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**HIV-1 specific T cells during prolonged
antiretroviral treatment in HIV-1 seroconverters**

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Background

- HIV-1 infection is associated with progressive immunodeficiency and death in the majority of subjects in the absence of treatment
- Dramatic change in the natural history of the disease with combination antiretroviral therapy (ART)
- Long-term aviremia (<50 HIV-1 c/mL) is achievable in the majority of subjects with ART with increases of CD4 T cell counts



Background

- ART is lifelong once initiated during chronic HIV-1 infection (costs, toxicity, resistance, Berlin patient)
- Early establishment of persistent viral reservoirs and immune defects
- Viremia rebound upon discontinuation of prolonged ART when initiated during chronic infection and short-term ART at seroconversion
- Recent report suggests that long-term control of viremia is possible after discontinuation of prolonged ART initiated at seroconversion in a subset of patients (Hocqueloux L, AIDS 2010)

*Chun TW, PNAS 1998; Chun TW, JCI 2005; Strain MC, JID 2005; Hoehn B, CID 2007; Yerly S, AIDS 2000
Hocqueloux L, AIDS 2010*



ART at seroconversion-LTNPs

- Can long-term ART initiated at PHI be associated with an immuno-virological profile similar to LTNPs
 - cross-sectional study: treated seroconverters vs LTNPs
- **Long-term non progressors (LTNPs):**
 - Absence of clinical progression and CD4 T cell loss in the absence of treatment
 - Control of viremia: “elite controllers”
 - Low viral reservoirs
- cross-sectional study: treated seroconverters vs LTNPs

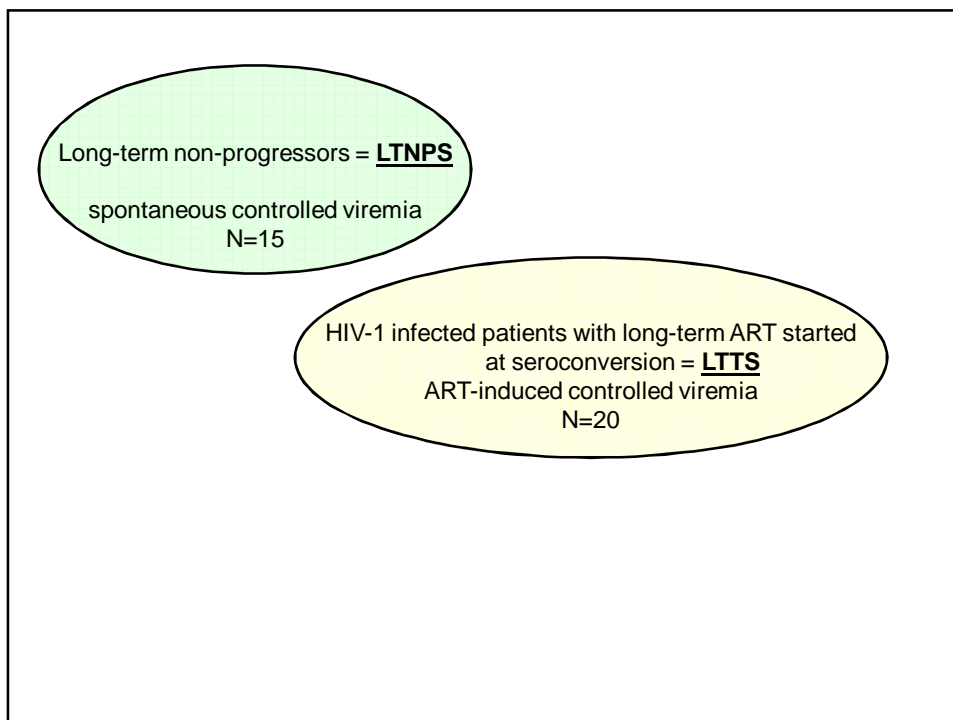


Immuno-virological parameters

- Size of viral reservoirs (cell-associated HIV-1 DNA) and residual replication (cell-associated HIV-1 RNA)
- Cellular immunity: HIV-1 specific CD4 and CD8 T-cells
- Role of HIV-1 specific CD8⁺ T cells in viremia control
- Functional properties such as polyfunctionality (simultaneous secretion of cytokines) associated with virological control
- Slow and incomplete improvement of HIV-1 CD8⁺ T cell functionality in progressors during ART initiated during chronic infection
- HIV-1 specific CD8⁺ T cells of LTNPs are functionally fit in terms of cytokine production, proliferative and cytotoxic capacity in contrast to viremic chronic progressors

