

Absence of Serological Response Following Early Treatment of Acute HIV Infection

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HIV Diagnostics Conference
Mar 22, 2016
Atlanta, GA

Background

Initiation of HAART at very early times in acute HIV infection (AHI) can reduce viral load to below detectable levels.

The reduction of plasma viremia may reduce HIV-1 immune response and emergence of HIV diagnostic markers in blood.

HIV infected infants who initiated treatment before 12 weeks of age frequently become HIV seronegative by 2 years of age, but have not cleared virus from latent reservoirs.

Examine evolution of HIV serological markers following early HAART Therapy

Study Populations and Assays

Evolution of HIV Markers in two Acute HIV Infection Cohorts

RV217 - Untreated population

RV254 – Initiated HAART Treatment during AHI

Viral markers were followed at various times post first infection

RNA	Screen – Aptima (Hologic) Viral Load – (Abbott m200)
p24 Ag	Bio-Rad p24 Ag (RUO)
4th Gen EIA	Bio-Rad Ab/Ag Combo
3rd Gen EIA	Bio-Rad EIA 1/2/O
Supplementary	Bio-Rad Western blot Bio-Rad MultiSpot

MHRP RV217

Acute Infection Surveillance Study

High risk populations in Uganda, Tanzania, Kenya, and Thailand

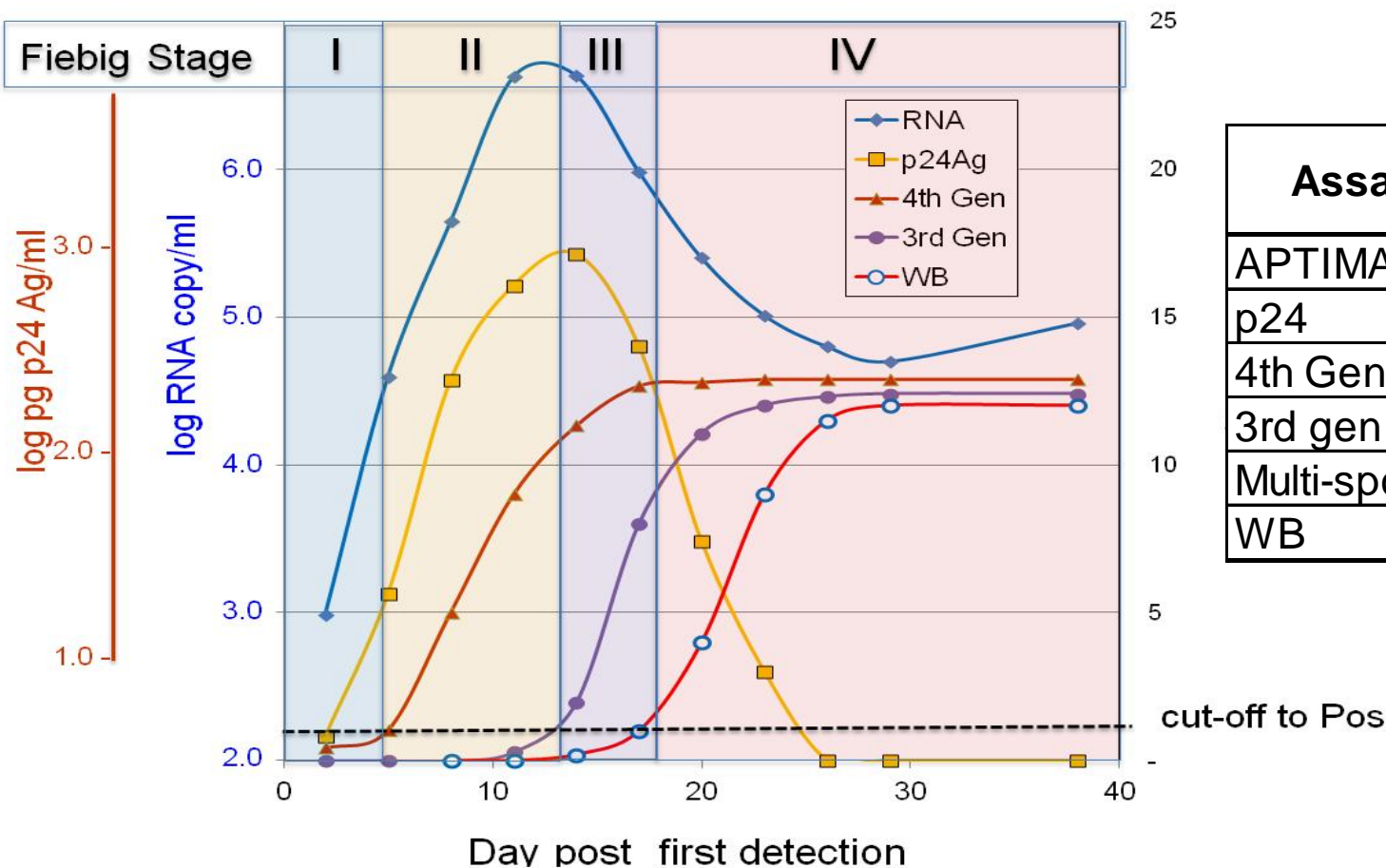
Commercial sex workers, bar workers, attendees of sexually transmitted infection clinics, and men who have sex with men

Individuals screened by 3rd Gen HIV-1/2/O EIA, (Bio-Rad)

If negative, subjected to twice weekly sampling by fingerstick and tested by Aptima Qualitative RNA (Hologic).

Participants with a reactive Aptima test were entered into a more comprehensive early HIV infection study.

