VERY EARLY ANTIRETROVIRAL TREATMENT (ART) OF SOUTH AFRICAN BLOOD DONORS AND DETECTION OF ART DRUGS IN NAT-NEGATIVE/ANTIBODY POSITIVE DONORS

24th International Plasma Fractionation Association (IPFA)

Zagreb, Croatia

16-17 May 2017

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REDS-III

Outline

- REDS-III MATHS (Monitoring and Acute Treatment of HIV Study)
  - Background
  - Study Objectives
  - Study Design
  - Results Update
- False Elite phenomenon
  - Background
  - Study Objectives
  - Study Design
  - Results
- Conclusion

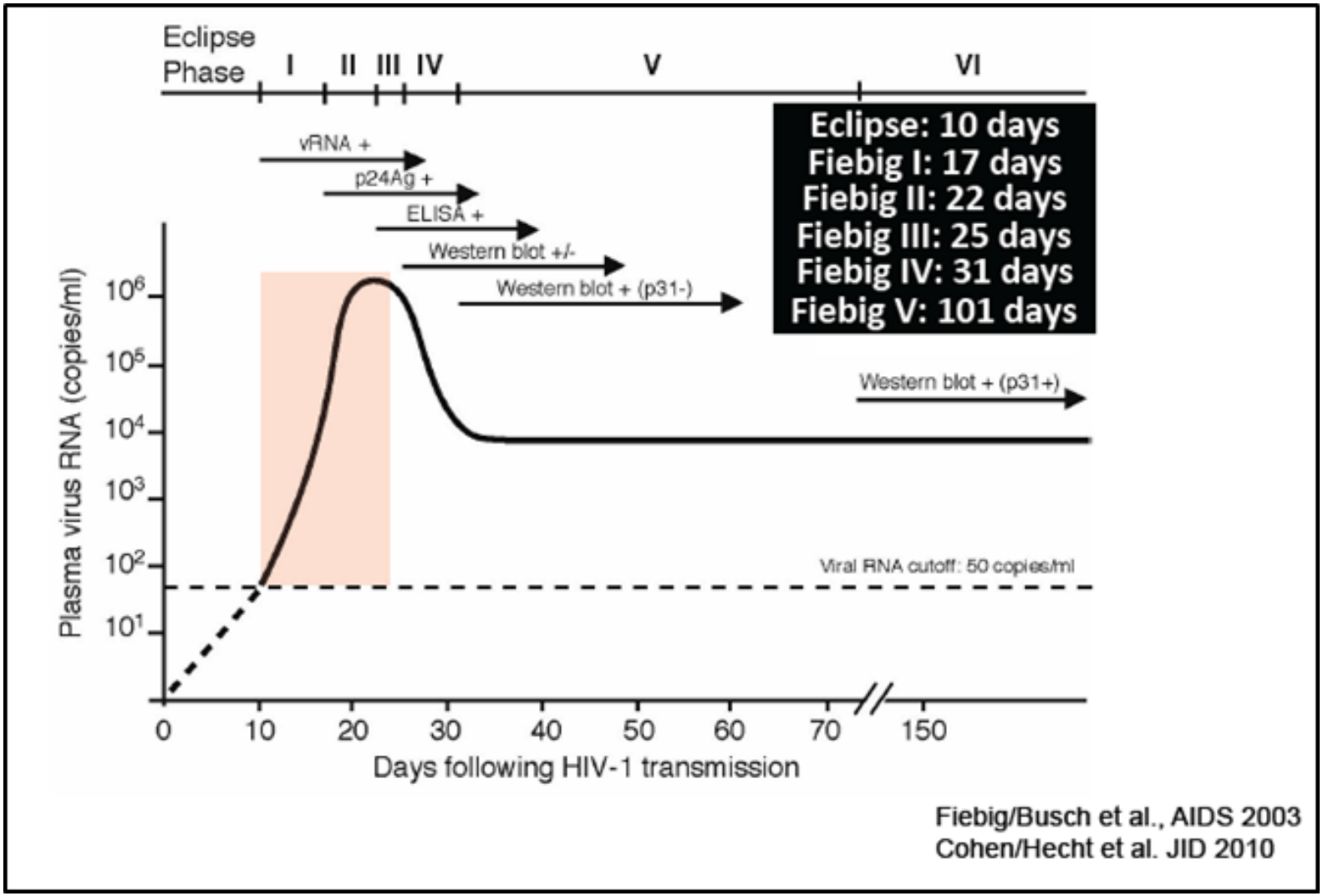
Background

- SANBS screens all donations for HIV, HBV & HCV using ID-NAT in parallel with serology testing.
- Although variable, eclipse period from HIV infection acquisition to disseminated viraemia is estimated ~10 days using ID-NAT[1]
- Very early initiation of combination antiretroviral treatment (cART) is likely to have a beneficial effect on the course of HIV disease and may facilitate HIV cure interventions[2]
- Use of ID HIV antibody and RNA testing of blood donors and the high incidence of HIV infection allows:
  - Identification of donors with very early (Fiebig stage I and II) infection, exactly the group for whom very early cART may be most beneficial in reducing the HIV reservoir
  - Identification of potential Elite Controllers (EC), a group who are able to control virus replications without treatment

