8)	0.7839	+281 (227;335)	0.7839

* Linear mixed models adjusted for CD4 count at baseline; age, Body Mass Index (BMI) and hemoglobin at ART initiation; initial ART regimen; calendar year of starting ART and country.
** For the reference group: baseline CD4 count <50 cells/µl, 16-24 years old women treated with nevirapine, starting ART in 2011, with BMI=18.5;25kg/m², baseline hemoglobin<7.5g/dl and followed-up in Ivory Cost.

Conclusion

- In West-Africa, pregnancy after post-ART initiation is a common event and reduces by roughly one-third both the risk of AIDS disease progression or death and the risk of LTFU at 48 months after ART initiation.
- Moreover, it appeared from this dataset that though pregnancy post-ART initiation had no deleterious impact on immune response, CD4 cells gain is more optimal when pregnancy occurs in the early post-ART period but these findings are yet not conclusive.
- It is suspected that an important number of pregnancies may have gone undetected and a significant proportion of LTFU might be dead. Sensitivity analyses will be conducted to address these two last issues.
- Further research is needed to fully understand the impact of pregnancy post-ART initiation on HIV-infected women health.