Fiebig Stage based on presence of HIV markers



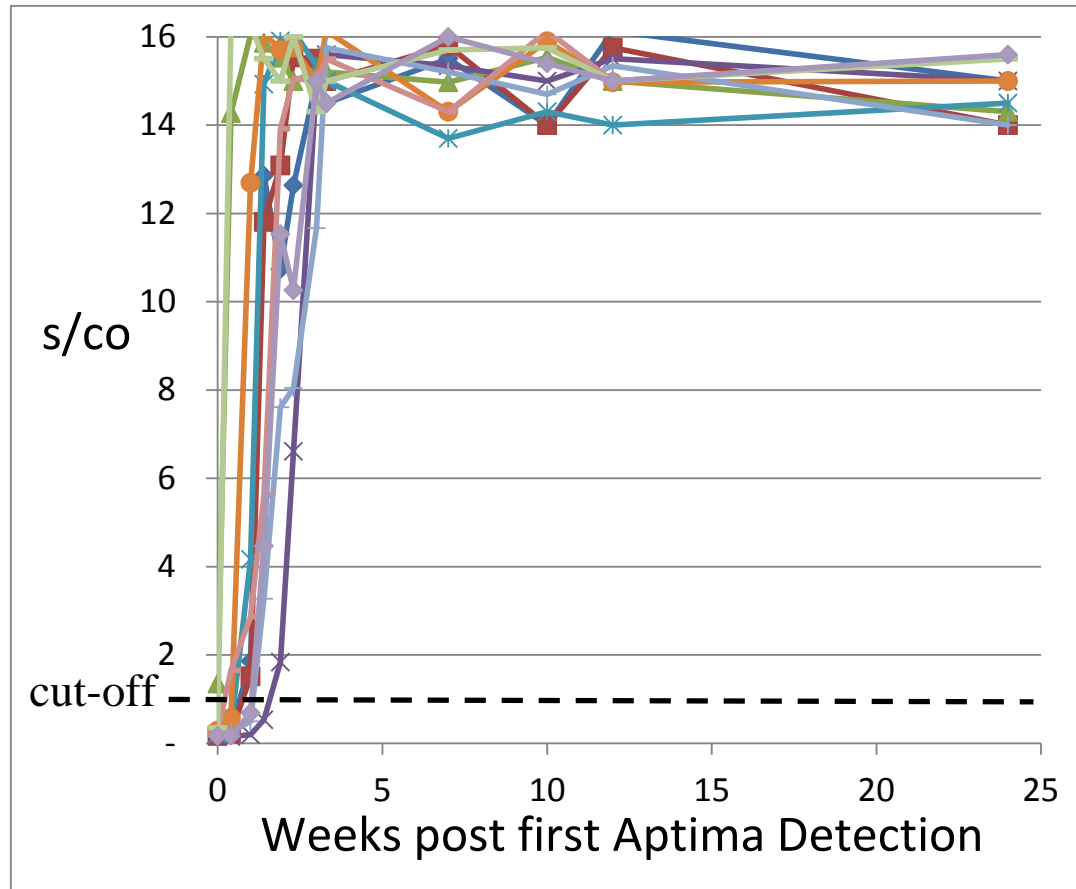
Assay	Day after Aptima
APTIMA	0.0
p24	5.4
4th Gen EIA	7.1
3rd gen EIA	15.9
Multi-spot	20.5
WB	22.6

RV217

Ave of 24 Seroconverters
Starting at Fiebig I

Marker	Stage	Day after RNA
RNA only	I	0 - 7
p24 Ag	II	8 - 16
EIA R, WB N/IND	III/IV	17 - 23
EIA R, WB POS	V	>24

3rd Gen EIA signal in Untreated HIV Volunteers



Untreated Volunteers were Reactive by 3rd Gen EIA by 2 weeks with s/co >14.

Once seroconversion took place, all samples remained EIA Reactive throughout subsequent testing periods

RV245 Early HAART Treatment

Volunteers seeking HIV counseling and testing at the Thai Red Cross AIDS Research Center in Bangkok, Thailand

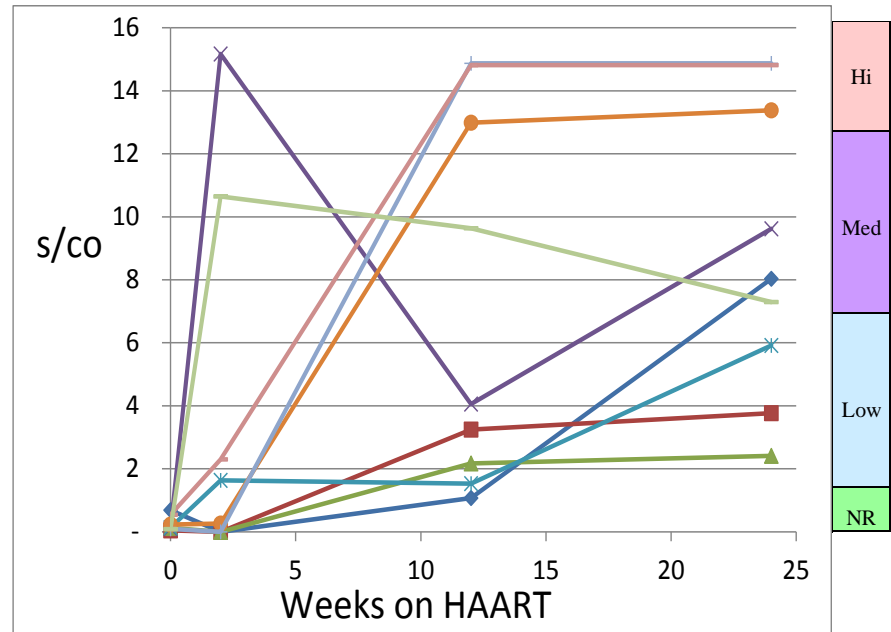
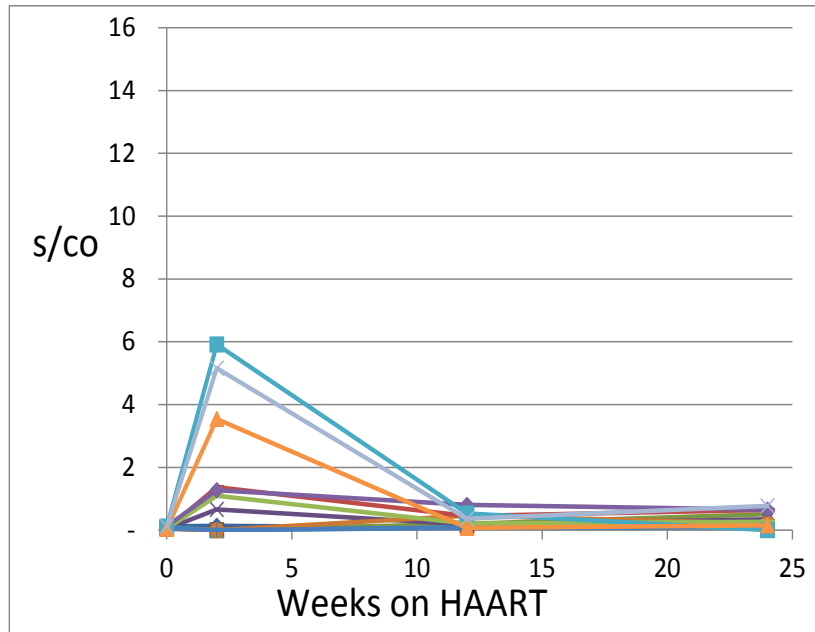
Blood samples were screened by a 4th generation EIA Ag/Ab Combo