[1] Lee *et al* **Journal of theoretical Biology** 2009

[2] Barouch & Deeks **Science** 2014; Okulicz **JAMA Intern Med** 2014

Fiebig Stages of HIV Infection



Fiebig/Busch et al., AIDS 2003
Cohen/Hecht et al. JID 2010

SANBS HIV+ donors according to year and Fiebig staging on index donation

Year / Fiebig Stage	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Grand Total
I	10	13	25	28	31	34	37	37	37	32	378
II	8	15	9	12	16	25	22	21	22	24	121
III-VI	745	1023	1407	1632	1634	1767	1553	1862	1784	1872	11,623
EC	2	14	7	9	14	21	18	36	40	45	206

MATHS Objectives:

1. Determine Fiebig stage at time of blood donation. For donors identified as being Fiebig stage I or II initiate cART, and ascertain Fiebig stage at the time of therapy initiation

2. Establish the size of the peripheral blood viral reservoir at the initiation of cART and at defined time points post cART initiation for donors enrolled in the treatment study

3. Conduct a “proof of concept study” to show how blood donors identified as having “hyper-acute” HIV infection by blood testing can be successfully linked to care with the initiation of early HIV treatment

MATHS Design

- Enrolment commenced end-October 2015
- Hyper-acute HIV infections (50 RNA+/Ab-)
  - Open label, non-randomized treatment study
  - Rapid (<4 weeks post index donation) administration of approved 3-drug antiretroviral therapy (cART)
- Recent HIV infections (25 HIV antibody positive, Limiting Antigen avidity (LAg) recent)
  - Open label, non-randomized treatment study
- Elite Controllers
  - Parallel prospective observational cohort of 20 elite controllers
- 2-year clinical and research follow-up
- Frequent research blood samples for HIV virology and immunology
- Less frequent, large volume leuka- and plasmapheresis for measurement of HIV reservoir

Hyperacute HIV infection (Enroll 75, target of 50 completing study protocol)

- Inclusion:
  - Allogeneic blood donors with Fiebig stage I & II HIV infection (HIV RNA positive by individual donation NAT but HIV antibody negative)
  - Donation at a SANBS site within reasonable proximity to the research staff
  - Age >= 18 years
  - English language
- Exclusion
  - Concurrent hepatitis B or C virus infection
  - Tuberculosis or cryptococcal meningitis
  - Pregnancy because of possible teratogenic effect of Efavirenz
  - Significant renal and liver impairment
  - Previous receipt of experimental HIV vaccine

Treatment and Monitoring

- Open label Rx Weeks 0 to 24:
  - Raltegravir 400 mg every 12 hours and
    - (To hasten reduction of viral load and avoid potential transmitted drug resistance to Efavirenz)
  - Emtricitabine 200 mg per day and
  - Tenofovir disoproxil fumarate 300 mg per day

- Open label Rx Weeks 25 to 96:
  - Rx with fixed-dose once per day combination containing
  - Efavirenz 600 mg and
  - Emtricitabine 200 mg and
  - Tenofovir Disoproxil Fumarate 300 mg

