



# The Role of Hydroxyurea in Enhancing the Virological Control Achieved through Structured Treatment Interruption (STI) in Primary HIV Infection (PHI): Final Results from a Randomised Clinical Trial

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## Introduction

STIs have been postulated to improve virological control in PHI by stimulating specific T-lymphocyte immunity. Durable virological control may be enhanced by using hydroxyurea, an anti-metabolite that suppresses T-lymphocyte activation. Early initiation of therapy in PHI may have a role in generating immune control, suppressing HIV, and limiting virological rebound.

## Aims

- To determine whether the addition of hydroxyurea to ART results in better viral control after STIs.
- To determine whether control of HIV can be achieved with intermittent or pulsed therapy, initiated in PHI.
- To assess the safety of these therapeutic combinations.

## Methods

Patients were recruited from a network of primary care sites and St Vincent's Hospital in Darlinghurst, Sydney, Australia. Eligible patients who had HIV detected by p24 antigen or plasma viremia and negative or evolving Western Blot (acute infection), or, a positive Western Blot and documented negative HIV antibody test within the previous 6 months (early infection) were invited to participate in the study.

Consenting patients were randomised to the following treatment arms in a 1:1 ratio:  
 1. Standard ART (indinavir 800mg/ritonavir 100mg bid, didanosine 400mg qd, and either lamivudine 150mg or stavudine 40mg bid daily)  
 2. Standard ART (as above) + Hydroxyurea 500mg bd  
 Treatment was administered according to the following trial phases:  
 1. **Phase A:** Induction – treatment administered for 6-12 months to induce viral load < 50 copies/ml  
 2. **Phase B:** up to 3 STIs (B1, B2, B3) of no longer than 6 months (the duration governed by viral load) and  
 3. **Phase C:** up to 2 re-introduction treatment periods (C1 and C2) of 3 months  
 After Phase A, patients achieving undetectable viral load (<50 copies/ml) were asked to commence a period of treatment interruption (Phase B). Treatment was reintroduced if viral load rebounded to above 5000 copies/ml.  
 Study visits: screening, baseline, weeks 1, 2, 4, 8 then second monthly until initial STI. During STIs, visits were fortnightly for the first month, then monthly.

### Primary endpoint:

Proportion of patients in each arm with treatment success; as defined by: viral load <5000 copies/ml 6 months after not more than three treatment interruptions

### Secondary endpoints:

- Time weighted change in viral load, CD4 and CD8 T-cell subsets from baseline to end of each phase
- CD4 count at endpoint (6 months after no more than three treatment interruptions)

Predictors of treatment success (primary endpoint) were assessed using logistic regression.

**Table 1: Baseline patient characteristics**

	ART + Hydroxyurea (n=35)	ART (n=33)	Total (n=68)
<b>Age</b>			
Median	36 years	34 years	35.5 years
< 35 years	17 (48.6%)	17 (51.5%)	35 (51.5%)
35 + years	17 (48.6%)	16 (48.5%)	33 (48.5%)
<b>Sex</b>			
Male	35 (100%)	33 (100%)	68 (100%)
<b>Mode of Transmission</b>			
Homosexual	34 (97.1%)	33 (100%)	67 (98.5%)
<b>Stage of Infection</b>			
Acute	13 (37.1%)	16 (48.5%)	29 (42.7%)
Early	22 (62.9%)	17 (51.5%)	37 (54.4%)
<b>Duration from estimated time of infection to initiating ART<sup>1</sup></b>			
Median	38 days	30 days	37 days
IGR	29-63 days	26-65 days	29-63.5 days
<b>Viral Load</b>			
Median	5.50 log <sup>10</sup>	5.86 log <sup>10</sup>	5.73 log <sup>10</sup>
<50,000	7 (20%)	5 (15.2%)	12 (17.5%)
50,000 - <750,000	15 (42.9%)	10 (30.3%)	25 (36.8%)
750,000 +	13 (37.1%)	18 (54.6%)	31 (45.6%)
<b>CD4 T lymphocyte count</b>			
On treatment	513	520	1035
<300	4 (11.4%)	1 (3%)	5 (7.4%)
300-499	13 (37.1%)	14 (42.4%)	27 (39.7%)
500+	18 (51.4%)	18 (54.6%)	36 (52.9%)

**Table 2: Predictors of treatment success**

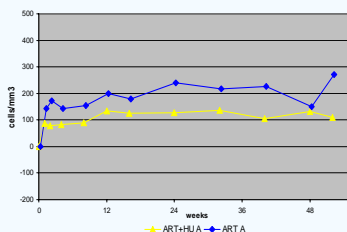
	Failure	Success	OR	95%CI	p-value	p-trend
<b>Total</b>	41	18				
<b>Treatment Arm</b>						
ART	21	9	1			
ART+Hydroxyurea	20	9	1.05	0.35 - 3.18	0.931	
<b>Age &lt; 35 years</b>	22	9	1			
Age ≥ 35 years	19	9	1.06	0.38 - 3.51	0.796	
<b>Acute Infection</b>	20	7	1			
Early infection	21	11	1.15	0.48 - 4.62	0.484	
<b>0-3 Western blot bands</b>	20	7	1			
4 + Western blot bands	21	11	1.15	0.48 - 4.62	0.484	
<b>0-2 primary HIV symptoms</b>	6	3	1			
3-4 primary HIV symptoms	8	5	1.25	0.21 - 7.41	0.806	
5+ primary HIV symptoms	27	10	0.74	0.15 - 3.54	0.707	0.559
<b>Duration of symptoms &lt; 14 days</b>	20	10	1			
Duration of symptoms ≥ 14 days	21	8	0.76	0.25 - 2.32	0.632	
<b>Time from infection to ART</b>						
< 37 days	22	9	1			
> 37 days	19	9	1.16	0.38 - 3.51	0.796	
<b>Baseline RNA group</b>						
<50000	4	7	1			
50000 - 750000	14	6	0.24	0.05 - 1.16	0.077	
>750000	23	5	0.12	0.03 - 0.58	0.009	0.011
<b>Baseline CD4 group</b>						
<500	18	9	1			
500+	23	9	0.576	0.21 - 2.38	0.055	

<sup>1</sup>Other covariates also tested include: duration of Phase A therapy, use of Hydroxyurea during interruption and time weighted CD4 and CD8 change during Phase A. All of these were not significant.

