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Poorer control of viral load in patients infected perinatally versus during adulthood

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Objective

Combined antiretroviral treatment (cART) allows most HIV-infected infants to reach adulthood.

We studied whether the current virological response to cART was similar in patients infected perinatally or infected during adulthood with a similar duration of infection and treatment history.

Methods

Sources of data
Five French national prospective ANRS cohorts of HIV patients:
- **Perinatally infected**, followed as children (ANRS EPF cohort) or as adults (ANRS COVERTE cohort)
- **Infected during adulthood** ≥ 15 years of age (ANRS PRIMO, SEROCO, and COPANA cohorts), included at primary HIV infection or diagnosis

Study Population
- **Patients :**
  - diagnosed < 2 years old if perinatally infected patients, or at the time of seroconversion if infected during adulthood
  - ≥ 1 viral load measurement ≥ 2012
  - on uninterrupted cART for ≥ 6 months at last evaluation

Outcome
- **Detectable viral load at the most recent visit in the cohort between 2012 and 2017:** HIV RNA ≥ 50 copies/ml

Main exposure
- **Period at HIV infection:** perinatal versus adulthood

Strategy of analysis
- **Stratified on time elapsed since HIV infection (= age in patients perinatally infected,** categorized in 5 classes, corresponding to evolution periods from childhood to adulthood: [2-5 years], [6-12 years], [13-17 years],[18-24 years], ≥ 25 years

→ The appropriateness of the age classes was validated by the relationship between virologic response and age of perinatally infected patients, studied using spline functions. We used these classes for duration of HIV infection in both exposure groups.

- **Univariate and multivariate logistic regression,** with viral load response as binary dependent variable → adjustment for gender, birth country, and treatment history

The analysis was performed on (Table 1):
- **347 perinatally infected patients: 56.2% female, 6.9% from sub-Saharan Africa**
- **1515 patients infected in adulthood: 13.8% male, 6.3% from sub-Saharan Africa**

Table 1. Therapeutic history according to the period of acquiring HIV infection, stratified on duration of HIV infection at time of last VL evaluation under ART between 2012 and 2017)

