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ART in HIV persons with pre-treatment viremia <3000c/mL: the START study

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Background

- The benefit of immediate initiation of ART regardless of CD4 T cell count was established in the Strategic Timing of Anti-Retroviral Treatment (START) study across many subgroups including plasma HIV viral load (pVL).
- It is though unclear how immediate ART may affect CD4, pVL and biomarkers in persons specifically with low pVL, who have low incidence of clinical events.

Methods

- Participants with low pre-ART (baseline) pVL ≤3000c/mL were included in this sub-analysis provided they had no current or previous history of ART use (N=1138 including 347 with pVL≤400c/mL and 94 with pVL≤50 c/mL). Clinical events were assessed as per the parent study.
- Biomarkers were measured in cryopreserved plasma (pre-ART and week 8 of ART).
- All analyses were ITT. We compared immediate (Imm) with deferred (Def) ART in terms of the CD4 cell count and pVL results at study time points and changes in biomarker levels from baseline at month 8.

Results

Table 1. Baseline participants characteristics by pVL level and treatment arm.*

Baseline HIV RNA (c/mL)		<3000			<50	
		Imm (N=557)	Def (N=581)	Both arms (N=1138)	Imm (N=43)	Def (N=51)
Age (years) Median(IQR)		37 (29, 44)	37 (29, 45)	37 (29,44)	41 (34, 48)	40 (31, 50)
Gender N (%)	Male	328 (59%)	351 (60%)	679 (60%)	17 (40%)	23 (45%)
	Female	229 (41%)	230 (40%)	459 (40%)	26 (60%)	28 (55%)
HIV mode of exposure N(%)	IDU	12 (2%)	9 (2%)	21 (2%)	0 (0%)	2 (4%)
	MSM	226 (41%)	229 (39%)	455 (40%)	10 (23%)	8 (16%)
	Hetero	275 (49%)	302 (52%)	577 (51%)	28 (65%)	37 (73%)
	Other	44 (8%)	41 (7%)	85 (7%)	5 (12%)	4 (8%)
Current CD4 (cells/µL)		721 (622, 860)	701 (615, 844)	714 (617, 854)	825 (711, 1022)	806 (667, 972)
Current CD8 (cells/µL)		935 (707, 1240)	920 (687, 1228)	926 (698, 1233)	789 (568, 973)	699 (527, 970)
Race N (%)	Black	250 (45%)	241 (41%)	491 (43%)	27 (63%)	30 (59%)
	Hispanic	54 (10%)	72 (12%)	126 (11%)	2 (5%)	8 (16%)
	Asian	40 (7%)	39 (7%)	79 (7%)	2 (5%)	2 (4%)
	White	189 (34%)	214 (37%)	403 (35%)	11 (26%)	9 (18%)
	Other	24 (4%)	15 (3%)	39 (3%)	1 (2%)	2 (4%)
Region N (%)	N America	75 (13%)	83 (14%)	158 (14%)	4 (9%)	9 (18%)
	Europe	133 (24%)	139 (24%)	272 (24%)	4 (9%)	8 (16%)
	S America	130 (23%)	143 (25%)	273 (24%)	6 (14%)	9 (18%)
	Oceania	11 (2%)	6 (1%)	17 (1%)	0 (0%)	0 (0%)
	Asia	36 (6%)	37 (6%)	73 (6%)	2 (5%)	2 (4%)
	Africa	172 (31%)	173 (30%)	345 (30%)	27 (63%)	23 (45%)
HCV Ab N (%)	Positive	26 (5%)	24 (4%)	50 (4%)	1 (2%)	5 (10%)
	Negatve	523 (96%)	553 (96%)	1076 (96%)	41 (98%)	46 (90%)
HbsAg N (%)	Positive	14 (3%)	15 (3%)	29 (3%)	2 (5%)	3 (6%)
	Negative	530 (97%)	562 (97%)	1092 (97%)	41 (95%)	48 (94%)

Results Cont.:

Table 2. Serious events by pVL level and treatment arm.*

Baseline HIV RNA (c/mL)		<3000			
		N of persons with event	total events)	Rate	HR (95% CI)
Grade 4	Imm	16	18	0.99	1.0
	Def	17	17	1.02	1.04 (0.52, 2.05)
Death	Imm	5	5	0.31	1.0
	Def	3	3	0.18	0.59 (0.14, 2.45)
Any hospitalization	Imm	58	80	3.81	1.0
	Def	54	63	3.40	0.89 (0.62, 1.29)
Any of above combined	Imm	64	88	4.21	1.0
	def	59	70	3.73	0.89 (0.62, 1.26)
Baseline HIV RNA (c/mL)		**<50**			
		N of persons with event	total events)	Rate	HR (95% CI)
Grade 4	Imm	0	0	0	
	Def	1	1	0.85	
Death	Imm	0	0	0	
	Def	0	0	0	
Any hospitalization	Imm	2	3	1.95	1.0
	Def	4	4	3.49	1.73 (0.32, 9.47)
Any of above combined	Imm	2	3	1.95	1.0
	def	5	5	4.52	2.21 (0.43, 11.4)

There were 3 AIDS events in the Imm and 8 in the Def arm, HR 2.66 (0.71-10.0). There were 8 serious non-AIDS events in the Imm arm and 4 in the Def, HR 0.49 (0.15, 1.64).
The primary end points were 11 in the Imm and 12 in the Def arm, HR 1.08 (0.48, 2.45). There were no important differences in laboratory AEs, except ATV associated high bilirubin.

