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Long term effects of treatment interruptions in adults and children

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Abstract *(italics updated)*

Background: Stockouts are relatively common in large ART programmes and cause treatment interruptions, but their long-term impact is rarely assessed. We investigated this using long-term follow-up of a structured treatment interruption (STI) randomisation 12 weeks on/off in a large adult trial (DART), and data on unplanned treatment interruptions (UPTIs) in this and a parallel paediatric trial (ARROW).

Methods: The DART STI randomisation stopped early; patients returned to continuous therapy (CT) and were followed for a further 3 years. Random effects models were used to assess differences in CD4s between those randomised to STI vs CT over the long-term back on ART. Linear regression was used to assess the impact of total time off ART on CD4 4 years (adults) or 3 years (children) after ART initiation. The impact of time-updated cumulative time off ART on mortality was assessed using Cox models. All models adjusted for sex, centre and pre-ART CD4/CD4% and age.

Results: DART STI patients had >100 cells/mm^3 lower CD4 when restarting CT (*Figure 1*). Subsequently STI patients gained 48 (95% CI 43-54) cells/year, significantly faster than the 31 (25-36) in CT patients (p<0.001). Extrapolating forward, those randomised to STI would have similar CD4 to those on CT 4-5 years after restarting ART.

32% (1055/3316) adults had total 1955 UPTIs lasting ≥4 days, vs 23% (281/1206) children (p<0.001) with 536 UPTIs, with median total 17 days (7-49) off treatment in adults vs 13 (7-34) in children. In both adults and children most UPTIs occurred in the first year on ART (p<0.001). The most common reason for UPTIs was inability to attend clinic (61% adults, 50% children). Adverse events were a more common reason in adults (22%, 1% children) and patient/carer decision in children (17%, 5% adults).

For every extra cumulative month off ART (UPTIs) *in adults CD4 4 years after ART initiation was 7 cells/mm^3 lower (95%CI 1-12, p=0.01);* in children CD4% 3 years after ART initiation was 2% lower (1-3%, p=0.001). Having ever interrupted ART increased mortality risk in adults (HR=3.0 [95% CI 2.1-4.2] p<0.001) with similar non-significant trend in children (HR=2.6 [0.7-10.4] p=0.18). There was no evidence of independent effects of cumulative time off ART in adults (HR=1.1 per doubling [1.0-1.2] p=0.26) or children (1.6 [0.9-2.8] p=0.11).

Conclusions: TIs lead to lower CD4 counts over the long-term even after returning to ART, highlighting the importance of avoiding ART interruption in programmes in resource limited settings.

Methods

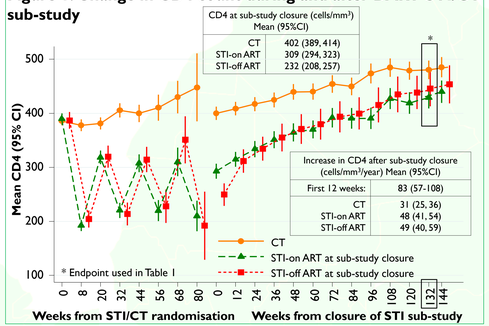
- **DART** (Development of Anti Retroviral Therapy)
  - Randomised trial (RCT) of management strategies
  - 3316 symptomatic ART-naïve adults with CD4<200 cells/mm^3 initiating triple drug ART in Uganda and Zimbabwe
- **DART STI sub-study**
  - Participants with CD4 ≥300 cells/mm^3 were randomised 52/76 weeks post strategy randomisation to either:
    (i) STI - 12 week off/12 week on ART; or
    (ii) CT - no planned treatment interruptions
- **ARROW** (Anti-Retroviral Research for Watoto)
  - RCT of the same management strategies
  - 1206 previously untreated children/adolescents meeting WHO criteria for ART; no STIs by design
- DART
  - Long term trends in CD4 counts were estimated using mixed models
  - Comparison of clinical event rates using Poisson regression
  - Effect of number of STI cycles on CD4 counts 132 weeks post sub-study closure: linear regression, adjusting for age at ART initiation, sex, centre, monitoring strategy, weeks on ART at STI randomisation, CD4 pre-ART and pre-STI/CT randomisation
- DART /ARROW
  - CD4% 3 years (ARROW) or absolute CD4 4 years (DART) after ART initiation was modelled to assess longer-term impact of total time off treatment (planned and unplanned) using an ever vs. never off /log$_2$ transformation to allow for non-linearity
  - Effect of cumulative time off treatment on clinical events (Figure 3) modelled using time dependent Cox regression
  - We adjusted for sex, pre-ART CD4 (CD4% ARROW), age at ART randomisation, centre, monitoring strategy, post-ART randomisation (DART) to reflect initial response to ART, and randomised first-line strategy (ARROW)

