A Clinical Trial to Evaluate the Impact of Broadly Neutralizing Antibodies VRC01LS and 10-1074 on Maintenance of HIV Suppression in a Cohort of Early-Treated Children in Botswana

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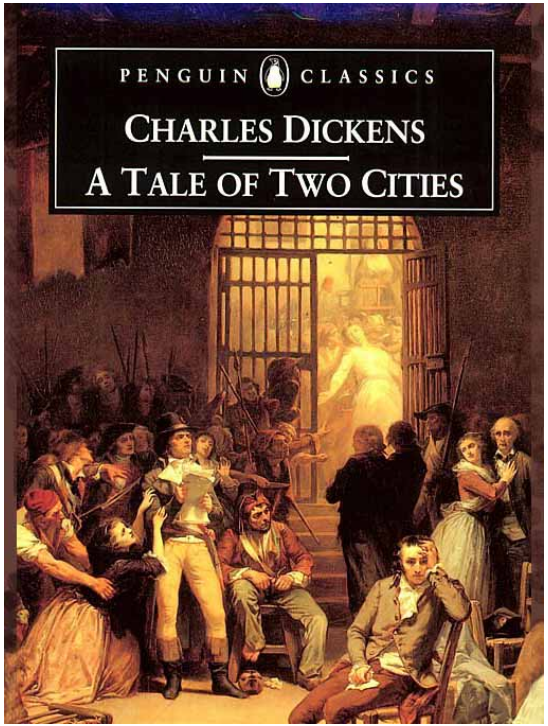
It was the best of times, it was the worst of times...

- HIV+ children have the potential to do very well, but often do very poorly



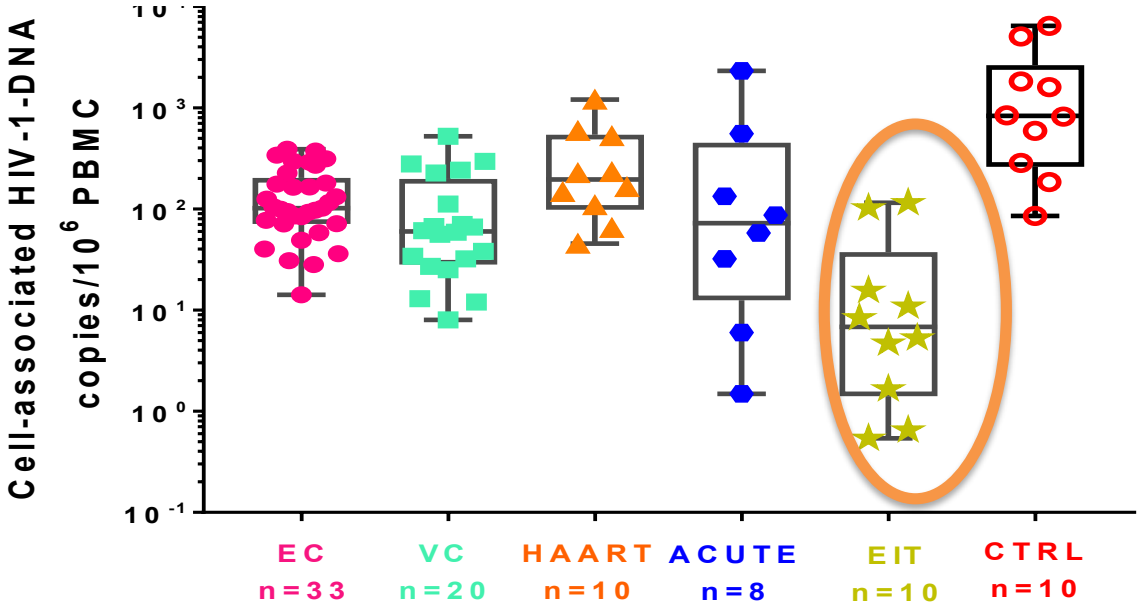
Best of times....

