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THE EARLIER CART IS INITIATED DURING PHI, THE MORE INTRACELLULAR HIV-DNA DECREASES

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Background

• During the earliest weeks of primary HIV infection (PHI), HIV establishes a reservoir mainly in CD4+ T cell subsets.
• cART initiation during PHI yields better immune restoration and larger decrease in cell-associated HIV-DNA than initiation during the chronic phase (1,2).
• In macaques, the reduction of SIV-DNA reservoir under cART was greater when initiated between 7 and 10 days than between 10 and 42 days after infection (3).

Our objective was to model the short- and long-term decay of the cell-associated HIV-DNA blood reservoir in patients initiating cART during PHI and to assess the impact of the earliness of cART initiation on HIV-DNA level decay.

Methods

Patients: We included 327 patients enrolled during primary HIV-1 infection in the multicenter ANRS PRIMO cohort, treated within the month following enrollment and achieving sustained virological response (HIV-RNA <50 cp/mL) as from Month 6, accounting for 1,305 HIV-DNA quantifications.

Virological procedures: Cell-associated HIV-DNA was quantified by real-time HIV-1 DNA PCR. Multiple replicates were performed to reach a detection limit of up to 5 copies/10^6 leucocytes.

Statistical analyses: The decay of cell-associated HIV-DNA over time while on successful cART was modeled with a 3-slope linear mixed-effects model. Different time points of slope changes were tested and chosen by minimization of the Akaike information criterion.

Overview

Studies comparing patients treated during CHI to patients treated during PHI found a faster decay and a more important reduction in the cell-associated HIV-DNA level among those treated during PHI (1,2).
Here, we assessed the impact of the earliness of cART initiated during PHI, in a large cohort of patients followed until cART discontinuation or end of virological response.
This study showed that the earlier cART is initiated after HIV infection during PHI, the faster cell-associated HIV-DNA level decreases during the first eight months, and that HIV-DNA decay is not blunted after several years of treatment when the treatment is initiated during PHI.

Results

Table 1. Baseline characteristics of the study population (N=327)

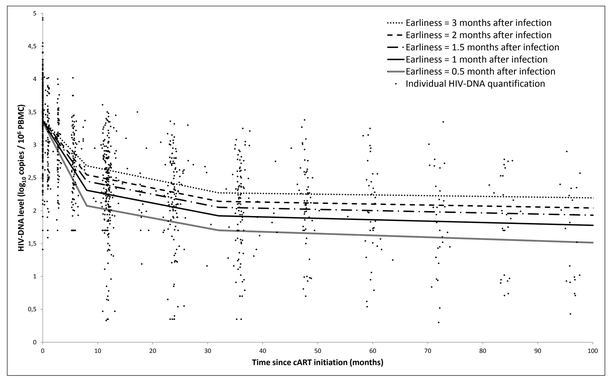
Characteristics	Distribution	
Men, *(%)*	82.9	
Median age at inclusion, years *(IQR)*	36	(29-43)
Symptomatic at primary HIV infection, *(%)*	91.4	
Median year of inclusion *(IQR)*	2002	(1999-2005)
Median time-lag between infection and cART initiation, days *(IQR)*	41	(33-54)
Median HIV-DNA level at inclusion, log_{10}copies /10^6 PBMC *(IQR)*	3.46	(3.04-3.80)
Median HIV-RNA PVL at inclusion, log_{10}copies /mL *(IQR)*	5.3	(4.8-5.9)
Median CD4 level at inclusion, cells/mm^3 *(IQR)*	450	(329-602)
Median duration of follow-up in the cohort, years *(IQR)*	8.5	(4.3-12.5)
First line cART including a protease inhibitor, *(%)*	81.6	
First line cART including a boosted protease inhibitor, *%*	47.4	
Median duration of uninterrupted cART, years *(IQR)*	2.3	(1.0-4.6)
Median number of HIV-DNA measurements during cART *(IQR)*	3	(2-4)

Table 2. Estimates of the slopes of decay of cell-associated HIV-DNA level (log_{10} copies/10^6 PBMC/month) under uninterrupted cART with virological response (<50 copies/ml from 6 months), according to cART initiation earliness from HIV infection

	Unadjusted estimates	p value	Adjusted estimates*	p value
Intercept				
cART initiation 1 month after infection	3.36		-	
+ 1 log_{10} month of cART initiation earliness	*+0.039*	*0.8203*	-	-
First slope (0-8 months)				
cART initiation 1 month after infection	-0.131	<0.0001	-0.131	<0.0001
+ 1 log_{10} month of cART initiation earliness	*+0.093*	*<0.0001*	*+0.093*	*<0.0001*
Second slope (8-32 months)				
cART initiation 1 month after infection	-0.016	<0.0001	-0.016	<0.0001
+ 1 log_{10} month of cART initiation earliness	*-0.0020*	*0.8466*	*-0.0020*	*0.8532*
Third slope (>32 months)				
cART initiation 1 month after infection	-0.0021	0.0007	-0.0020	0.0019
+ 1 log_{10} month of cART initiation earliness	*+0.0021*	*0.2299*	*+0.0019*	*0.3007*

* 3-slope linear mixed-effects model adjusted for sex, age at inclusion (≤ or > 40 years), and calendar period (1996-2002 vs. 2003-2013)

Figure. Slopes of decay of cell-associated HIV-DNA under uninterrupted cART with successful virological response (<50 copies/ml from 6 months) predicted by a mixed-effects model, according to cART initiation earliness from HIV infection



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Findings

The impact of the earliness of cART initiation was statistically significant on the first slope of HIV-DNA decrease ($p<0.0001$): **the earlier cART was initiated after HIV infection, the faster the HIV-DNA level decreased during the first 8 months of cART**: -0.171, -0.131, and -0.068 log_{10} copies/10^6 PBMC /month when cART was initiated 15 days, 1 month, and 3 months after infection, respectively.
The HIV-DNA level continued to decrease significantly under cART after Month 8 but with a lower steepness, and the second and third slopes were similar regardless of cART initiation earliness.
The predicted mean HIV-DNA level achieved after 5 years of uninterrupted successful cART was:

- 1.62 log_{10} copies/10^6 PBMC when cART was initiated 15 days after infection,
- and 2.24 log_{10} copies/10^6 PBMC when cART was initiated 3 months after infection ($p=0.0006$).

Similar impact of cART earliness on HIV-DNA decrease was found when using the number of antibodies on western blot assay performed at cART initiation as a measure of precocity.

Conclusions

This study showed that:
• the earlier cART is initiated after HIV infection during PHI, the faster cell-associated HIV-DNA level decreases during the first eight months,
• HIV-DNA decay is not blunted after several years of treatment when the treatment is initiated during PHI.

It provides strong arguments in favor of cART initiation at the earliest possible time point after HIV infection, and thus in favor of early screening.
In some patients (in whom cART was initiated very early during PHI, and who did not discontinue it for several years), cART reduction or interruption could be considered if cell-associated HIV-DNA load is low enough, opening possible perspectives for functional remission.

cART: combined antiretroviral therapy - IQR: interquartile range - PBMC: peripheral mononuclear blood cells - PVL: plasma viral load