Early initiation rather than prolonged duration of antiretroviral therapy in HIV infection contributes to the normalization of CD8 T-cell counts: Relevance for clinical outcome

Wei Cao[1,2,3], Vikram Mehraj[1,2], Benoit Trottier[4], Jean-Guy Baril[5], Roger LeBlanc[2,6], Bertrand Lebouché[2], Joseph Cox[2], Cécile Tremblay[7,8], Joel Singer[9], Jean-Pierre Routy[1,2,10]

1 Research Institute, McGill University Health Centre, Montreal, Quebec, Canada
2 Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada
3 Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China
4 Clinique Médicale l'Actuel, Montreal, Quebec, Canada
5 Clinique Médicale Quartier Latin, Montreal, Quebec, Canada
6 Clinique Médicale OPUS, Montreal, Quebec, Canada
7 CHUM Research Centre, Montreal, Quebec, Canada
8 University of Montreal, Department of Microbiology and Immunology, Montreal, Quebec, Canada
9 School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
10 Division of Hematology, McGill University Health Centre, Montreal, Canada

Abstract

Background: Elevation of CD8 T-cells occurs during primary HIV infection (PHI) and persists following long-term antiretroviral therapy (ART), which has been associated with increased risk of non-AIDS-related morbidity and mortality independently of CD4 T-cell recovery. We examined factors associated with trajectories of CD8 T-cell counts in PHI and assessed influence of early vs. chronic ART initiation on CD8 T-cell elevation over time.

Methods: 280 individuals were enrolled during PHI and 251 were followed for 24 months, where 84 started ART before 6 months of infection (eART), 49 between 6 and 24 months (dART) and 118 remained untreated (nART). Plasma HIV viral load, CD4 and CD8 T-cells were assessed at each study visit. CD8 T-cell counts were also examined in 182 age-matched HIV-infected individuals who initiated ART during chronic infection and maintained undetectable plasma viral load for at least 5 years.

Results: At PHI baseline, higher CD8 T-cell counts were associated with more recent infection (p=0.019), higher CD4 T-cell counts (p<0.001) and higher viral load (p<0.001). The CD8 T-cell count in the eART group decreased from 797 to 588 cells/μl over 24 months (p<0.001), to a level lower than that of untreated PHI (834 cells/μl, p=0.004) or long-term treated chronic individuals (743 cells/μl, p=0.047). More prominent CD4 T-cell recovery was observed in the eART group compared to the dART group.

Conclusions: ART initiated in early HIV infection is associated with improved resolution of CD8 T-cell elevation compared to long-term ART initiated in chronic infection. Early ART may contribute to reducing the risk of non-AIDS-related events by alleviating CD8 T-cell elevation.

Background

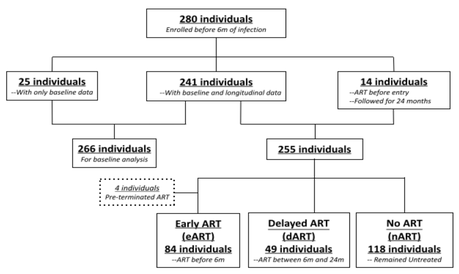
HIV infection is featured by profound immune dysfunction and skewed T-cell homeostasis. Elevation of CD8 T-cells occurs during PHI and persists following long-term ART, which has been associated with increased risk of non-AIDS-related events independently of CD4 T-cell recovery. Mechanisms underlying CD8 persistence remain unclear, and may include immune activation, alteration of lymph node architecture, gut mucosal dysfunction, microbial translocation and T-cell trafficking or redistribution. Whether an early approach could alleviate ongoing elevation of CD8 T-cell counts remains unknown. Here we examined factors associated with trajectories of CD8 T-cell counts in early HIV infection. By comparing individuals receiving early vs. delayed ART, we also assessed the impact of timing and duration of ART on CD8 T-cell elevation over time.

Methods

Study population

- **280** Participants from Montreal Primary HIV Infection Study Cohort (Montreal, Quebec, Canada) from May, 1996 to December, 2012, who were recruited before 6 months of infection and had bee followed for 24 months (Figure 1). Plasma viral load (VL), CD4 and CD8 T-cell counts measured at a maximum interval of 3 months.
- **182** age-matched HIV-1-infected adults who started ART during chronic infection and maintained undetectable VLs for at least 5 years. The CD4 and CD8 T-cell counts measured each calendar year after VLs became undetectable were examined.
- **40** age-matched uninfected healthy controls.