- Recent infection, and developing immune system, may improve treatment outcomes
  - Small population of long-lasting memory CD4 T cells may limit reservoir
  - Long-lived CD4 T memory stem cells and central-memory CD4 T cells may be less permissive to HIV-1 than corresponding cells from adults
  - Less immune activation may reduce susceptibility of HIV target cells to infection and limit reservoir seeding

EIT Study Overview

- The EIT Study started in 2015, and enrolls HIV+ children during the first week of life to start ART
- It is an open-label clinical trial of up to 40 children infected *in utero*, and a small number of additional children with peripartum infection
  - *36 in utero infected children at present*
  - *2 peripartum infected children at present*
- The “earliest possible start” of ART is already recommended by Botswana guidelines and other clinical guidelines; however, the PCR testing schedule (at 6 weeks) limits very early initiation

Very low DNA levels in PBMCs from the first EIT children



- EC = VL undetectable, no ART, any CD4 T cell count (Intl HIV Controllers Study)
- VC = VL< 2000 copies, no ART, any CD4 T cell count (Intl HIV Controllers Study)
- HAART = started on ART in chronic infection, VL undetectable, on ART for >5 years (NIH/MGH cohorts)
- ACUTE = started on ART in acute/early HIV-1 in Boston, on ART for ~ 2 years (Boston Acute HIV Cohort)
- CTRL = control children from Botswana who started ART < 1 yr, suppressed through >2 yrs

Worst of times....

Poor viral suppression in pediatric cohorts

- Children generally do poorly with standard approach to ART
  - 121 infants in Kenya (median age 3.9 mos at ART start): 32% < 250 copies/ml after 6 months (AIDS 2016)
  - NNRTI-based ART in Mali (median age 31 mos): 44% had viral rebound (J Anitmicrob Chemo 2010)
  - LPV/r-based ART in France (median age 4.8 yrs) : 46% had viral rebound (Ped Infect Dis 2011)

- Data from Botswana (2013-15): even with available ART, with standard 6-week and 18-month testing in the government program, 38% of HIV+ children in Botswana had died by 24 months

Even closely-monitored early treated children rebound when adherence is poor

Enrollment	1	2	4	8	12		24		36	48	60	72	84	96
1661	1990	123	53	<40	<40		<40		<40		<40		< 40	<40
17244	512	195	186	62	<40		11182		52		<40		< 40	634 / <40
1636	1053	597	408	116	<40		<40		<200		3648	50	<40	<40
1111950	10595	97078	1413	132	42		860		<40		98	1478301 / 2069	49993 / 365	69
1375	1111	367	161	80	72		<40		<40		<40		<40	33727
>10000000	2298	782	191	42	<40		<40		<40		<40		<40	<40
<40	<40	<40	<40	<40	<40		<40		<40		<40	<40	<40	<40
60247	25682	5224	307	100	50		164		46		< 40		< 40	<40
3145	1439	872	533	307	<40		<40		<40		<40		<40	<40
1005	831	523	561	206	42		<40		<40		<40		<40	<40
272	<40	<40	6591	<40	<40		735	4255	55	<40	106	41895/2531	339	1128

- Among first 10 EIT children who have reached 96 weeks on ART, 5/10 (50%) had one or more visits with a detectable VL after initial suppression
  - All are able to re-suppress quickly with improved adherence, but very labor intensive, beyond program resources

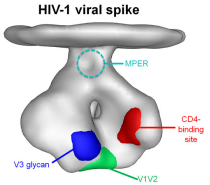
Broadly neutralizing monoclonal antibodies

(bNAbs) may be an alternative to standard ART for children

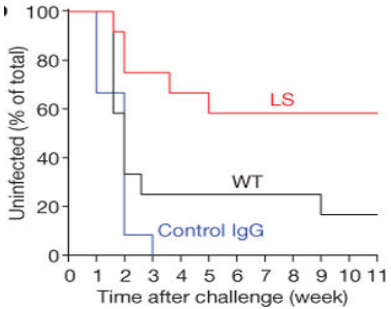
Overview of dual bNAb treatment study in Botswana

- Design:
  - Children in the EIT Study > 96 weeks on ART and > 24 weeks of continuous viral suppression will be eligible to begin a period of overlapping ART + dual bNAbs, and then dual bNAbs alone for up to 6 months
    - Up to 35 participants
  - ART will be re-started in all children after 6 months, and will be re-started immediately in any child with detectable viral load (with 1-2 week monitoring)

Which bNAbs?