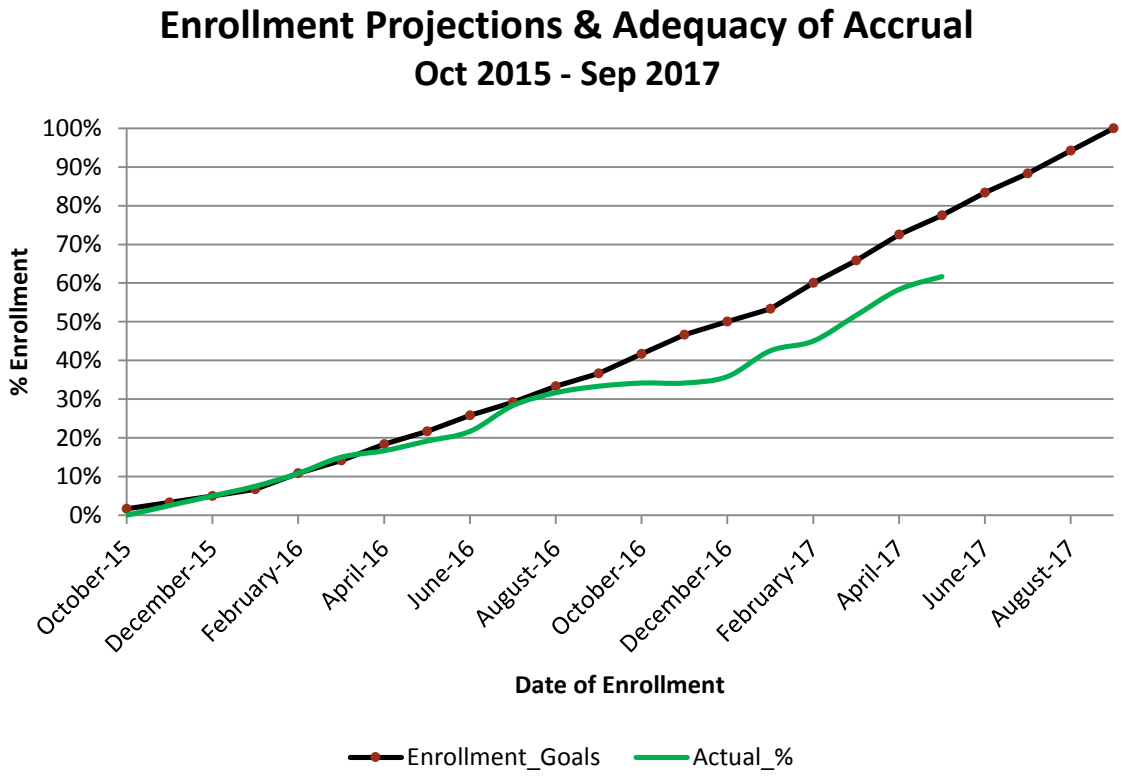
Treatment and Monitoring

ACUTE HIV PARTICIPANTS	0	2	4	8	12	16	24	36	48	56§	60	72	84	96
Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Qaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief Phys Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X				X		X		X	X		X		X
ALT, Creat	X				X		X		X			X		X
CD4*	X		X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cell-assoc HIV RNA	X		X	X	X	X	X	X	X	X	X	X	X	X
Proviral HIV DNA	X		X	X	X	X	X	X	X	X	X	X	X	X
Biorepos. Samples	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma/WBC pheresis					X			X		X				
HIV Viral load	X	X	X	X	X	X	X	X	X	X	X	X	X	X
P24 Ag (until negative)	X	X	X	X										
Anti-HIV	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV genotype and drug resistance	X						X		X					X

Elite controllers

Week	0	2	6	12	24	36	48	56§	60	72	84	96
Symptom Q'aire	X	X	X	X	X	X	X	X	X	X	X	X
FBC	X	X	X	X	X	X	X	X	X	X	X	X
ALT and Creatinine	X											
Corrected Calcium and Potassium								X				
CD4	X						X					X
HIV cell-assoc RNA & Proviral DNA	X	X	X	X	X	X	X	X	X	X	X	X
Biobank Samples (2x PBMCs and 2x Plasma, 1xserum)	X	X	X	X	X	X	X	X	X	X	X	X
Plasma/WBC Apheresis								X				
HIV Antibody	X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA (qualitative/NAT)#	X	X	X	X	X	X	X	X	X	X	X	X
Western Blot until p31 is Positive	X	X	X	X	X	X	X	X	X	X	X	X

Enrollment as of 30 April 2017 - 32 of 50 Hyper-Acutes, 17 of 25 Recents, and 5 of 20 Elites



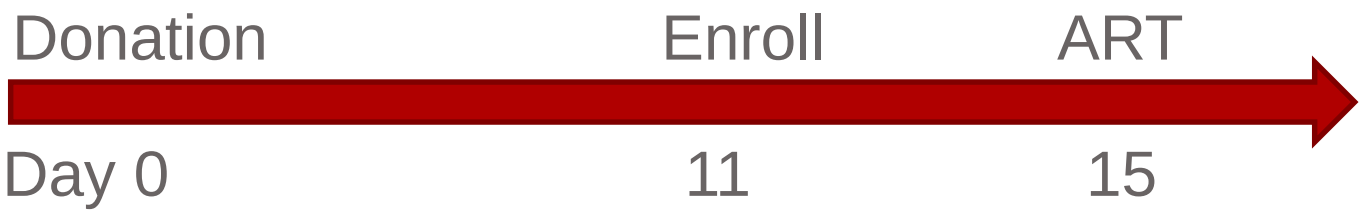
- **55** Actively Participating/Enrolled
- Median age: **27**
- **39** are female
- Racial distribution
  - **50 African**
  - **1 Asian**
  - **3 White**
  - **1 Coloured**

