Barts and The London School of Medicine and Dentistry

Disease Progression in HIV Controllers; Uptake and Outcome of Antiretroviral Therapy

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Background

We have previously reported a cohort of 86 HIV-1 controllers and defined a subset, "discord controllers (DC)" with low or declining CD4 counts (<450) despite control of plasma viral RNA[1]. We showed that DCs are distinct both clinically and immunologically, having depletion of naïve CD4 cells and higher activation in all CD4 subsets compared with typical controllers (CD4 counts >450, TC). Data on clinical management and outcome of controllers are limited so we undertook a follow-up study of the cohort.

Methods

A prospective cohort of HIV-1 infected individuals was recruited, with written informed consent, from outpatient departments at Barts and the London and Homerton University Hospital Trusts. Viremic controllers (VC) were defined by plasma HIV RNA levels below 200 copies/ml (≥ 3 measurements over 12 months without ART), as per the International HIV Controller Consortium. VCs were assigned to one of two groups based on the geometric mean titre of the last three CD4 counts; typical controllers (TC) >450, discord controllers <450. Elite controllers (EC) were defined by plasma HIV RNA levels consistently below the limit of detection (0 - <40 c/ml). Controls were uninfected individuals, and viremic non-controllers (ART-naïve, infected >12 months, HIV RNA load >10,000 c/ml), who were further defined as HIV progressors with CD4 counts <450. Epidemiological, clinical and laboratory data were collected. Baseline HIV-1 DNA load in peripheral blood mononuclear cells was determined by quantitative PCR as previously described[1] and expressed as per cell equivalent (copies per 10^6 CD4+ T-cells).

Results

Eighty two VCs were identified (2.7% of clinic population), of whom 64 were TCs (2.1%) and 18 DCs (0.6%). There were no significant differences in viral load or demographic factors between the two groups at baseline. DCs had higher HIV DNA loads (13 - 1529, median 601 copies/10^6 CD4 cells) compared to TCs (0 - 755, median 87) (p=0.002) and were similar to those in non-controllers (27 - 2188, median 852). Two DCs were lost to follow up; 16 were included in the current study. Ten DCs had started ART and had received 12 -55 months of therapy (median 37). HIV RNA loads were 85 - 19837 (median 796) at ART initiation and all became undetectable on therapy (<40 c/ml). Baseline CD4 counts at time of first receipt of ART were low; 163 - 308 (median +272). Despite undetectable HIV RNA loads on ART, CD4 gain was modest (Figure 1). CD4 change -35 - 191 (median +56) at 6/12 of ART AND -25 - +318 (median +130) over follow-up. Those with lower nadir CD4 had lowest CD4 gain despite extended ART (Table 1).

Six DCs remained ART naïve. Five had lost viral control with one remaining undetectable. CD4 counts were unexpectedly low at 217 - 464 (median 304). Of particular note is that 5 patients had declined to start ART despite low and declining CD4 counts (Table 2).

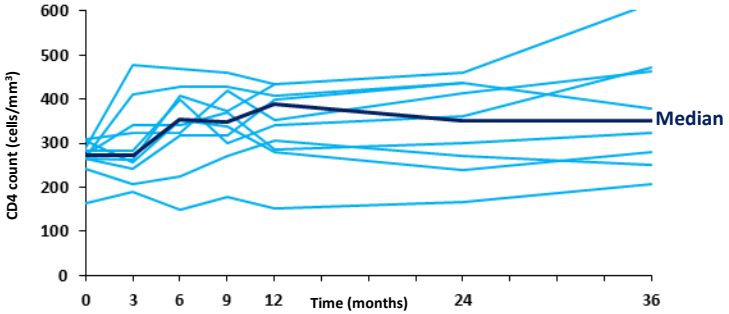
Table 1. Baseline and follow-up results in Discord Controllers who started ART

	ART regimen	CD4 count at ART	CCD4 count at 6/12	Latest CD4 count	HIV RNA load at ART	Latest HIV RNA load
1	Atripla	284	399	482	1945	<40
2	ATV/ r / Truvada	305	352	280	4617	<40
3	ATV / r / Truvada	275	340	325	85	<40
4	Atripla	264	409	582	240	<40
5	EFV / Kivexa	288	479	434	10274	<40
6	DRV / r / Truvada	266	318	379	19837	<40
7	ATV / r / Kivexa	163	148	206	273	<40
8	Atripla	268	429	438	1205	<40
9	ATV / r / Truvada	308	324	462	386	<40
10	Atripla	243	224	250	286	<40

Table 2. Follow-up results in ART-naive patients

	Plasma HIV RNA load (copies/ml)	CD4 count (/mm³)	Comment
1	29,616	217	Declined ART
2	798	237	Declined ART
3	1,852	450	Declined ART
4	502	333	Declined ART
5	0	464	Elite Controller
6	16,176	275	Declined ART

Figure 1. Change in CD4 count after ART



Conclusions

DCs were found to have a more marked depletion of the naive T-cell subset than TCs. CD8 T-cell activation was increased to a similar level in both controller groups. Increased immune activation in controllers is associated with increased coronary atherosclerosis.[2] This may explain the observed increased all-cause and cardiovascular hospitalisations in controllers compared to those with medical control secondary to ART[3]. The significantly higher baseline HIV DNA loads in the DC group compared to TCs suggest productive ongoing HIV-1 replication and are more similar to that seen in HIV progressors. These results suggest that HIV DNA load may be a better marker of viral replication and disease progression than HIV RNA load.

Ten of 16 DCs started ART. However, ART initiation occurred late; all DCs had CD4 counts below 350 at first receipt of ART (median 272). All DCs achieved or maintained undetectable HIV RNA loads after ART but CD4 gain was modest and appeared to plateau, even after extended therapy (Figure 1).Other, larger studies have also shown that controllers have a reduced CD4 increase after ART compared to non-controllers.[4,5] Follow-up on ART in this cohort was longer (median 37 months) but no further increase in CD4 count with time was seen in most individuals despite sustained viral suppression. Six DCs were not receiving ART at follow-up despite low CD4 counts in most (5 had CD4 counts <350, median 305). Four had maintained viral control (1 EC, 3 VC). All DCs in whom ART is indicated had declined to start therapy. However, it is known that ART confers benefit in controllers by terms of significant decreases in ultrasensitive HIV RNA loads, HIV antibody levels and markers of immune activation and dysfunction.[1,4,5,6,7] The results of this study suggest that DCs may benefit from earlier ART regardless of HIV RNA load. Consideration should be given to starting ART at higher CD4 counts than in non-controllers. Ongoing longitudinal follow-up of this cohort is planned to address these issues further.

Summary

- HIV controllers experience disease progression even if plasma HIV RNA load remains low or undetectable
- HIV DNA load may be a better marker of viral replication and disease progression than HIV RNA load
- Discord controllers initiated ART late and had only modest increase in CD4 count despite HIV suppression
- Both clinicians and patients may be falsely reassured by low or undetectable HIV RNA loads
- HIV controllers may benefit from early ART initiation regardless of HIV RNA load

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