Non-reactive samples were pooled and tested by HIV-1 Qualitative RNA (Aptima)

Volunteers diagnosed with acute HIV infection were placed on HAART and followed for viral markers

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3rd Gen EIA signal at Wk 24: Treated at Fiebig I



Treated at Fiebig I N = 20

11 (55%) Non Reactive (NR) [6 (30%)

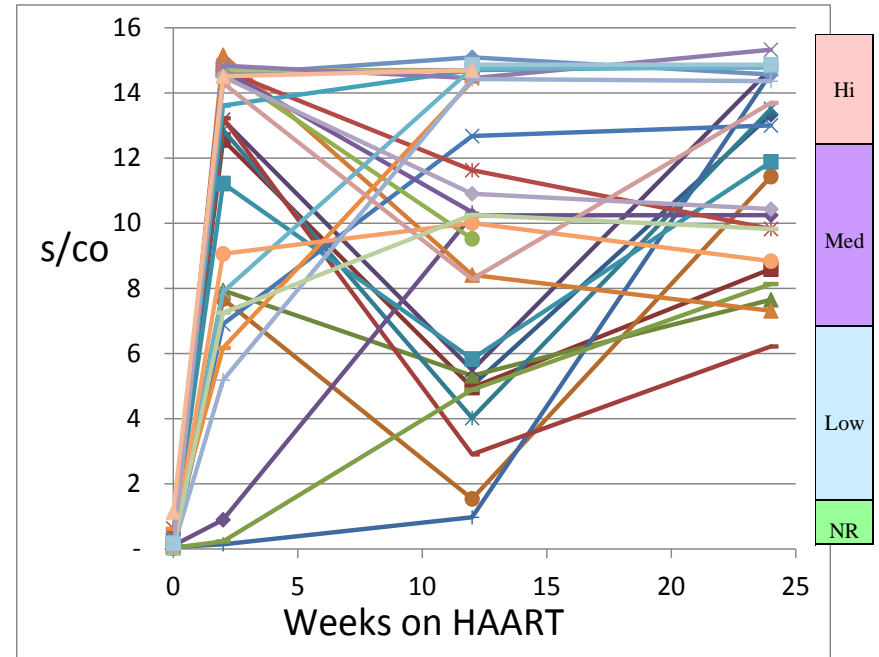
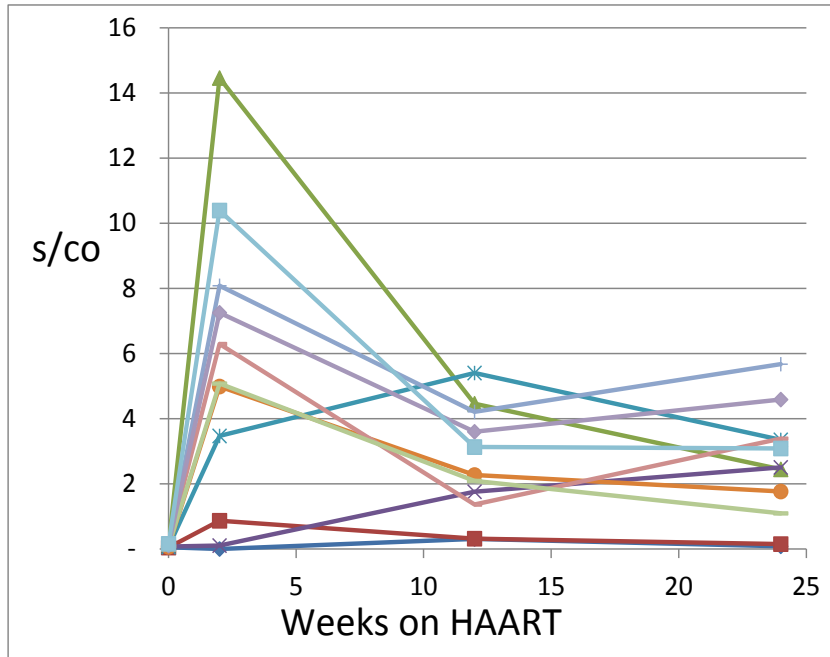
Transient]

3 (15%), Low

3 (15%) Medium

3 (15%) High.