5 hyper acutes were enrolled but have subsequently dropped out

Timing and Fiebig stages – Hyper Acute

Median time to enrollment = 11 days; to ART = 15 days

Fiebig I	18 (56%)	3 (9%)
Fiebig II	12 (38%)	9 (28%)
Fiebig I/II	2* (6%)	0 (%)
Fiebig III	0 (%)	3 (9%)
Fiebig III-VI	0 (%)	4# (13%)
Fiebig V	0 (%)	12 (38%)
Fiebig VI	0 (%)	1 (3%)



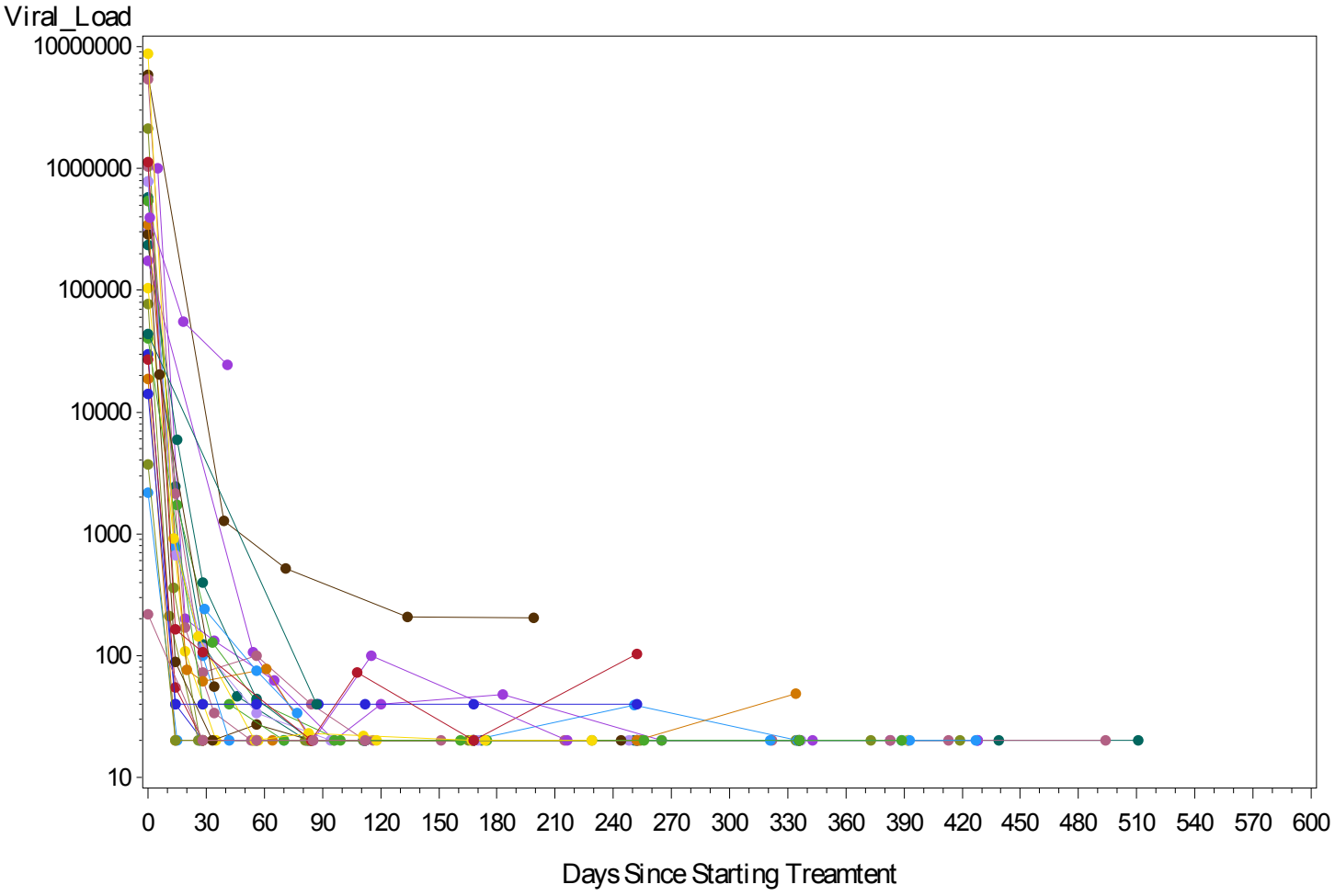
*No p24 Ag results

- 2 donors VL on enrolment(22 days) – 20239 & 397000

#No WB results.

