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Rapid decay of HIV persistence markers in acutely ART-treated individuals in Peru

Marta Massanella[1,2], Rachel Bender Ignacio[3,4], Javier R. Lama[5], Sayan Dasgupta[3], Amélie Pagliuzza[1], Ricardo Alfaro[5], Jessica Rios[5], Carmela Ganoza[5], Delia Pinto-Santini[3], Trupti Gilada[3], Ann Duerr[3,4], Nicolas Chomont[1,2] on behalf of the MERLIN study group.

[1] Centre de Recherche du CHUM, Montréal, Canada, [2] Département de microbiologie, infectiologie et immunologie, Université de Montréal, Canada,
[3] Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4] University of Washington, Seattle, WA, USA
[5] Asociación Civil Impacta Salud y Educación, Lima, Peru

Marta Massanella
marta.massanella.luna@umontreal.ca
Nicolas Chomont
nicolas.chomont@umontreal.ca

BACKGROUND

► Early ART initiation confers several benefits on HIV-related morbidity and clinical outcomes and can lead to natural control of HIV replication upon ART interruption in a subset of individuals.

► Because initiation of ART during acute infection may not currently be a viable public health strategy, it is important to investigate whether early ART initiation can promote durable decrease in the HIV reservoir.

OBJECTIVE

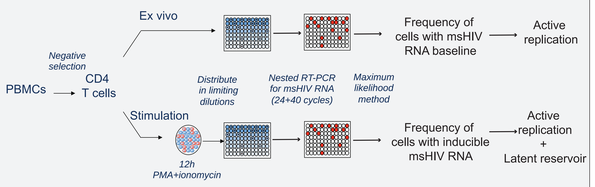
To evaluate how timing of ART initiation impacts the size of the HIV reservoir during early infection in a subset of the Sabes study, a randomized clinical trial in Peru.

METHODS

► Study cohort: HIV-infected MSM or transgender (n=30) were selected from the Sabes study in Peru and categorized according to the estimated date of infection (EDDI) in acute (EDDI <30 days, n=14) and recent (31-86 days from EDDI, n=16) HIV infection. At enrollment, participants were randomized to receive ART immediately (acute immediate, n=8 and recent immediate, n=12) or after 24 weeks deferral (n=10).

► Total and integrated HIV DNA: Total (LTR-gag) and integrated (LTR-Alu) HIV DNA were quantified in CD4 T cells by real-time PCR.

► Inducible HIV reservoir was measured by *Tat/rev* Induced Limiting Dilution Assay (TILDA). We enriched CD4⁺ T cells from PBMCs and quantified the frequency of cells that spontaneously produce HIV multiply-spliced RNA (ex vivo) or after stimulation with PMA/ionomycin for 12h in the presence of antiretroviral drugs.



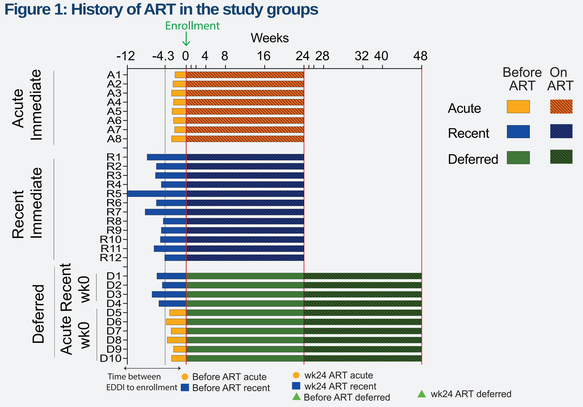
► Statistical analysis: continuous variables were expressed as the median (interquartile ranges) and compared using non-parametric tests (Mann-Whitney). Discrete variables were described as percentages and compared using Fisher exact test.

Table 1. Characteristics of immediate and deferred groups at enroll-

	Immediate n=20	Deferred n=10	*p-value*
Sex, male n (%)	20 (100)	10 (100)	*ns*
Age, years	27 [21-30]	22 [19-28]	*ns*
Acutely infected (EDDI<30 days), n(%)	8 (40)	6 (60)	*ns*
Recently infected (31-86 days from EDDI), n(%)	12 (60)	4 (40)	*ns*
Time from EDDI to enrollment (days)	35 [19-44]	28 [22-40]	*ns*
CD4 T cell counts, cells/µl	448 [248-576]	479 [365-590]	*ns*
CD8 T cell counts, cells/µl	851 [510-1380]	663 [453-1270]	*ns*
Ratio CD4/CD8	0.6 [0.2-1]	0.8 [0.4-1.1]	*ns*
log10VL (cp/mL)	6.3 [5.7-7.6]	6.0 [5.6-7.1]	*ns*

RESULTS

Figure 1: History of ART in the study groups



Before ART initiation

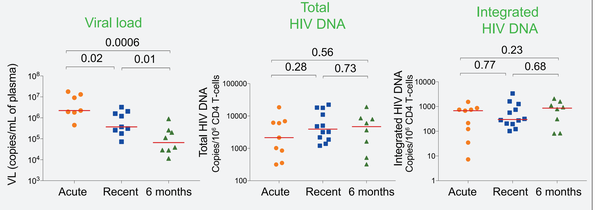


Figure 2: Viral load, Total and integrated HIV DNA before ART initiation

► As expected, acutely infected subjects show significant higher viral loads compared to recently and 6 months infected participants.