Figure 1. Enrollment of PHI participants



Results

Table 1. Characteristics of PHI participants, chronically infected individuals and uninfected controls

Characteristics	PHI eART N=84	PHI dART N=49	PHI nART N=118	Chronic Long-term ART N=182	Uninfected Controls N=40
Age, mean±SD, y	37.0±9.7	36.0±9.8	36.0±9.0	42.2±5.3	45.4±7.4
Gender, male (%)	78 (92.9)	47 (95.9)	114 (96.6)	157 (86.3)	27 (67.5)
EDI at enrollment, median (IQR), d	71 (49-108)	96 (76-145)	91 (66-135)	-	-
ART after EDI, median (IQR), d	81 (57-133)	436 (302-642)	-	-	-
ART after enrollment, median (IQR), d	9 (0-28)	357 (187-526)	-	-	-
		At PHI enrollment		At the 5th undetectable year	
HIV viral load, mean±SD, log copies/ml	4.67±1.30	4.53±0.91	4.24±0.94	Undetectable	-
CD8 T-cell count, median (IQR), cells/μl	770 (532-1343)	780 (660-1450)	825 (605-1152)	743 (600-926)	376 (256-458)[2]
CD4 T-cell count, median (IQR), cells/μl	403 (305-610)[1]	510 (407-600)	565 (460-735)	539 (431-677)	858 (570-1000)[2]
CD4/CD8 ratio, median (IQR)	0.54 (0.26-0.86)[1]	0.61 (0.36-0.79)	0.68 (0.47-1.00)	0.75 (0.56-1.03)	2.1(1.81-3.02)[2]

[1] The eART group had lower CD4 T-cell count (p<0.001) and lower CD4/CD8 ratio (p<0.01) compared to the dART and nART groups;
[2] The control group had higher CD4 T-cell count (p<0.001), lower CD8 T-cell count (p<0.001) and higher CD4/CD8 ratio (p<0.001) than all the infected individuals.

Table 2 Univariate and multivariate analyses of factors associated with CD8 T-cell levels for PHI individuals at baseline

Characteristics	Participants No	CD8 T-cell count cells/μl, Median (IQR)	P value *Univariate*	P value *Multivariate*
Overall	266	800 (598-1265)		
Origin				
Caucasian	246 (92.5%)	817 (600-1284)	0.025	0.168
Non-Caucasian	20 (7.5%)	720 (549-992)		
Age, years				
< 50	247 (92.9%)	826 (600-1265)	0.771	0.991
≥ 50	19 (7.1%)	710 (566-1211)		
Gender				
Male	254 (95.5%)	824 (600-1281)	0.641	0.308
Female	12 (4.5%)	715 (627-1076)		
Presumed route of infection				
MSM	207 (77.8%)	853 (602-1417)	0.148	0.824
Heterosexual	21 (7.9%)	660 (560-830)		
IDU	38 (14.3%)	790 (594-1156)		
Time of infection				
Fiebig stages II/III	40 (15.0%)	935 (709-1790)	0.118	**0.019**
Fiebig stage IV	81 (30.5%)	810 (557-1470)		
Fiebig stages V/VI	145 (54.5%)	787 (607-1148)		
HIV RNA load, log copies/ml				
<3	19 (7.1%)	650 (525-794)	< 0.001	**< 0.001**
3-5	152 (57.1%)	782 (592-1088)		
>5	95 (35.7%)	1140 (702-1783)		
CD4 T-cell count, cells/μl				
< 500	124 (46.6%)	740 (549-1140)	0.005	**< 0.001**
≥ 500	142 (53.4%)	880 (665-1450)		

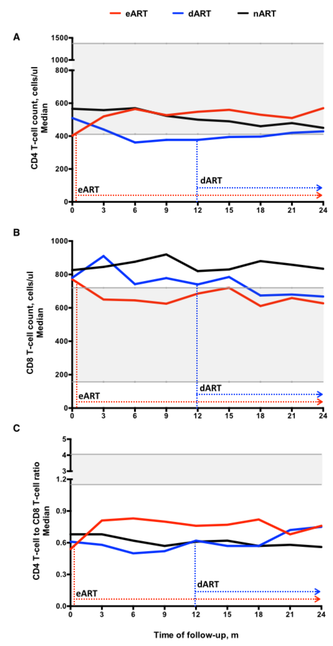


Figure 3. Trajectories of CD4 and CD8 T-cell count, and CD4/CD8 ratio over time in PHI (Median)

(A) CD4 T-cell count in eART group was higher than in dART group (p=0.048) or nART group (p=0.01) at 24 months.
(B) CD8 T-cell counts in nART group remained stable; at 24 months, CD8 T-cell counts in eART group were lower than those of the nART group (p=0.004), though still elevated compared to the control group (p<0.001).
(C) CD4/CD8 ratio in the nART group declined over time; the ratio in eART group was higher than that of the nART group (p<0.001) at 24 months.