DART STI/CT patients

- 813 DART participants were randomised to STI vs. CT from 26 July 2004 to 16 March 2006 (sub-study closure)
- 404 STI participants had at least 1 STI cycle: all patients on NVP used 2 week staggered stop of NRTIs
- Reasons for stopping STIs were sub-study closure in 302 (75%), and clinical/patient reasons in 102 (25%) (mostly low CD4/WHO 3/4 events/death (61/102))
- Patients restarting CT for clinical/patient reasons had fewer STIs than those restarting for sub-study closure

Results

Figure 1: Change in CD4 count during and after DART STI/CT sub-study



- STI patients on and off ART at sub-study closure had CD4 93 and 170 cells/mm^3 lower than CT respectively (both p<0.001)
- Those off ART gained 83 cells/mm^3 during first 12 weeks back on ART, subsequently both STI groups gained CD4 at similar rates (48 and 49 cells/mm^3/year respectively, p=0.78), faster than the 31 cells/mm^3/year in CT (p<0.001) (Figure 1)
- From the model, mean CD4 in STI patients on/off ART at sub-study closure would equal that in CT 5 years after sub-study closure

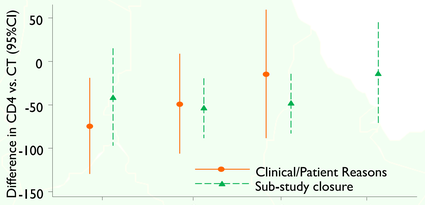
Table 1: Long term effects of STIs on CD4 count 132 weeks after sub-study closure

Factor		N (%) or median (IQR)	Estimate (95% CI)	p-value
Number of STIs:	0 (CT)	375 (51)	0	-
	1	71 (10)	-58 (-99, -17)	0.006
	2	137 (18)	-53 (-84, -22)	0.001
	3	127 (17)	-43 (-76, -11)	0.009
	4	31 (4)	-14 (-73, 45)	0.64
Pre ART CD4† (per 50 cells/mm^3 higher)		133 (83-168)	10 (-0.6, 21)	0.06
Pre STI/CT CD4† (per 50 cells/mm^3 higher)		358 (325-419)	28 (21, 35)	<0.001
Age at ART initiation† (per 10 years older)		36 (31-42)	12 (-3, 27)	0.10
Sex:	Male	191 (26)	0	-
	Female	550 (74)	66 (39, 93)	<0.001
Centre:	Entebbe, MRC/UVRI	302 (41)	0	-
	Kampala, JCRC	156 (21)	11 (-21, 42)	0.51
	University of Zimbabwe, Harare	237 (32)	2 (-25 29)	0.88
	Infectious Disease Institute*, Mulago	46 (6)	-27 (-77, 23)	0.28
CD4 Monitoring strategy:				
	LCM (monitoring)	380 (51)	0	-
	CDM (no monitoring)	361 (49)	7 (-16, 30)	0.55
Weeks on ART at STI randomisation:				
	52 weeks	454 (61)	0	-
	76 weeks	287 (39)	-16 (-41, 9)	0.20
Mean CD4 in reference category		-	439 (406, 472)	<0.001

†Reference category: pre ART CD4=100cells/mm^3; pre STI/CT=400cells/mm^3; age=40 years

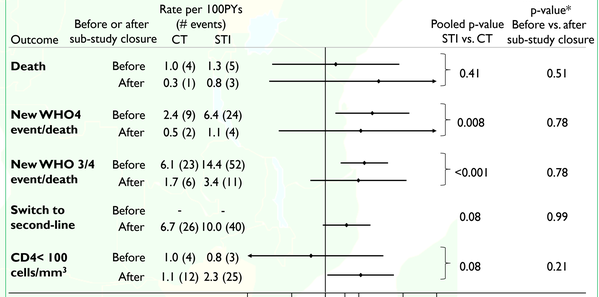
- Overall CD4 132 weeks after sub-study closure was 51 cells/mm^3 lower in STI vs. CT (95%CI 28-74, adjusted p<0.001) (Table 1)
- Estimated reductions in CD4 associated with having 1, 2, 3 or 4 STI cycles >132 weeks previously were 58, 53, 43 and 14 cells/mm^3 compared to CT, with no evidence of variation across number of cycles (heterogeneity p=0.61) (Table 1)
- 132 weeks after sub-study closure CD4 was higher in those with higher pre ART and STI/CT randomisation CD4 (p=0.06, <0.001 respectively) and females (p<0.001)

Figure 2: Impact of number of STI cycles and reason for stopping STIs on CD4 132 weeks after sub-study closure



Although patients who stopped STIs for clinical/patient reasons might have been expected to have lower CD4 than those stopping STIs for sub-study closure, reductions in CD4 vs. CT 132 weeks after sub-study closure were similar (adjusted p=0.67)

Figure 3: Effect of STIs on clinical events & switch to second-line before & after sub-study closure