Duration of HIV infection	2 – 5 years			6-12 years			13-17 years			18-24 years			25-32 years		
	Perinatally N=22	Adulthood N=472	p-value	Perinatally N=66	Adulthood N=703	p-value	Perinatally N=83	Adulthood N=210	p-value	Perinatally N=84	Adulthood N=82	p-value	Perinatally N=92	Adulthood N=48	p-value
FIRST ART															
Time since HIV infection, months (median,IQR)	4.0 (2.2 - 12.6)	1.4 (1.1 - 2.4)	**	3.2 (1.1 - 11.8)	15.5 (1.9 - 36.9)	****	2.8 (1.4 - 6.8)	1.9 (1.2 - 24.7)		8.2 (2.5 - 21.6)	1.6 (1.2 - 3.8)	****	17.8 (6 - 51.8)	80.6 (47.6 - 98.5)	****
Calendar period of initiation (median,IQR)	2012 (10 - 13)	2013 (12 - 14)	**	2007 (05 - 08)	2009 (07 - 10)	****	1999 (97 - 02)	2002 (00 - 04)	****	1994 (93 - 96)	1997 (96 - 98)	****	1991 (90 - 95)	1995 (92 - 97)	***
AT LAST EVALUATION															
Duration of treatment, years (median,IQR)	4.6 (3.6 - 5.4)	3.5 (2.5 - 4.4)	**	9.4 (7.4 - 10.7)	7 (5.8 - 9)	****	16.2 (14.1 - 17.1)	14 (12.9 - 15.4)	****	22.2 (20 - 23.2)	19.1 (18.4 - 20)	****	25.5 (21.6 - 26.7)	20.9 (19.1 - 24.2	****
Number of different ART regimen (median,IQR)	3 (1 - 3)	2 (1 - 3)		3 (2 - 4)	3 (2 - 4)		5 (3 - 7)	5 (3 - 7)		9 (7 - 12)	5 (4 - 8)	****	10 (6 - 14)	9 (6 - 15)	
Year of initiation of last ART regimen, %(n)															
≤ 2006	0 (0)	0 (0)		9.1 (6)	2.7 (19)	**	10.8 (9)	8.1 (17)		0 (0)	17.1 (14)	***	1.1 (1)	14.6 (7)	***
2007-2013	45.5 (10)	34.1 (161)		60.6 (40)	53.9 (379)		51.8 (43)	54.8 (115)		47.6 (40)	36.6 (30)		33.7 (31)	47.9 (23)	
2014-2017	54.5 (12)	65.9 (311)		30.3 (20)	43.4 (305)		37.3 (31)	37.1 (78)		52.4 (44)	46.3 (38)		65.2 (60)	37.5 (18)	
Last ART regimen, %(n)															
Integrase inhibitor, or Entry inhibitor (± NRTI)	13.6 (3)	41.9 (198)	***	10.6 (7)	32.7 (230)	****	14.5 (12)	29 (61)	****	34.5 (29)	30.5 (25)	*	60.9 (56)	33.3 (16)	****
PI and NNRTI (± NRTI)	0 (0)	0.2 (1)		3 (2)	1.3 (9)		3.6 (3)	1.4 (3)		3.6 (3)	2.4 (2)		2.2 (2)	0 (0)	
PI (± NRTI)	63.6 (14)	20.6 (97)		59.1 (39)	18.1 (127)		51.8 (43)	14.3 (30)		35.7 (30)	18.3 (15)		23.9 (22)	18.8 (9)	
NNRTI (± NRTI)	22.7 (5)	36.4 (172)		27.3 (18)	46.9 (330)		27.7 (23)	54.3 (114)		25 (21)	43.9 (36)		13 (12)	27.1 (13)	
Only NRTI	0 (0)	0.8 (4)		0 (0)	1 (7)		2.4 (2)	1 (2)		1.2 (1)	4.9 (4)		0 (0)	20.8 (10)	
Last viral load measurement, %(n)															
2012-2013	15.8 (3)	5.7 (27)	**	12.5 (8)	7.3 (51)	*	29.6 (24)	5.2 (11)	****	6.1 (5)	8.5 (7)		1.1 (1)	8.3 (4)	*
2014-2015	26.3 (5)	10.6 (50)		18.8 (12)	11.4 (80)		27.2 (22)	13.3 (28)		17.1 (14)	8.5 (7)		12.5 (11)	20.8 (10)	
2016-2017	57.9 (11)	83.7 (395)		68.8 (44)	81.4 (572)		43.2 (35)	81.4 (171)		76.8 (63)	82.9 (68)		86.4 (76)	70.8 (34)	

*p≤0.05 ** p≤0.01 ***p≤0.001 **** p≤0.0001*
PI: Protease inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor , NRTI: Nucleoside reverse transcriptase inhibitor

Results

- **Detectable viral load VL ≥ 50 cp/mL (Figure 1)**
  - ✓ **< 5% in patients infected in adulthood** whatever the time since HIV infection
  - ✓ **ranging from 12.1% to 38.3% in patients infected perinatally**
  - ✓ **associated** with oldest calendar periods at last measurement, type of current regimen, in both groups
  - ✓ **not associated** with the calendar period and the type of first ART, in both groups

- **Detectable viral load VL ≥ 50 cp/mL significantly higher in patients infected perinatally than in patients infected during adulthood**
  - ✓ **In univariate analysis, in all the age strata,** with highest differences observed in [2-5], [13-17] and [18-24] categories.
  - ✓ **In multivariate analysis, after adjustment** for gender, country of birth, time to first ART, number of different ART regimen received, type of last ART regimen, and calendar period of the last viral load measurement, in the [2-5], [13-17] and [18-24] categories.
  - ✓ Similar results in analysis restricted to patients with no change in CART regimen within the last 6 months

Conclusion

- **Non optimal virological control currently remains very high in treated young patients diagnosed before 2 years of age, in a context of free care with very effective ART drugs** leading to very low proportion of detectable viral load in patients infected during adulthood with similar duration of treatment, even > 20 years.

- The highest proportion of viral load > 50 cp/ml concerns:
  - **youngest children (2-5 year),** possibly due to the limited ability of once-daily and single-tablet regimens and palatable formulations for infants and young children
  - **adolescent and young adult,** probably related to specific adherence issues during these transitional periods of life, especially in patients living with chronic disease

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Figure 1. Percentage of detectable viral load (VL ≥ 50 copies/ml) at last evaluation in treated patient (2012-2017)