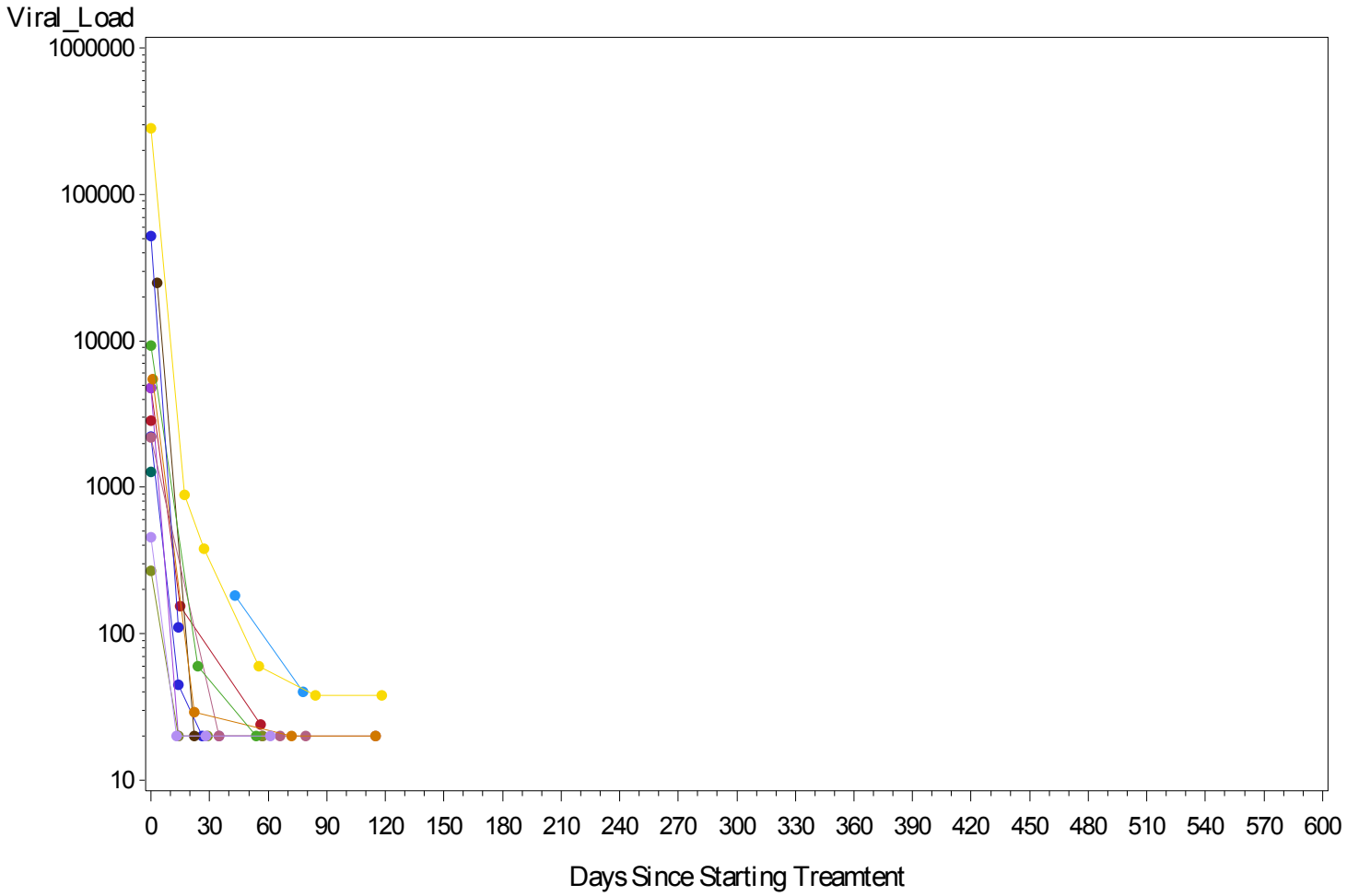
- 2 donors Index Fiebig I – enrollment 25 & 26 days
- 2 donors Index Fiebig II – enrollment 14 & 19 days