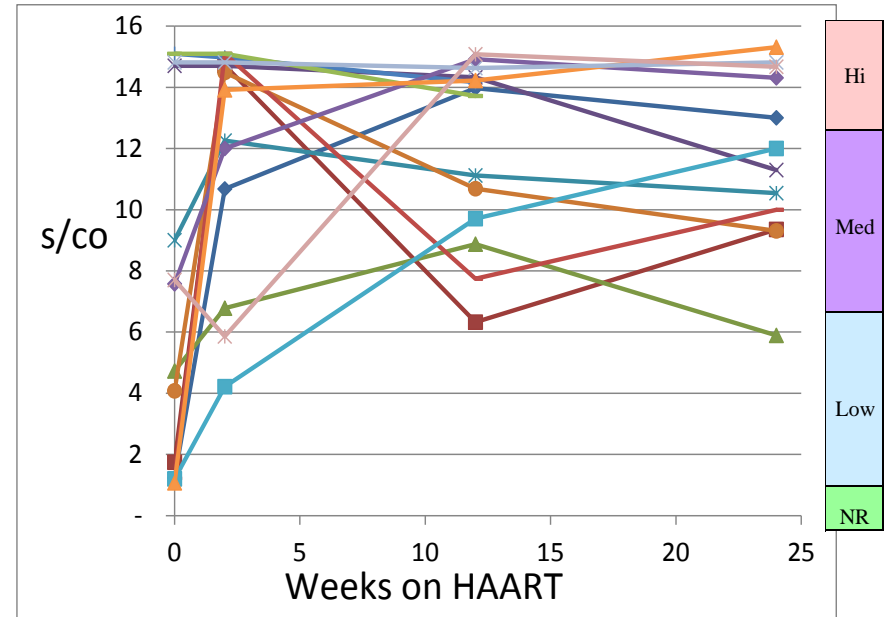
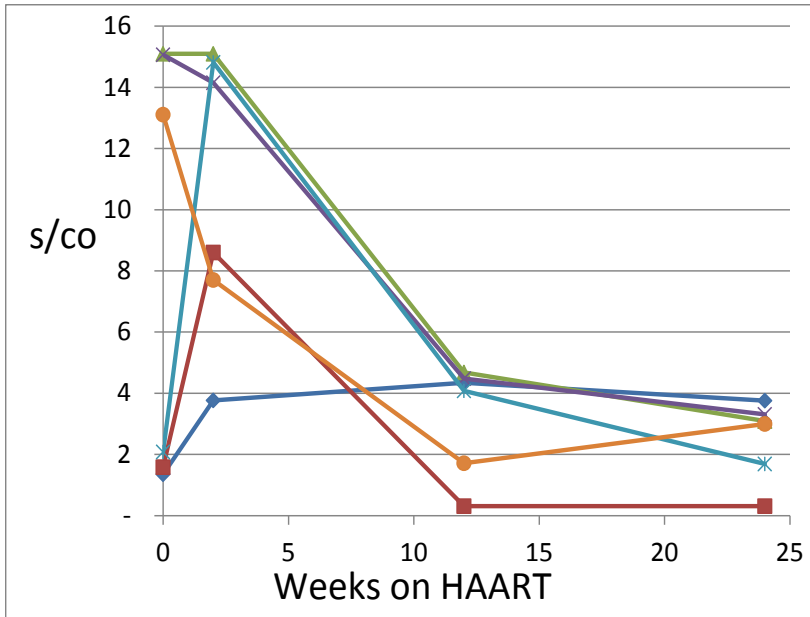
3rd Gen EIA signal in Individuals Treated at Fiebig II



Treated at Fiebig II N = 30

2 (6.7%)	NR
8 (26.7%)	Low
14 (46.7%)	Medium
6 (20%)	High

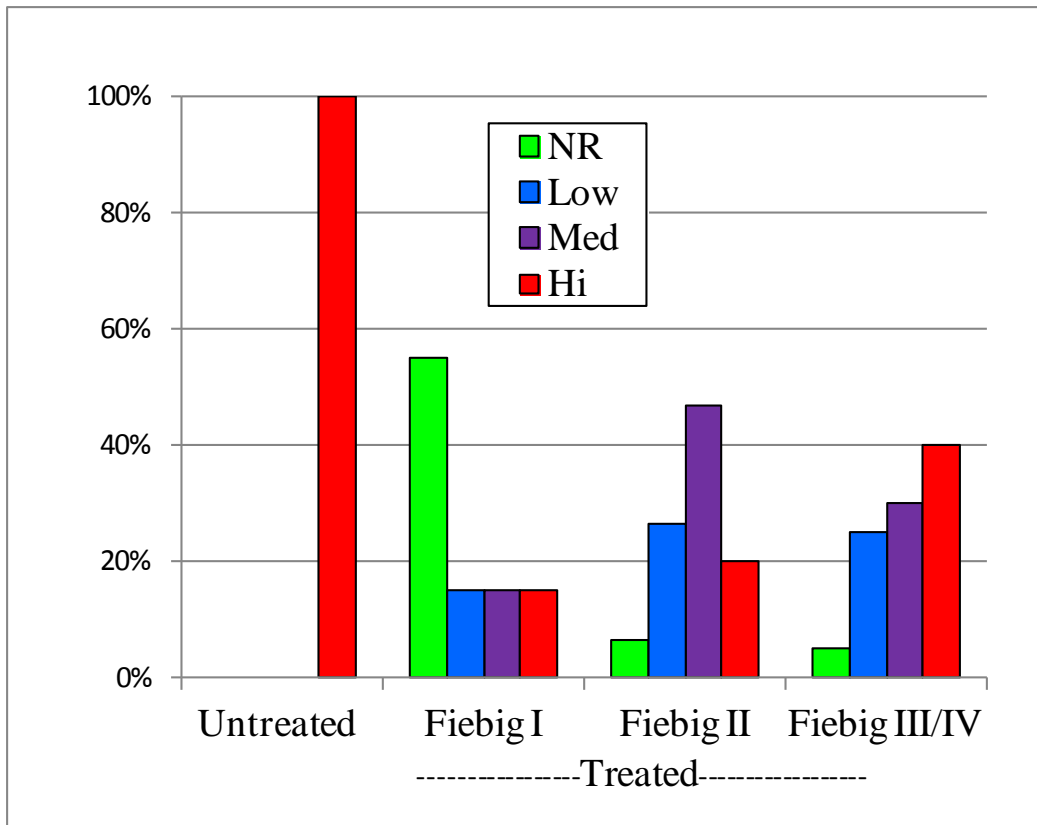
3rd Gen EIA signal in Individuals Treated at Fiebig III/IV



Treated at Fiebig III/IV N = 20

1 (5.0%)	NR
5 (25.0%)	Low
6 (30.0%)	Medium
8 (40%)	High.