Betts M, Blood 2006; Rehr M, J Virol 2008; Lopez M, Eur J Immunol 2008; Julg B, J Virol 2010;





Subjects

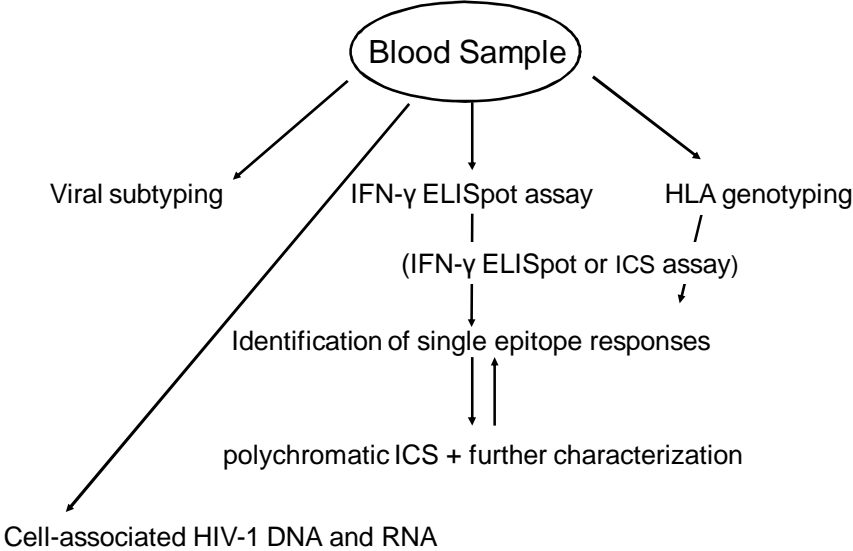
Inclusion criteria:

- LTT: HIV-1 infected subjects on ART since seroconversion, ART_≥ 4 years and long-term aviremia (<50 copies/mL)
- LTNP: ≥7 years with <1000 HIV-1 copies/mL, CD4>500 cells/uL in the absence of ART, clinically healthy and with no history of opportunistic diseases

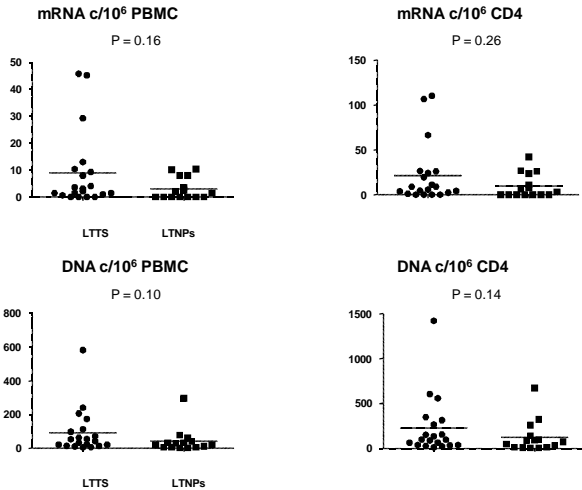
	LTTS ^a (n = 20)	LTNPs ^a (n = 15)	P value (n = 0.003)
Males (%)	19 (95)	11 (73)	0.14
Age ^b (range)	40 (29 - 59)	41 (27 - 67)	0.5
Caucasian (%)	19 (95)	14 (93)	1
MSM ^c (%)	18 (90)	8 (53)	0.02 (N.S.) ^c
HTS ^d (%)	2 (10)	5 (33)	0.11
HAEM ^e (%)	0 (0)	2 (13)	0.18
Years of infection ^b (range)	6 (4 - 7)	13 (7 - 25)	n.a. ^d
CD4 ^f T-cells ^g (cells/μL; range)	800 (567 - 1412)	783 (433 - 1648)	0.29
CD4 ^f /CD8 ^g T-cell ratio ^g (range)	1.1 (0.65 - 3.70)	1.2 (0.31 - 1.90)	0.06
CD8 ^g /CD38 ^h T-cells ^g (x10 ⁶ cells/L; range)	0.05 (0.008 - 0.274)	0.06 (0.016 - 0.534)	0.23
CD8 ^g /CD38 ^h T-cells ^g (%; range)	7 (3 - 25)	6 (3 - 30)	0.28
pVL ^e (HIV-1 RNA copies/mL)	all <50	11 <50, 4 <1000	n.a. ^d
Cell-associated HIV-1 RNA ⁱ (copies/10 ⁶ PBMCs; range)	3.9 (0 - 36)	5.8 (0 - 10.3)	0.16
Cell-associated HIV-1 DNA ⁱ (copies/10 ⁶ PBMCs; range)	47.7 (4.8 - 583.2)	19.7 (0.5 - 295.5)	0.10
Patients with HLA-B*5701 allele (%)	1 (5)	4 (27)	0.14
Patients with HLA-B*5701, -B*2705, -B*5801, -B*5101, -B*1302 alleles (%)	5 (25)	6 (40)	0.45
Patients with HLA-B*3503, -B*5301, -B*1801 alleles (%)	3 (15)	2 (13)	1