Acute HIV: RNA load



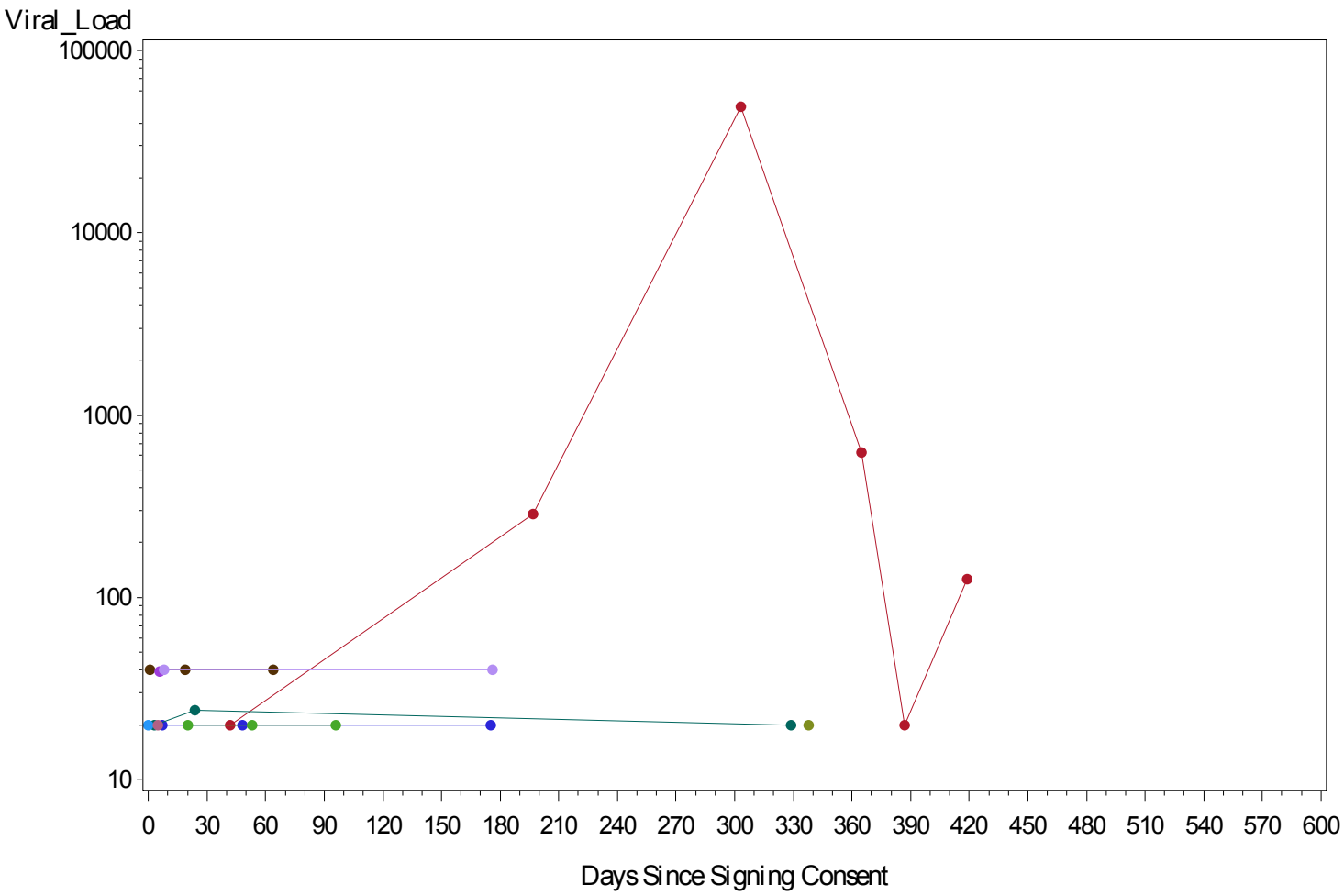
- Data available for **30** participants;
- Median HIV RNA at enrolment: **295,188; range 220 to >8.7 million**
- In **26** evaluable participants, viral suppression occurred after a median of **38.5** days

Recent HIV: RNA load



- Data available for **13** participants;
- Median HIV RNA at enrolment: **4,756; range 270 to <284,000**
- In **11** evaluable participant, viral suppression occurred after mean of **26** days

Elite HIV: RNA load



- Data available for **12** participants;
- Median HIV RNA at enrolment: **20; range 20 to 40**
- *In 1 treated elite, viral suppression occurred between 60 and 90 days*
- *High level drug resistance in NNRTI region to Nevirapine and Efavirenz at week 24*

False Elite controllers

Background

- Anecdotal evidence of Elite Controllers reporting ART and therefore “false EC”
- Apparent increase in EC during a winter incentive campaign