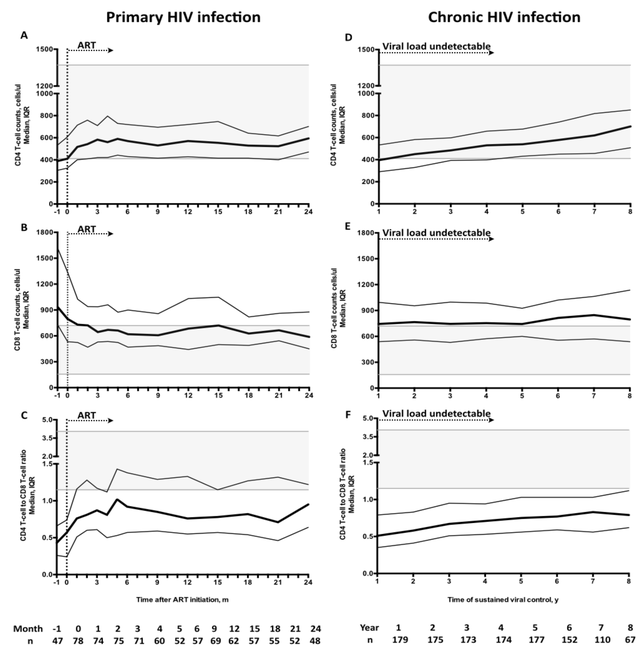


Figure 2. Trajectories of T-cell counts over time in early treated primary HIV infection and chronic long-term treated chronic infection (median, IQR)
In PHI, when ART was initiated within 6 months of infection, CD8 T-cell counts were prominently decreased at 24 months compared to the level at ART initiation (2B, p=0.01). CD4 T-cell counts (2A, p=0.002) and CD4/CD8 ratio (2C, p<0.001) were significantly increased compared to when treatment started.

In long-term treated chronic patients, CD4 T-cell counts (2D) and CD4/CD8 ratio (2F) continued to increase over the 8 suppressive years. CD8 T-cell counts remained stable over time and were higher than that of the eART group (24 months).

HYPOTHESIS

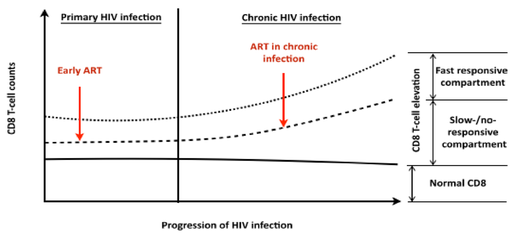


Figure 4. Dynamics of CD8 T-cell counts during the course of HIV infection
Elevation of CD8 T-cell counts in HIV infection could be divided to two major compartments, the fast-responsive and slow-or-no-responsive compartments. The fast-responsive compartment may mainly includes activated T-cells such as CD38+/DR+ CD8 T-cells and is associated with viral antigenic stimulation, which could be corrected by effective ART. The slow-/non-responsive compartment may associate with gut mucosal damage, acquired "immunoaging", and impaired distribution and homing capacity of T-cells .

Conclusions

Early ART initiated in PHI was associated with a significant decrease in CD8 T-cell counts coupled with VL reduction and CD4 T-cell recovery, which was even more prominent when ART was initiated within 6 months of infection. In contrast, although prolonged ART initiated in chronic HIV infection was associated with more recovery in CD4 T-cell counts and CD4/CD8 ratio, CD8 T-cell counts remained persistently elevated, and were higher than those observed with ART initiation in PHI. Timing rather than duration of ART appears to be more critical for normalization of CD8 T-cell counts in HIV infection. In addition to the recovery of CD4 T-cells and delay in disease progression, ART initiation during PHI may further contribute to reducing future risks of non-AIDS morbidity and mortality by alleviating CD8 T-cell elevation.

Acknowledgment

We acknowledge: The participants of Montreal Primary HIV infection Cohort; the collaborative physicians: Drs S. Vézina, L. Charest, M. Milne, E. Huchet, S. Lavoie, J. Friedman, M. Duchastel, and F. Villielm, at l'Actuel Medical Clinic; P. Côté, M. Potter, B. Lessard, M. A. Charron, S. Dufresne, and M. E. Turgeon, at Quartier Latin Medical Clinic; Drs D. Rouleau, L. Labrecque, C. Fortin, A de Pokomandy, B. Trottier, V. Hal-Gagné, M. Munoz, B. Deligne, and V. Martel-Laferrière, at UHRESS CHUM Hôtel-Dieu and Notre-Dame; and N. Gilmore, M. Fletcher, and J. Szabo, at MUHC Chest. This work was supported by the Fonds de la Recherche Québec-Santé (FRQ-S): Thérapie cellulaire and Réseau SIDA/Maladies infectieuses; Canadian Institutes of Health Research (grants MOP 103230 and CTN 257); the Canadian Foundation for AIDS Research (CANFAR; grant 023-512); and the Canadian HIV Cure Enterprise Team Grant HIG-133050 from the CIHR in partnership with CANFAR. Dr. Wei Cao is supported by CTN postdoctoral fellowship award. We thank Mario Legault and Costas Pexos for database management; Angie Massicotte for coordination and assistance in manuscript writing; Jacquie Sas and Jim Pankovich from the CIHR Canadian HIV Trials Network, for coordinating the international research collaboration between McGill University Health Centre and Peking Union Medical College Hospital with the support of CIHR/CTN.