Outcome	Before or after sub-study closure	Rate per 100PYs (# events) CT	STI	Pooled p-value STI vs. CT	Interaction p-value* Before vs. after sub-study closure
Death	Before	1.0 (4)	1.3 (5)	0.41	0.51
	After	0.3 (1)	0.8 (3)		
New WHO4 event/death	Before	2.4 (9)	6.4 (24)	0.008	0.78
	After	0.5 (2)	1.1 (4)		
New WHO 3/4 event/death	Before	6.1 (23)	14.4 (52)	<0.001	0.78
	After	1.7 (6)	3.4 (11)		
Switch to second-line	Before	-	-	0.08	0.99
	After	6.7 (26)	10.0 (40)		
CD4< 100 cells/mm^3	Before	1.0 (4)	0.8 (3)	0.08	0.21
	After	1.1 (12)	2.3 (25)		

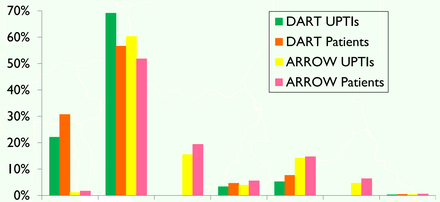
*Test whether the difference between STI vs. CT varies during randomised phase and post sub-study closure (16th March 2006)

- For mortality, WHO4/death and WHO3/4/death there was no evidence that the relative difference between STI and CT varied pre and post sub-study closure (heterogeneity p>0.5) supporting persistently increased risk of poorer clinical outcomes from prior STIs (Figure 3).
- Overall new WHO3/4/death and WHO4/death were higher in STI vs. CT, with similar trend for switch to second-line and CD4 failure, and non-significant trend for mortality where power was low.

Unplanned treatment interruptions (UPTIs) DART and ARROW

- 1055 (32%) adults in DART had at least one UPTI lasting ≥4 days (total 1955 UPTIs), median total UPTI duration per patient was 17 days (IQR 7-49)
- Overall 1434 (43%) adults had at least one TI (planned or unplanned) ≥4 days, 1253 (38%) and 1006 (30%) with a TI lasting >7 or >14 days respectively with a median total time off treatment 56 days (IQR 13-163)
- 285 (24%) children had at least one UPTI, significantly fewer than DART (p<0.001)
- 211 (17%) and 115 (10%) children had a TI >7 or >14 days respectively with median total time off treatment 13 days per child (IQR 7-34)

Figure 4: Reasons for unplanned treatment interruptions (DART and ARROW)



- In both trials the most common reasons for UPTIs were structural, mostly being unable to attend clinic. Followed by adverse events in DART, of which >50% were blood disorders, and voluntary decision to stop ART in ARROW
- In DART 65 (3%) UPTIs were due to other illness including 12 related to psychosis/mental illness including hearing voices. 102 (5%) were due to voluntary decisions by patient to stop ART including 13 related to divine healing/faith

Effect of total duration off treatment on long term CD4 and clinical events

- 2826 (85%) adults had CD4 available at 4 years; 339 (10%) died prior to 4 years, 139 (4%) were lost to follow-up and 12 had no CD4 count available
  - For every extra cumulative month off ART for UPTI, CD4 4 years post ART initiation was 7 cells/mm^3 lower (95%CI 1-12, p=0.01)
  - CD4 was 55 cells/mm^3 [35-75] lower in those who had had STIs (p<0.001), but there was no additional effect of longer STIs
- 1145 (95%) children had CD4% available at 3 years; 45 (4%) died prior to 3 years and 16 (1%) were lost to follow-up
  - For every extra cumulative month off ART CD4% 3 years after ART initiation was 1.7% lower (0.8-2.6%, p=0.001)
- In adults, having any time off treatment increased mortality risk (HR=2.97 [95%CI 2.09-4.22], p<0.001) with no independent effect of (time-updated) cumulative time off ART (HR=1.05 per doubling [0.96-1.16], p=0.26)
  - Results were similar for WHO 4 events/death and CD4 <100 cells/mm^3 after 48 weeks
- In children, having ever interrupted ART was associated with a non-significant trend of increased mortality (2.60 [0.65-10.45], p=0.18) with a non-significant trend to risks increasing further with increasing (time-updated) cumulative time off ART (1.60 per doubling [0.90-2.83], p=0.11)
  - Results for WHO4 event/death were more similar to adults (1.36 [0.26-2.12], p=0.17 and 1.01 [0.35-2.89], p=0.99 respectively)
  - Increasing cumulative time off ART increased the risk of CD4<100 cells/mm^3 after 48 weeks (1.42 per doubling [1.05-1.91] , p=0.02) but there was no independent effect of ever vs. never having previously interrupted ART (HR=1.15 [0.50-2.68], p=0.74)

Conclusion

In adults, treatment interruptions are associated with lower CD4 counts and poorer clinical outcomes over the long-term even after returning to ART. In children, unplanned treatment interruptions showed similar results. Both highlight the importance of avoiding ART interruption and maintaining drug supplies in ART programmes in resource limited settings.

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