Delay/Reversion of 3rd Gen EIA following early HAART

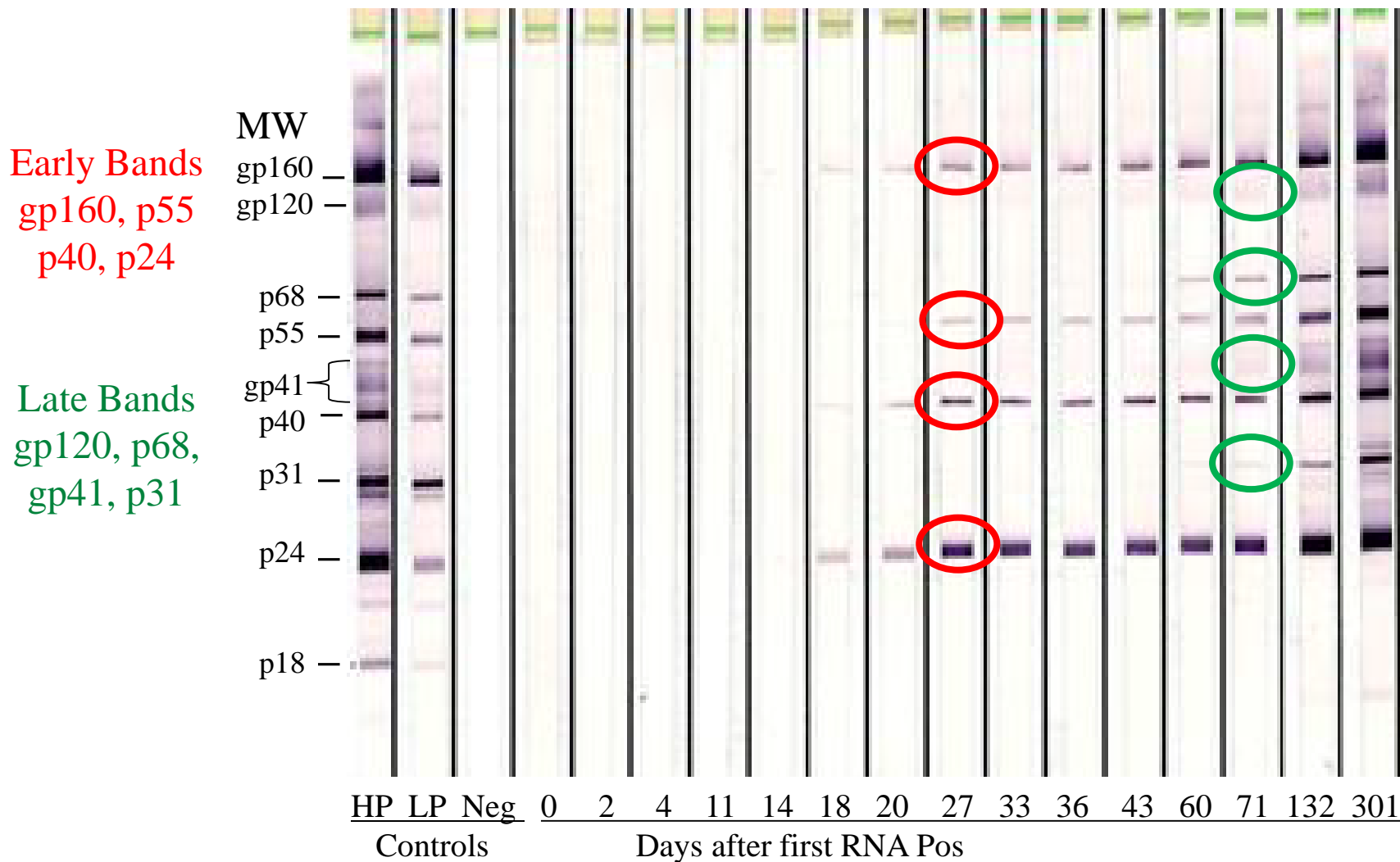


EIA Reactivity by Wk 24

HAART treatment at Fiebig I - IV results in decreased seroreactivity at later times.

		3rd Gen EIA Reactivity (s/co)								
		N	NR (<1.0)		Low (1 - 50)		Med (6 - 12)		High (>12)	
Untreated		24	0	0%	0	0%	0	0%	24	100%
Treated	Fiebig I	20	11	55.0%	3	15.0%	3	15.0%	3	15.0%
	Fiebig II	30	2	6.7%	8	26.7%	14	46.7%	6	20.0%
	Fiebig III/IV	20	1	5.0%	5	25.0%	6	30.0%	8	40.0%