Table 3. Median changes in biomarker levels at month 8 by pVL level and treatment arm.*

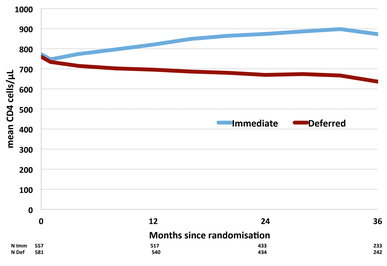
Baseline HIV RNA (c/mL)		<3000 c/mL IQR		<50 c/mL IQR	
D-dimer (mcg/mL)	Imm	-0.017	-0.114, 0.076	-0.008	-0.070, 0.139
	Def	0.009	-0.063, 0.092	0.008	-0.058, 0.107
CRP (mcg/mL)	Imm	0.181	-0.440, 2.210	0.078	-0.397, 0.969
	Def	0.024	-0.755, 0.995	-0.007	-0.803, 1.093
Serum Amyloid A (mgL)	Imm	-0.171	-2.135, 1.738	-0.680	-3.335, 1.242
	Def	0.040	-1.742, 1.775	-0.314	-1.091, 0.575
sICAM (mcg/mL)	Imm	0.927	-103.918, 102.405	25.776	-64.424, 139.834
	def	6.896	-63.859, 76.110	-6.770	-105.570, 66.022
sVCAM (mcg/mL)	Imm	-14.768	-133.710, 85.987	46.693	-75.417, 156.217
	Def	-16.780	-68.764, 60.772	-36.638	-102.747, 37.916
IL-6 (pg/mL)	Imm	0.000	-0.415, 0.440	0.000	-0.394, 0.334
	Def	-0.058	-0.363, 0.280	-0.082	-0.357, 0.263
IL-27 (pg/mL)	Imm	-0.400	-60.800, 83.100	25.600	-49.300, 121.700
	Def	14.950	-59.750, 117.050	4.300	-42.200, 117.800

* The <50 group is included in the larger <3000 group in all analyses presented.

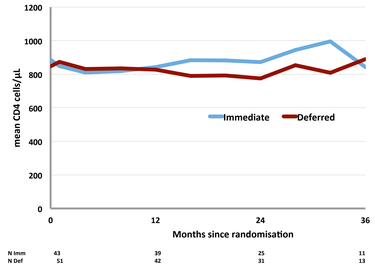
Results Cont.:

Figure 1. CD4 counts in Imm vs Def arms in all participants in <3000 (A) and in the group of <50 c/mL (B). Proportion of participants with VL <200 c/mL by treatment arm at follow up in all (<3000) participants (C) and in the <50 group (D).

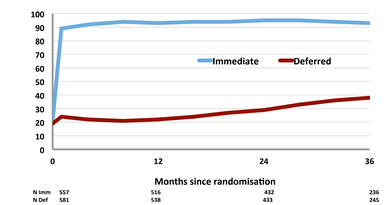
A. Mean CD4 counts at study follow up in participants with baseline pVL(<3000c/mL)



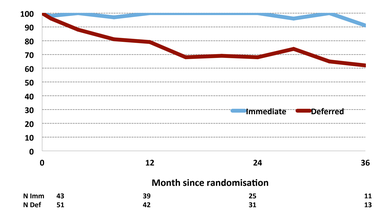
B. Mean CD4 counts at study follow up in participants with baseline pVL(<50 c/mL)



C. Proportion of participants (<3000) with pVL below detection at follow up by treatment arm



D. Proportion of participants (<50) with pVL below detection at follow up by treatment arm



The risk of HIV transmission was estimated based on the 12-month pVL data, assuming:

1. Risk of transmission was proportion to viral load (with no risk below 200 c/mL)
2. 40% MSM, 40% heterosexual females and 20% heterosexual males
3. Per contact transmission risk of 0.0075 per act for MSM, 0.0008 and 0.0004 for heterosexual females and males respectively
4. An average of 200 acts per year, 10% without condoms, and condoms reducing risk by 95% and
5. Sexual behaviour not affected by randomisation to immediate or deferred treatment and current viral load

Based on these assumptions, absolute risk of HIV transmission was estimated to 0.3 transmission per 100 patient years in the immediate ART arm and 3.7 per 100 patient years In the deferred ART arm.

Conclusions

In this sub-analysis of START participants with pre-treatment pVL ≤3000 c/mL randomized to Imm vs Def ART, the Imm ART group had greater suppressed viremia during follow-up, which may significantly reduce transmission, and higher CD4 cell counts although the CD4 increases were not as evident in the <50 c/mL group.
The number of clinical events was small and not different between the 2 groups; additional follow-up is required.

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