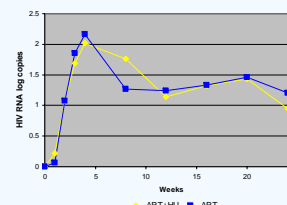
**Table 3: Time weighted change in CD4, CD8 and log viral load by phase**

	ART+ Hydroxyurea		ART		non-p <sup>2</sup>
	n	Mean (SD)	n	Mean (SD)	
<b>CD4</b>					
<b>On treatment</b>					
Phase A	35	100.74 (120.90)	33	195.73 (156.12)	0.014
Phase C1	23	32.48 (79.70)	19	101.31 (161.23)	0.181
Phase C2	22	37.97 (42.64)	15	93.42 (107.81)	0.395
<b>Off treatment</b>					
Phase B1	29	-46.10 (74.91)	30	-42.79 (114.21)	0.868
Phase B2	23	12.00 (134.79)	18	-86.38 (146.47)	0.055
Phase B3	22	-35.08 (92.35)	15	-63.55 (118.15)	0.395
<b>CD8</b>					
<b>On treatment</b>					
Phase A	35	-326.08 (395.30)	33	-219.96 (532.96)	0.211
Phase C1	23	-123.34 (274.19)	19	8.21 (299.82)	0.130
Phase C2	22	-136.37 (261.92)	15	-18.72 (208.62)	0.199
<b>Off treatment</b>					
Phase B1	29	61.16 (141.85)	30	92.75 (125.92)	0.934
Phase B2	23	151.88 (407.30)	18	28.10 (146.59)	0.486
Phase B3	22	111.80 (232.74)	15	31.04 (196.50)	0.584
<b>Log viral load</b>					
<b>On treatment</b>					
Phase A	35	-2.93 (0.61)	33	-3.09 (0.84)	0.141
Phase C1	23	-2.08 (0.69)	19	-2.05 (0.67)	0.762
Phase C2	22	-1.83 (0.70)	15	-1.95 (0.54)	0.676
<b>Off treatment</b>					
Phase B1	29	1.25 (0.55)	30	1.22 (0.48)	0.838
Phase B2	23	1.41 (0.41)	18	1.36 (0.49)	0.627
Phase B3	22	1.11 (0.38)	15	1.04 (0.58)	0.841

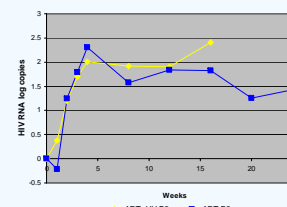
<sup>2</sup>Non-parametric p-value



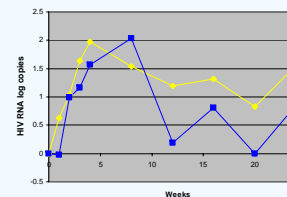
**Fig 1: Change in CD4 from baseline during induction Phase A**



**Fig 2: Change in log viral load from baseline during interruption Phase B1**



**Fig 3 Change in log viral load from baseline during interruption Phase B2**



**Fig 4: Change in log viral load from baseline during interruption Phase B3**

## Results

Baseline characteristics are shown in Table 1.

68 patients were randomised: 35 to ART+HU and 33 to ART alone. 59 patients had VL<500 copies at the end of the induction phase and underwent up to 3 STIs. 18 of these patients were able to maintain VL<5,000 copies for at least 6 months of therapy.

There was no significant difference between the randomised treatment arms in the proportion maintaining undetectable viral load for six months during an STI (9 [25.7%] ART+HU, 9 [27.3%] ART, p=0.88).

The single independent predictor of maintaining undetectable viral load for six months during an STI was a baseline viral load below 50,000 copies (p=0.011). Other baseline covariates such as acute or early infection, number of western blot bands and baseline CD4 cell count were not significantly associated with treatment success (see Table 2).

The mean CD4 count at endpoint did not significantly differ between the randomised treatment arms (ART+HU: mean: 655 cells/mm<sup>3</sup>; SD:285) (ART : mean 727 cells/mm<sup>3</sup>; SD: 230) p=0.29).

Patients randomized to ART alone had a significantly greater mean CD4 (95 cells/mm<sup>3</sup>) increase from baseline during the induction phase (Phase A) (p=0.014) (Table 3; Figure 1). There were no significant differences between treatment arms in mean change from baseline in CD8 cell count or in viral load during any of the treatment or interruption phases (Table 3; Figure 2-4) A greater proportion of patients receiving ART+HU were recorded as having experienced serious adverse events 9/35 (26%) compared to patients receiving ART alone (3/33 (9%)), though this difference was not statistically significant (Fischer's exact: p=0.1111).

## Conclusions

- Hydroxyurea was not beneficial in improving virological control during an analytical treatment interruption following ART administered according to an STI protocol initiated during PHI
- Baseline RNA was a significant predictor for maintaining undetectable viral load for six months during a treatment interruption
- Hydroxyurea significantly blunted CD4 cell increases during therapy
- A non significant increase in SAEs was noted with Hydroxyurea

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