Evolution of Western Blot Ag Reactivity: No Treatment



Band intensities scored as 0.5, 1. and 2

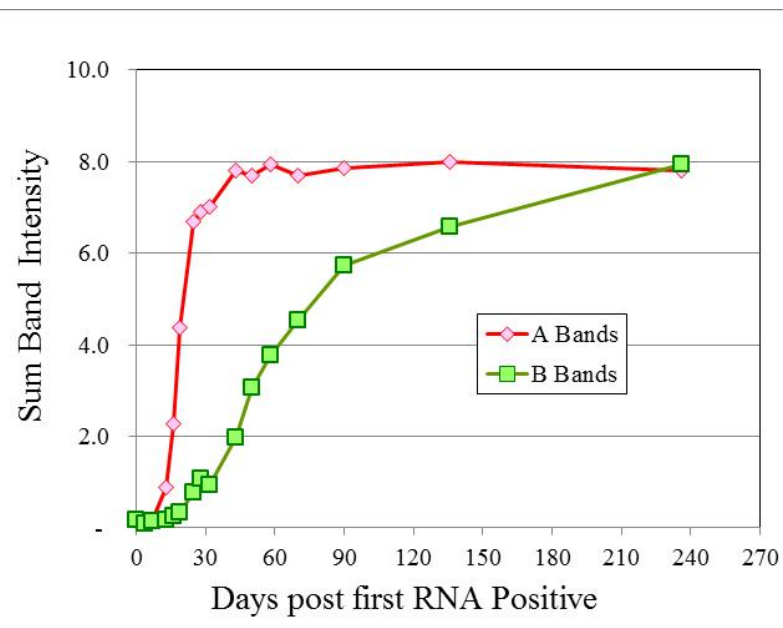
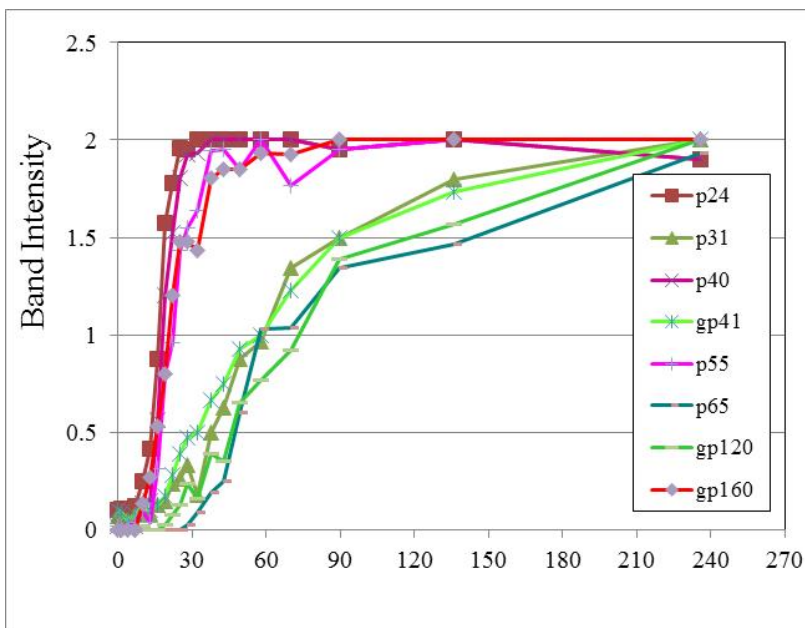
Intensity of WB Antigen Reactivity

PIN	Day	p24	p31	p40	gp41	p55	p65	gp120	gp160	Early	Late
30112-B	0	0	0	0	0	0	0	0	0	-	-
30112-1	2	0	0	0	0	0	0	0	0	-	-
30112-2	4	0.5	0	0	0	0	0	0	0	0.5	-
30112-3	7	0.5	0	0	0	0	0	0	0	0.5	-
30112-4	11	0.5	0	0	0	0	0	0	0	0.5	-
30112-5	13	1	0	0.5	0	0	0	0	0	1.5	-
30112-6	18	1	0.5	1	0.5	1	0	0	0	3.0	1.0
30112-7	20	2	1	2	0.5	2	0	0	0.5	6.5	1.5
30112-8	25	2	1	2	1	2	0	0	1	7.0	2.0
30112-9	28	2	1	2	1	2	0	0	1	7.0	2.0
30112-11	42	2	1	2	1	2	0	0	2	8.0	2.0
30112-12	56	2	2	2	1	2	0.5	0.5	2	8.0	4.0
30112-13	85	2	2	2	1	2	1	1	2	8.0	5.0
30112-14	182	2	2	2	2	2	2	2	2	8.0	8.0

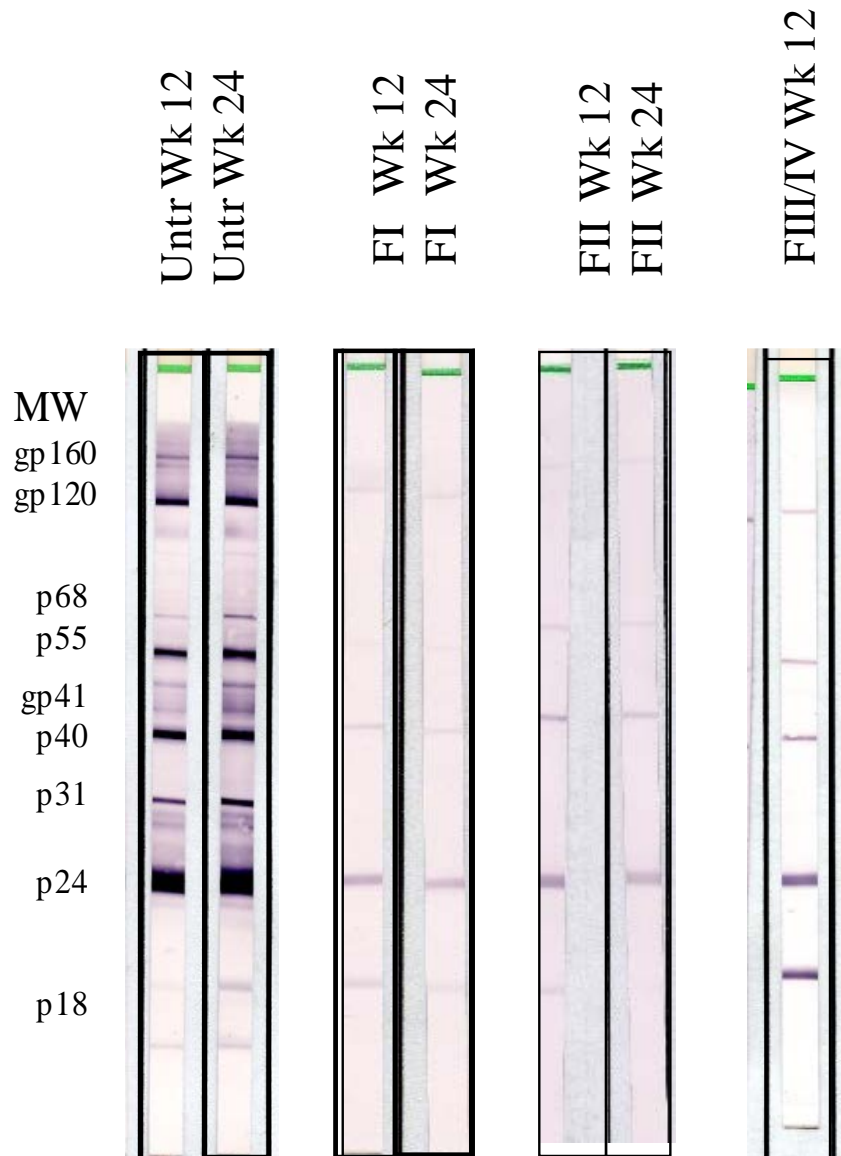
Quantitate Antigen Reactivity (AR)
based on intensity