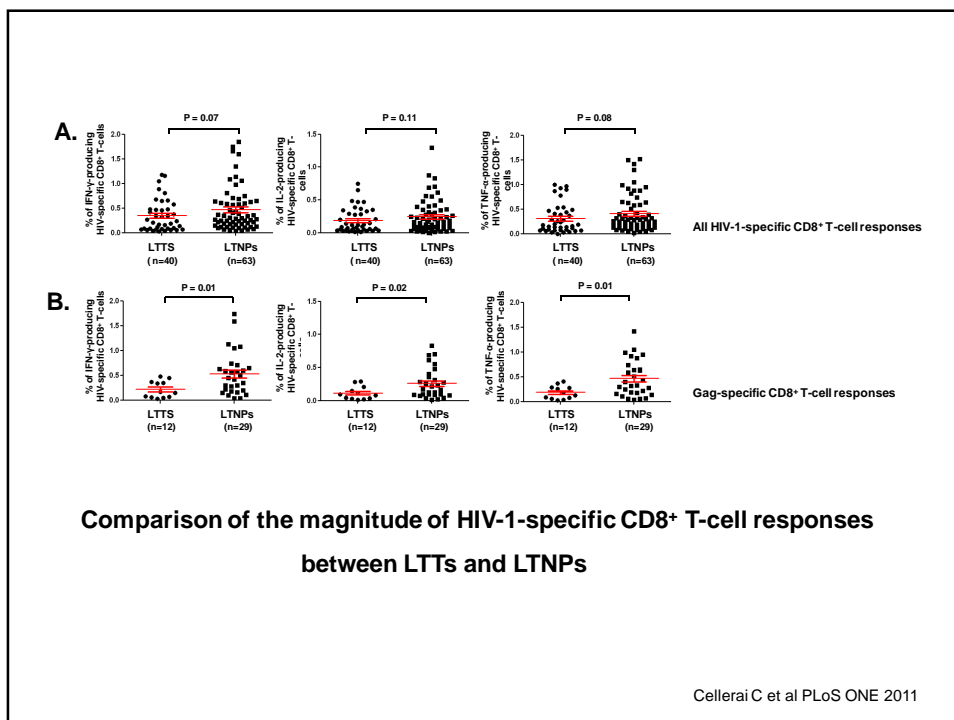
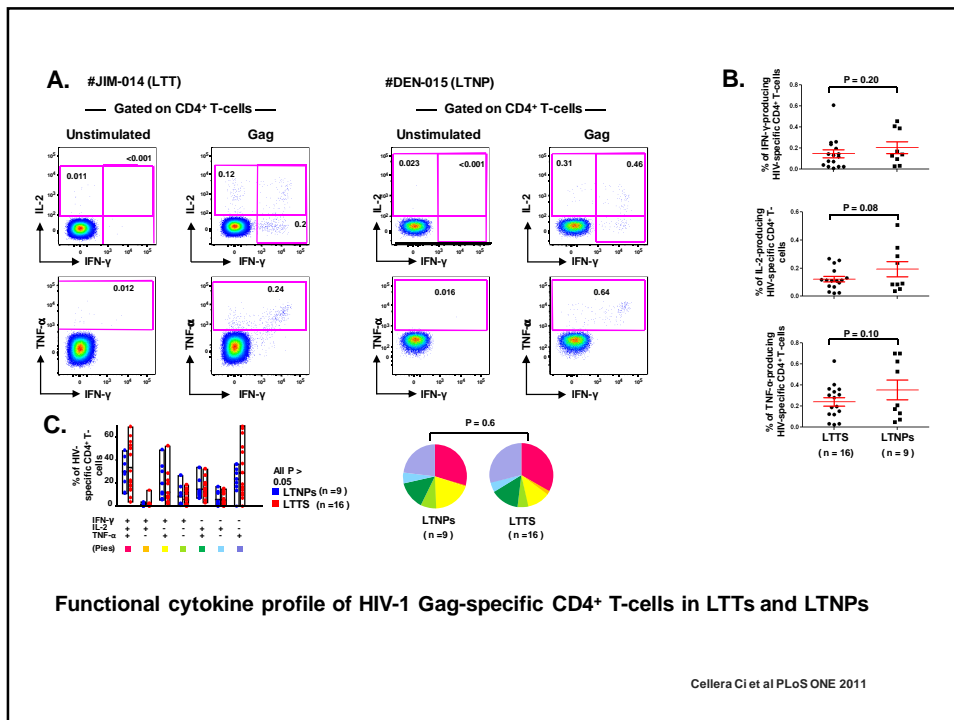
^aLTTS, long-term treated HIV-1 seroconverters; LTNPs: HIV-1 long-term non-progressors.
^bMSM, men-having-sex-with-men; HTS, heterosexuals; HAEM, haemophiliacs.
^cN.S., not statistically significant.
^dn.a., not applicable.
^epVL, plasma viral load.
^fMedian values at time of sampling.