► No difference in the frequency of CD4 T cells harboring total and integrated HIV DNA between groups

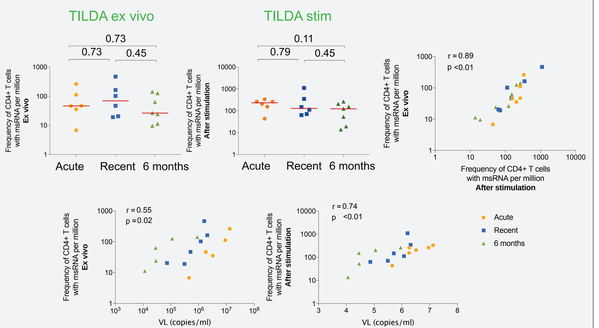


Figure 3: Frequency of productively and latently infected cells before ART initiation

► No differences in active replication (TILDA ex vivo) between groups

► Acutely infected individuals tend to have higher TILDA values after stimulation (latently infected cells + active replication) compared to participants infected for 6 months.

► TILDA ex vivo and after stimulation significantly correlate with VL

After 24 weeks of ART

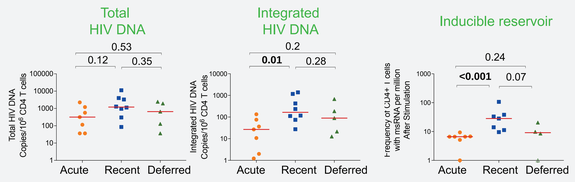


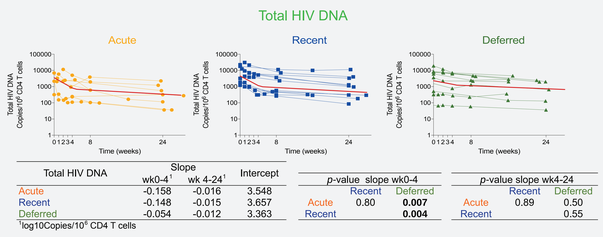
Figure 4: HIV reservoir after 24 weeks of ART

►The frequency of cells harboring integrated HIV DNA is significantly lower in acutely infected participants compared to recently infected individuals 24 weeks after ART initiation.

►No difference is observed between acutely treated participants and deferred group after 24 weeks of ART

► The inducible reservoir is significantly lower in acutely treated subjects compared to early treated subjects, but not in subjects treated 6 months after diagnosis.

Longitudinal analysis



Total HIV DNA	Slope wk0-4[1]	Slope wk 4-24[1]	Intercept
Acute	-0.158	-0.016	3.548
Recent	-0.148	-0.015	3.657
Deferred	-0.054	-0.012	3.363

p-value slope wk0-4	Recent	Deferred
Acute	0.80	**0.007**
Recent		**0.004**

p-value slope wk4-24	Recent	Deferred
Acute	0.89	0.50
Recent		0.55

[1]log10Copies/10⁶ CD4 T cells

Integrated HIV DNA	Slope wk0-4[1]	Slope wk 4-24[1]	Intercept
Acute	-0.209	-0.011	2.545
Recent	-0.124	-0.009	2.575
Deferred	-0.060	-0.009	2.605

p-value slope wk0-4	Recent	Deferred
Acute	0.10	**0.007**
Recent		0.162

p-value slope wk4-24	Recent	Deferred
Acute	0.82	0.83
Recent		0.99

[1]log10Copies/10⁶ CD4 T cells

TILDA stim	Slope wk0-4[1]	Slope wk 4-24[1]	Intercept
Acute	-0.551	0.010	2.474
Recent	-0.318	-0.035	2.136
Deferred	-0.277	0.035	1.516

p-value slope wk0-4	Recent	Deferred
Acute	**<0.0001**	**<0.0001**
Recent		0.921

p-value slope wk4-24	Recent	Deferred
Acute	**0.01**	0.27
Recent		0.18

[1]log10Copies/10⁶ CD4 T cells

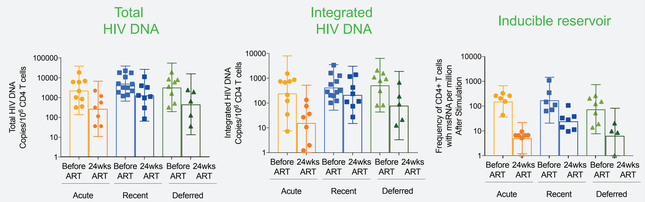
Figure 5: Longitudinal models of HIV reservoir decay after 24 weeks of ART

►The frequency of cells harboring total HIV DNA decays significantly faster in acutely treated individuals compared to recently and deferred groups.

►There is a faster decay in the integrated HIV DNA in the acute group compared to the deferred

► Inducible reservoir decay significantly faster in acutely treated participants compared to recently and deferred groups.

Fold-change in reservoir markers between baseline and 24 weeks of ART



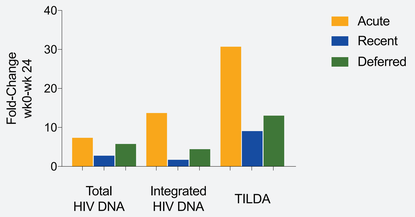


Figure 6: HIV reservoir after 24 weeks of ART

►Fold changes in the three markers of HIV persistence tend to be greater in acutely treated individuals

CONCLUSIONS

► ART initiation during the first month of HIV infection limits the pool of cells harboring integrated HIV DNA and the size of the inducible reservoir, but the apparent benefit does not extend to persons who initiated ART at a later stage

► Markers of HIV persistence had a steeper decay in acutely treated individuals compared to those who started later.

Initiating ART during acute infection may facilitate HIV remission in concert with additional eradication strategies.

Acknowledgments

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