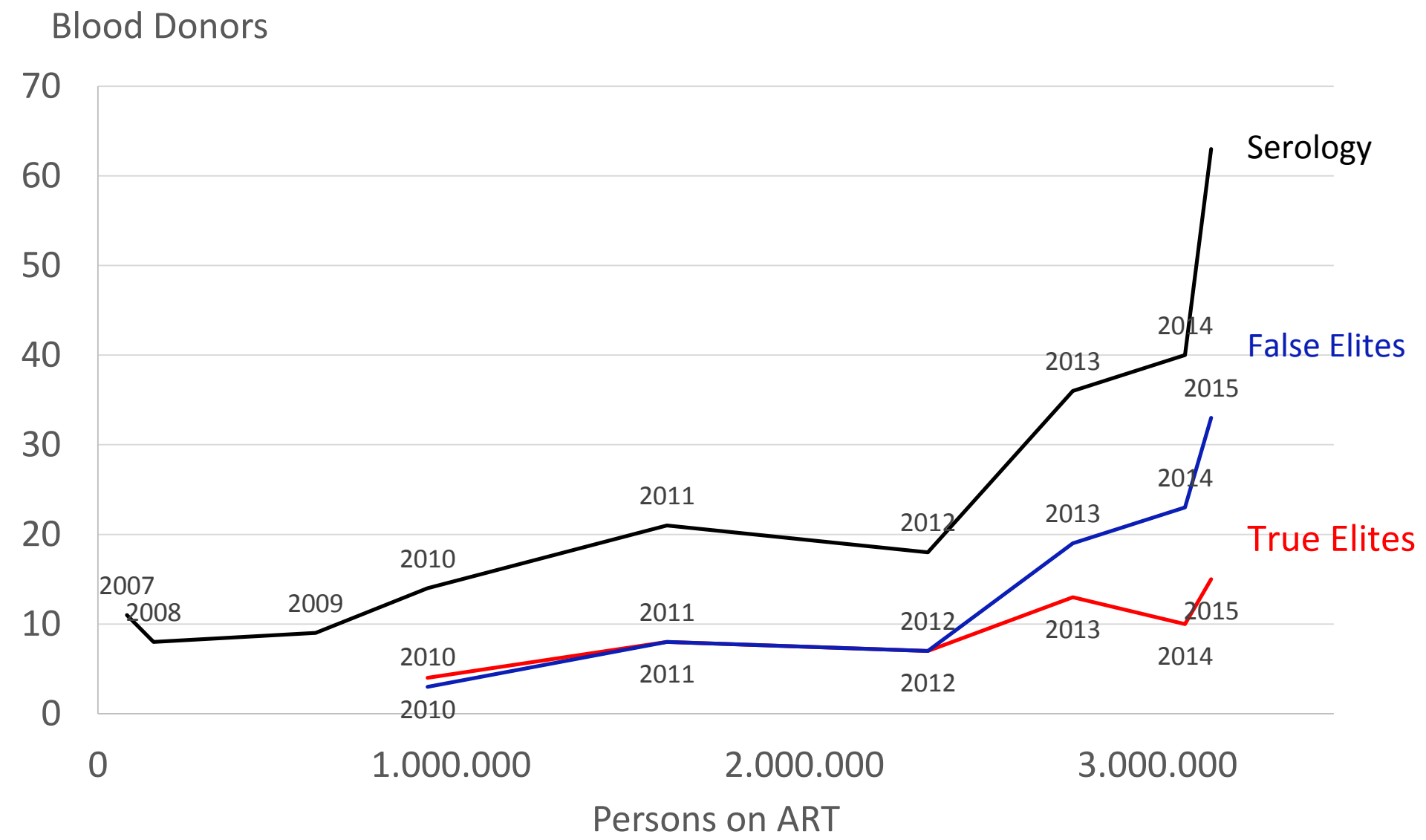
Aim

- To understand the extent of the false EC phenomenon and generate hypothesis for its genesis and prevention

Methods

- 211 Potential EC tested for five ARV drugs using qualitative liquid chromatography tandem mass spectrometry (sensitivity 0.02µg/mL)
- Compare the frequency of false EC against blood drive characteristics, donor incentives and the temporal trend of ART rollout in South Africa using chi-square, fisher exact and trend tests

