The Impact of Immunoglobulin in Acute HIV Infection on the HIV Reservoir: A Pilot Randomized Controlled Trial

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BACKGROUND

- Immediate ART during acute HIV infection can minimize the size of the latent reservoir and in a minority of individuals can lead to post-treatment control [1].

- Additional strategies will be needed to induce a cure. Agents under investigation include HDAC inhibitors and the passive infusion of neutralizing antibodies [2].

- Intravenous immunoglobulin is used in autoimmune conditions. Safe and although not HIV specific has been shown in chronic HIV infection to temporarily reduce viral reservoir in the presence of ART [3,4]

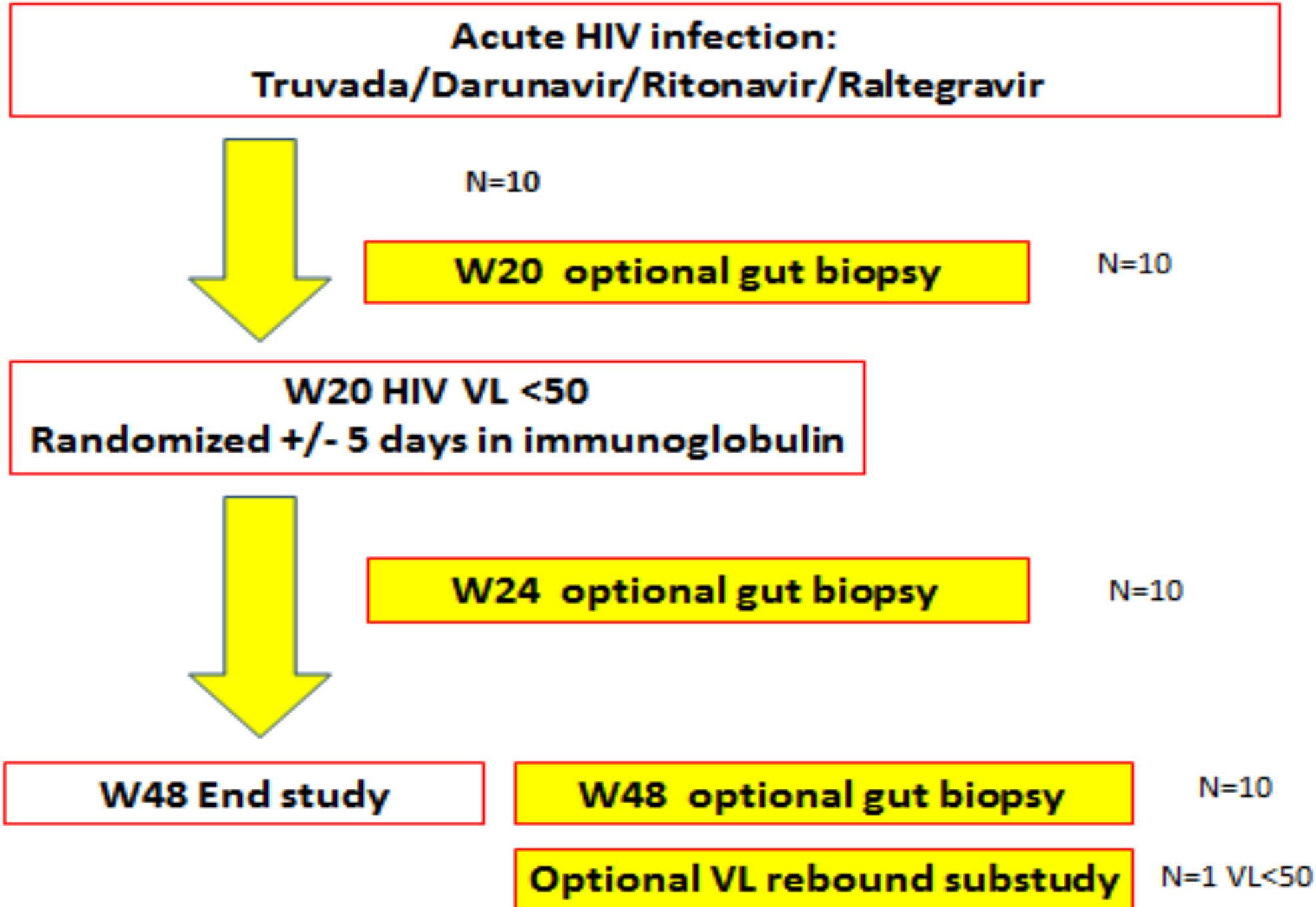
1.Massanella M, et al. J Clin Invest. 2016;126:464–72. 2. Conway J, et al. Proc Natl Acad Sci US 2015, A 112, 5467–5472. 3. Lindkvist A, et al. AIDS Res Ther. 2009; 6:15. 4. Gisslén M, et al. Scand J Infect Dis. 2005; 37(11-12):877-81.