Calculate sum of Early AR and
Sum of Late AR

Use Average table to estimate time
of infection based on Sum of ARs



Reduced Western Blot Reactivity after HAART

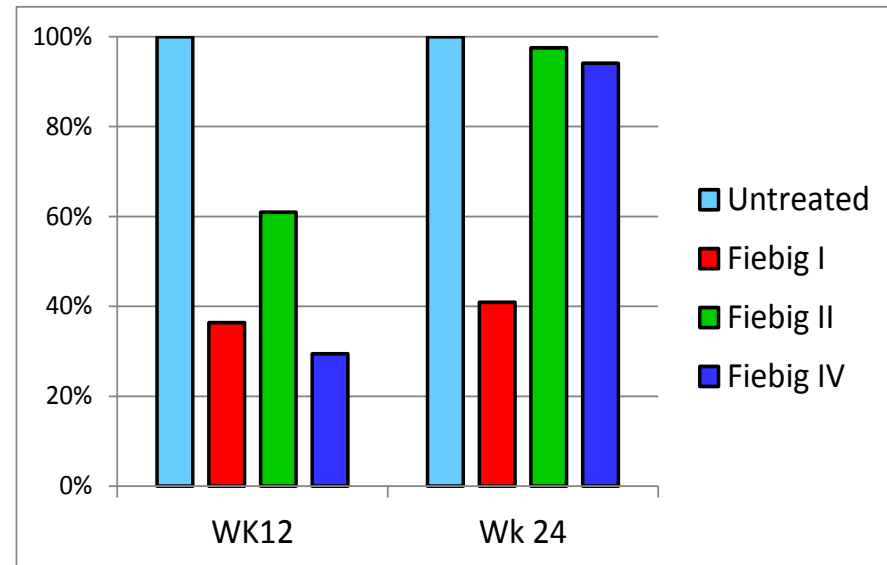


Western Blot reactivity after HAART is delayed and significantly weakened

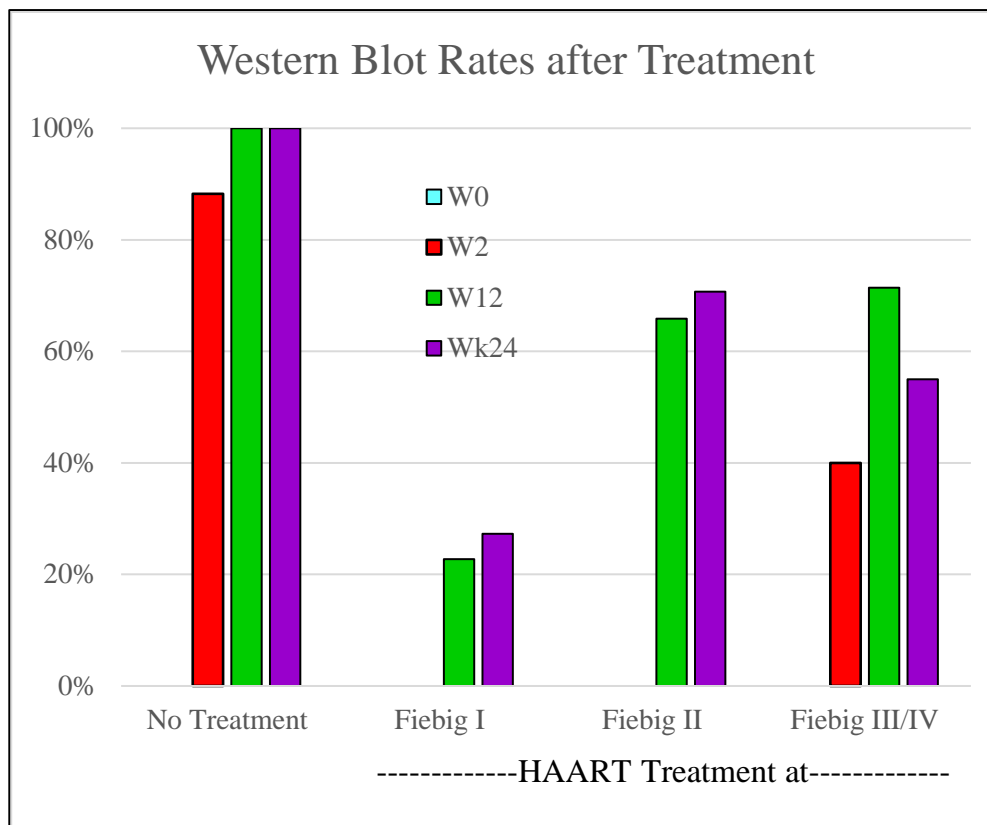
Early WB Ag R after HAART

Untreated				HAART Treatment at											
W0	W2	W12	W24	Fiebig I				Fiebig II				Fiebig IV			
W0	W2	W12	W24	W0	W2	W12	W24	W0	W2	W12	W24	W0	W2	W12	W24
-	-	8.0	8.0	0	0	0	0	0	0	0	0	0	0	0	0
-	-	8.0	8.0	0	0.5	0	0	0	1.5	0	0	0	0	0	3.5
-	-	8.0	8.0	0	0	0	0	0	0	0	3	0	0	0	3.5
-	-	8.0	8.0	0	0	0	0	0	0	0	4	0	0	0	4
-	-	8.0	8.0	0	0	0	0	0	0	0	4	0	0	0	4
-	-	8.0	8.0	0	0	0	0.5	0	0	0	5	0	0	0	4.5
-	0.5	8.0	8.0	0	0	0.5	0	0	0	0	5	0	0	0	5.5
-	0.5	8.0	8.0	0	3	0	0	0	0	0	5	0	0	0	6.5
-	0.5	8.0	8.0	0	0	5.5	0	0	0	0	5	0	0	0	7
-	0.5	8.0	8.0	0	0	6	0	0	0	0	6	0	0	0	7
-	0.5	8.0	8.0	0	0.5	6	0	0	0	0	7	0	0	0	7
-	1.0	8.0	8.0	0	0	7	0	0	0	0	7	0	0	0	8
-	1.5	8.0	5.0	0	0	8	0	0	0	0	8	0	3.5	5.5	5.5
-	1.5	8.0	8.0	0	0.5	0	2.5	0	0	0	8	0	3.5	8	8
-	3.0	8.0	8.0	0	0	0	3.5	0	0	0	8	0.5	3.5	3	3
-	4.0	8.0	8.0	0	0	0	4.5	0	0	0	8	0.5	6	6	5
-	4.0	8.0	8.0	0	0	0	5.5	0	0	1.5	2	2.5	5.5	7	7
-	4.5	8.0	8.0	0	0	0	7	0	0	1.5	2.5	5	5	5	5
-	5.0	8.0	8.0	0	0	0	8	0	0	3.5	1	4	4	4	4
-	7.0	8.0	8.0	0	0.5	7	6	0	0	3.5	5.5	6	6	6	6
0.5	-	5.0	8.0	0	0	3	7	0	0	4.5	4.5	6	6	6	6
0.5	-	8.0	8.0	0	0	4.5	8	0	0	5	5	6	6	6	6
0.5	-	8.0	8.0	0	0	4.5	8	0	0	5	5	6	6	6	6
0.5	0.5	8.0	8.0	0	0	5.5	4	0	0	5.5	4	6	6	6	6
0.5	1.0	8.0	8.0	0	0	6	5.5	0	0	6	5.5	6	6	6	6
1.5	1.5	8.0	8.0	0	0	6	6	0	0	6	6	6	6	6	6
				0	0	6.5	6.5	0	0	6.5	6.5	6	6	6	6
				0	0	7	6	0	0	7	6	6	6	6	6
				0	0	8	8	0	0	8	8	6	6	6	6
				0	0.5	3.5	7	0	0.5	3.5	7	6	6	6	6
				0	0.5	5.5	6	0	0.5	5.5	6	6	6	6	6
				0	0	8	8	0	1	4	6	6	6	6	6
				0	1	6	6	0	1	6	6	6	6	6	6
				0	1	8	7	0	1	8	7	6	6	6	6
				0	1.5	4	3	0	1.5	4	3	6	6	6	6