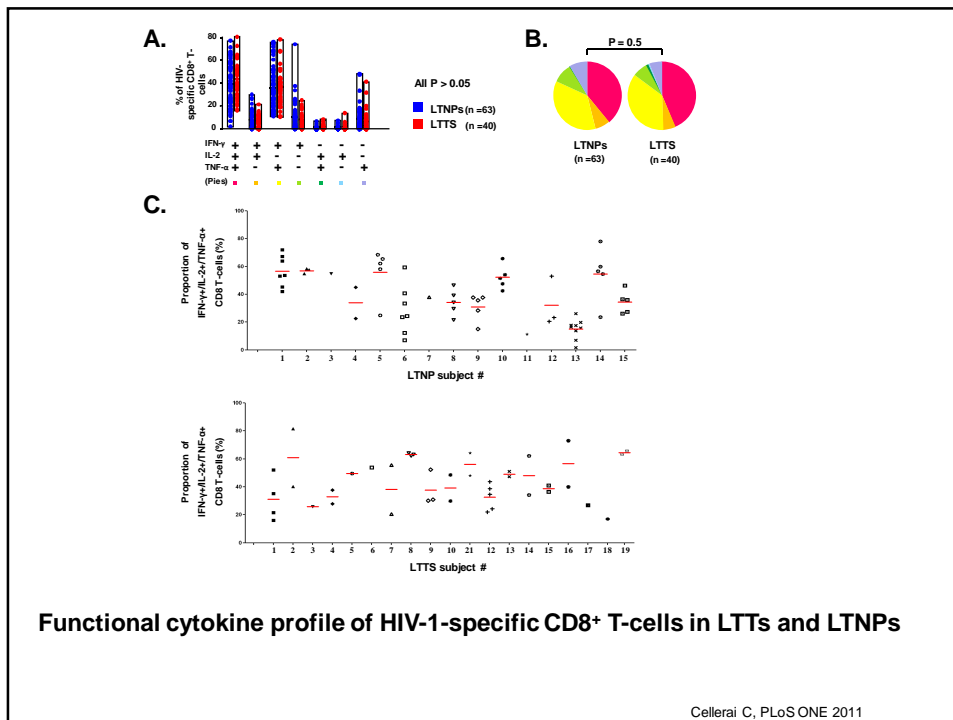
Study Flow Chart



Cell-associated HIV-1 RNA and DNA







Conclusions

- Comparable levels of highly polyfunctional HIV-1 specific CD4⁺ and CD8⁺ T cells in LTTs and LTNPs
- Polyfunctional T-cell profile and low viral burden in the presence or absence of treatment
- Trend towards a higher magnitude and breadth of HIV-1 specific CD8⁺ T cells in LTNPs as compared to LTTs driven by responses against gag
- Prolonged ART initiated at HIV-1 seroconversion is associated with immuno-virological features which resemble those of HIV-1 LTNPs

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