AIM

To investigate whether immunoglobulin plus ART in acute HIV infection reduces HIV reservoir and immune activation compared with ART alone.

METHODS

- Prospective, proof of concept 48- week randomized study
- Acutely HIV-infected adults were enrolled at a single site
- Acute HIV infection defined as:
  - HIV Ab negative with p24/PCR DNA positive or
  - HIV Ab positive with a negative HIV test in preceding 3/12 months or
  - HIV incident assay
- At enrolment all initiated 4-drug ART (tenofovir, emtricitabine, ritonavir boosted darunavir and raltegravir).


Acute HIV infection:
Truvada/Darunavir/Ritonavir/Raltegravir
N=10
W20 optional gut biopsy
N=10
W20 HIV VL <50
Randomized +/- 5 days in immunoglobulin
W24 optional gut biopsy
N=10
W48 End study
W48 optional gut biopsy
N=10
Optional VL rebound substudy
N=1 VL<50

INVESTIGATIONS

Reservoir measurement

- HIV-1 DNA in peripheral blood CD4 cells [1]
- Low copy HIV RNA - RT-PCR able to detect 3 copies/ml
- Gut HIV DNA – qPCR

Bacterial translocation

- Plasma bacterial 16s DNA - real time PCR [2]

Immune activation and lymphocyte subsets

- Flow cytometry

Immunohistochemistry

- Rectal biopsies stained for CD4 and CD8 Abs. Images analysed in ImageJ [2]

1.Conway J, et al. Proc Natl Acad Sci US 2015, A 112, 5467–5472. 2.Jiang W, et al. J Infect Dis.2009;199:1177-85.

Baseline characteristics of participants

	Treatment (n=5)	Control (n=6)	*p- value*
Male	5 (100%)	6 (100%)	*1.00*
Ethnicity White Black	 5 (100%) 0 (0)	 5 (83.33%) 1 (16.67%)	*1.00*
Age	31.2 (3.3)	31.3 (5.4)	*0.96*
Genotype: wildtype virus	5	6	*1.00*
HIV VL (log_{10} copies/million CD4 cells)	4.82 (4.82)	6.28 (6.48)	*0.20*
CD4:CD8 ratio	0.71 (0.35)	0.5 (0.22)	*0.30*
CD4 count	678 (218.75)	508.6 (72.45)	*0.16*
Total HIV DNA(log_{10} copies/million CD4 cells)	3.80 (3.43)	4.04 (3.74)	*0.14*

No difference in HIV DNA in PBMCs or gut tissue

	Mean change from week 19 to 48			
Primary outcome: Reservoir	**Treatment group**	**Control group**	**Difference between groups (95% CI)**	***P-value***
Total HIV DNA in PBMCs (log_{10} copies/million CD4 cells)	2.09	-3.10	3.14 (-3.4, 3.7)	*0.38*
Total HIV DNA in gut (log_{10} copies/million CD4 cells)	4.72	-4.82	5.09 (-5.54, 5.77)	*0.55*
Low copy RNA copies/ml	5.2	12.25	-7.05 (-40.87, 26.77)	*0.57*

No change in immune activation, exhaustion or microbial translocation

	Mean change from week 19 to 48			
Primary outcome: Reservoir	**Treatment group (n=5)**	**Control group (n=5)**	**Difference between groups (95% CI)**	***P-value***
Immune activation				
CD8+CD38+	18.25	5	13.25(-47.63,74.12)	*0.5*
CD8+HLA.DR+	2.14	-0.1	2.25(-7.54,12.03)	*0.43*
Immune exhaustion				
CD8+ Lag3	0.55	-3.15	3.69(-19.28,26.67)	*0.43*
CD8+ Pd1	5.81	3.96	1.85(-18.29,21.99)	*0.79*
CD8+ Tim3	13.27	0.94	12.33(-26.82,51.48)	*0.28*
Microbial translocation				
16S RNA copy/nl	24.16	14.77	9.39(-83.09,101.87)	*0.8*

CONCLUSIONS

1. IVIG was safe and highly acceptable to individuals with AHI

2. IVIG in acute HIV infection had no impact on viral reservoir in the blood or gut measured by total DNA and low copy RNA

3. Furthermore it had no impact on immune activation, immune exhaustion or bacterial translocation

4. This is a small proof of concept study powered to detect only large changes between the groups

5. The rapid recruitment to this study and fact that all participants volunteered for the optional gut biopsies highlights the willingness of individuals with acute HIV to take part in cure research.

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