				0	1.5	4.5	4.5	0	1.5	4.5	4.5	6	6	6	6
				0	1.5	8	7	0	1.5	8	7	6	6	6	6
				0	3.5	1.5	2.5	0	3.5	1.5	2.5	6	6	6	6
				0	3.5	7	6	0	3.5	7	6	6	6	6	6
				0	5	4.5	5	0	5	4.5	5	6	6	6	6

	WK12	Wk 24
Untreated	100%	100.0%
Fiebig I	36.4%	40.9%
Fiebig II	61.0%	97.6%
Fiebig IV	29.4%	94.1%



WB rates following Early HAART



		W0	W2	W12	Wk24
No Treatment		0/17 0%	15/17 88%	17/17 100%	17/17 100%
Stage at Treatment Initiation	Fiebig I	0/22 0%	0/19 0%	5/22 22.7%	6/22 27.3%
	Fiebig II	0/41 0%	0/41 0%	27/41 65.9%	29/41 70.7%
	Fiebig III/IV	0/20 0%	8/20 40.0%	15/21 71.4%	11/20 55.0%

Conclusions

In untreated individuals, serological markers evolve with time post first infection:

4th Gen EIA (Ag/Ab Combo) Reactive within 7 days,

3rd Gen (Ab) within 14 days, and

WB/MS Pos within 24 days post infection.

Treatment at Fiebig I blocks subsequent emergence of anti-HIV

72.7% of individuals remained serologically HIV negative by week 24

Treatment at Fiebig II caused delay or decrease of serological markers,

68.6% of individuals at Wk 12, and 70.7% by Wk 24.

Treatment at Fiebig III and IV results in delay/decrease in seroreactivity

in 60% participants

Western Blot reactivity is significantly delayed/reduced

45% of individuals had IND or Neg WB even after Wk 12 and 24.

Caution is urged in interpretation of negative serological signal

in individuals on HAART as the absence of infection.

Acknowledgements

WRAIR - Maryland

- Sheila Peel
- Jennifer Malia
- Linda Jagodzinski
- Nelson Michael

MHRP HJF – Maryland

- Jintanat Anaworanich
- Leigh Anne Eller
- Merlin Robb
- Ashley Shutt

MHRP/AFRIMS

- Alexandra Schuetz
- Rapee Trichavaroj
- Siriwat Akapirat
- Donn Colby

Thai Red Cross AIDS Research Centre

- Praphan Phanuphak
- James Fletcher
- Nitiya Chomchey

Volunteers

Funding from DAIDS and US Military HIV Research Program