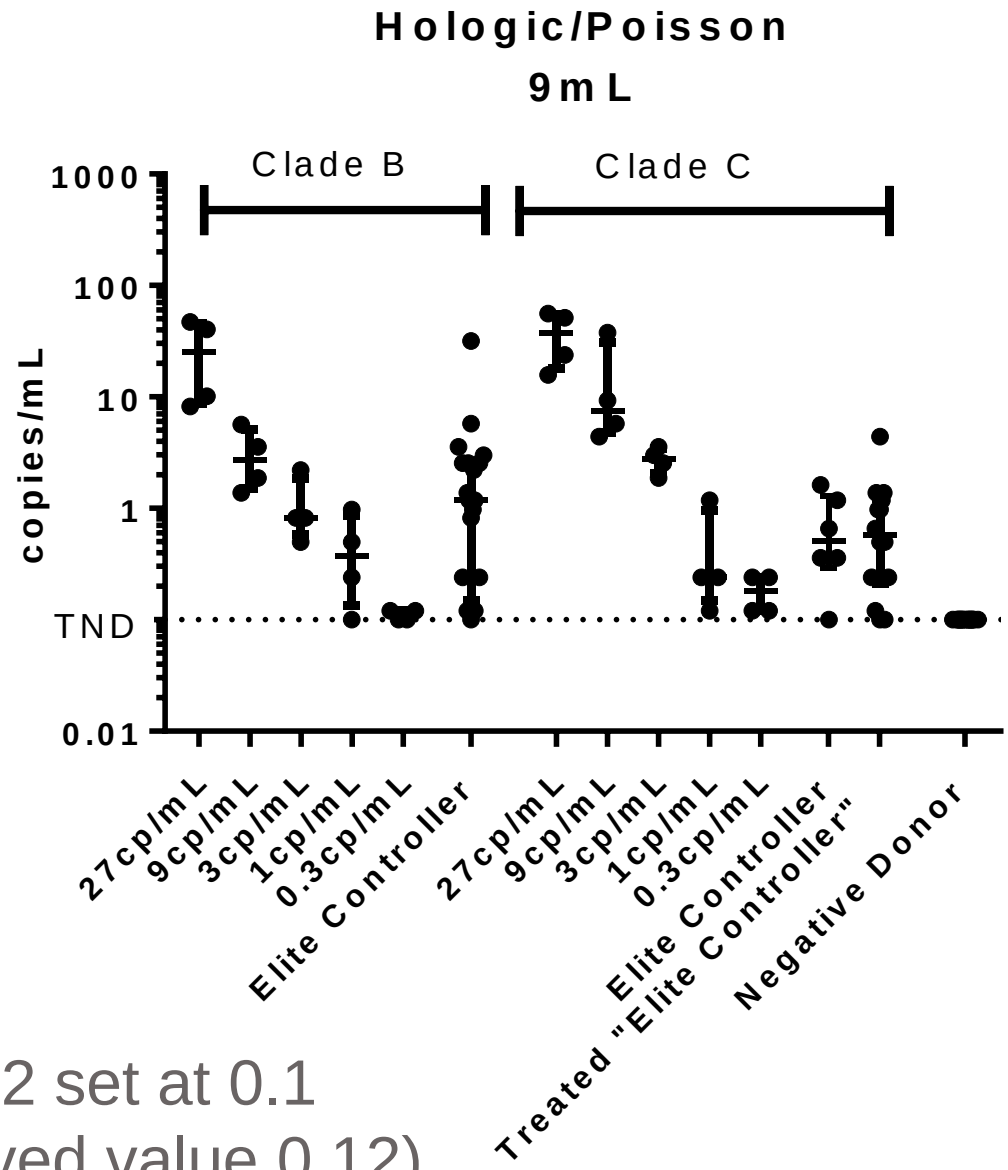
ART Rollout


Blood Donors
70
60
50
40
30
20
10
0
0
1.000.000
2.000.000
3.000.000
Persons on ART
Serology
False Elites
True Elites
2007
2008
2009
2010
2011
2012
2013
2014
2015
2010
2011
2012
2013
2014
2015
2010
2011
2012
2013
2014

"False" Elite controllers by donation site and incentives

Of 211 Potential Elite Controllers tested, 129 (61%) had evidence of ART and were therefore "False Elite Controllers.

	False Elites n=129 (%HIV+)	True Elites n=82 (%HIV+)	p value (n)
Donation Site			0.20
Mobile	116 (1.6)	68 (1.0)	
Fixed	13 (0.75)	14 (0.81)	
p value (%)	**0.008**	**0.64**	
Donor Incentives			0.88
Incentive period	26 (2.4)	15 (1.4)	
Non-incentive period	103 (3.9)	67 (2.5)	
p value (%)	**0.03**	**0.04**	



TND= 0/18 reps; <0.12 set at 0.1
(1/18 reps – poisson derived value 0.12)

Conclusions

- A partnership between a Blood Service and a treatment NGO can be used to rapidly detect persons with hyper-acute HIV infection and initiate ART.
- Preliminary results suggest that:
  - 37% of enrollees were still in Fiebig Stages I/II at enrolment
  - rapid viral suppression can be achieved once ART is initiated
- False EC due to undisclosed ART use, represent a large and growing proportion of potential EC in SA blood donors
- False EC do not seem to be associated with small incentives, in fact the opposite but may be associated with blood drive characteristics
- False EC may seem to be increasing with ART coverage
- EC and False EC do still have viremia

Ways forward

- Enrol False Elite controllers into a social behaviour study to determine
  - Peer pressure at Mobile clinics
  - Donors believe they are cured
  - If more education is required at the treatment clinics
  - Donors test seeking

Acknowledgements

Karin van den Berg Marion Vermeulen Genevieve Jacobs Tinus Brits Ronel Swanevelder Ute Jentsch Cynthia Nyoni REDS Research Nurses	South African National Blood Service (SANBS)
Rachel Lockyear	Right to Care
Coreen Barker Amisha Rama	Wits Health
Chris McClure Nathan Sikes	RTI
Brian Custer Mars Stone Marion Lanteri Edward Murphy Mike Busch	Blood Systems Research Institute and University of California San Francisco