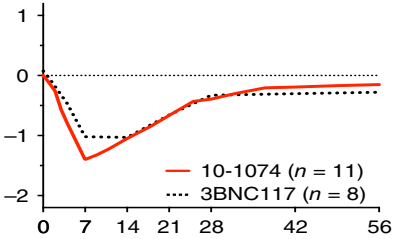


- VRC01LS:
  - CD4-binding site
  - Has been used in children
  - VRC01LS offers improved half-life and tissue concentrations



Ko, Nature 2014

- 10-1074:
  - V3 glycan supersite
  - Adult trial: 1.52 log decline
  - Escape mutants remain VRC01-sensitive



Caskey, Nature Med, 2017

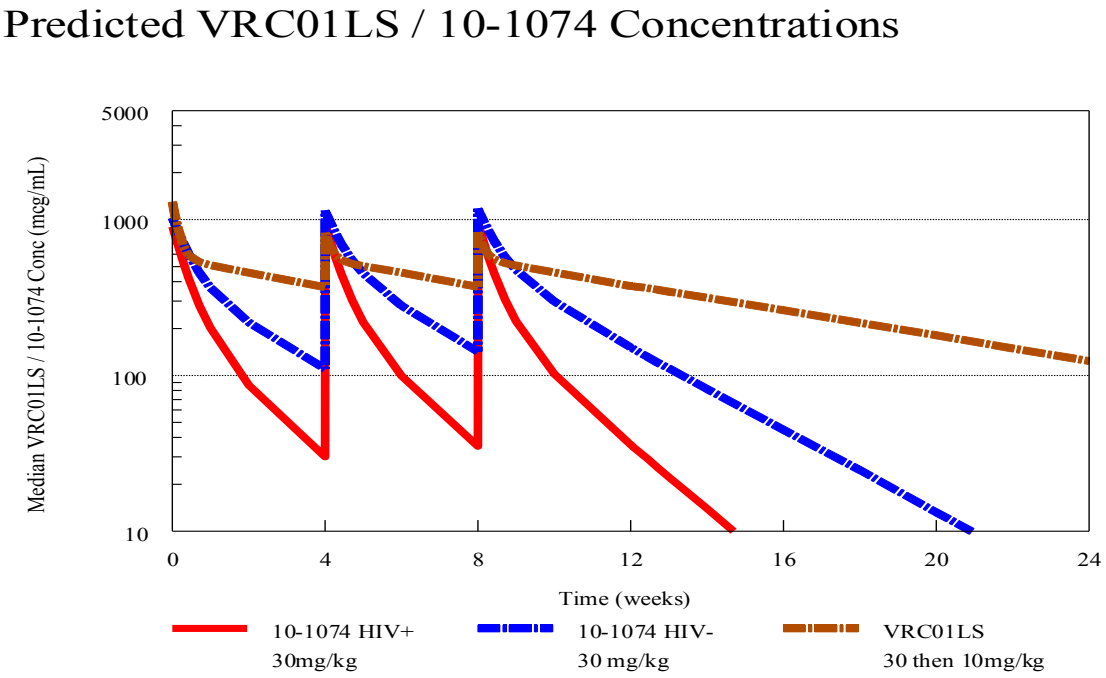
Study Schema: Initial PK Study

- 6 children remain on ART and receive 3 doses VRC01LS
  -- Dose: 30mg/kg load, then 10 mg/kg every 4 weeks

- 6 children remain on ART and receive 3 doses 10-1074
  -- Dose: 30 mg/kg every 4 weeks

	PK Step											
Study week	0	0+1 day	1wk	2wks	4 wks	4wks+ 1day	5 wks	6wks	8 wks	8wks+ 1 day	9wks	12wks
10-1074	X[$] / 0				X[$] / 0				X[$] / 0			
VRC01LS	0 / X[$]				0 / X[$]				0 / X[$]			
Exam	X		X		X	X	X	X	X	X	X	X
Baseline Characteristics	X											
Adherence/Acceptability Assessments	X		X		X		X		X			X
HIV RNA[∞]	X				X				X			X
CBC^	X		X				X		X			
CD4	X		X		X		X		X			
Chem / LFTs^	X		X#				X#		X		X#	
Stored Plasma	X				X				X			
Stored PBMC	X				X				X			
HIV-1 Qualitative DNA	X		X		X		X		X			
Proviral Genome Sequencing	X								X			
HIV-1 DNA Analysis by ddPCR[%]	X				X				X			
Immune Profiling	X								X			
ELISA	X								X			X
PK Testing	X*	X	X	X	X*	X	X	X	X	X	X	X
ADA Testing	X								X			
Blood Volume (mL)	12	2	6	2	10	2	6		12	2	4	6

Dosing Considerations



Study Schema: Intervention (Step 1)

- Step 1: ART + dual bNAbs for 8+ weeks
  -- PK review after first 6 children (to confirm dual dosing unchanged from single agent dosing)
  -- First 6 children remain in Step 1 while awaiting approval to proceed to Step 2

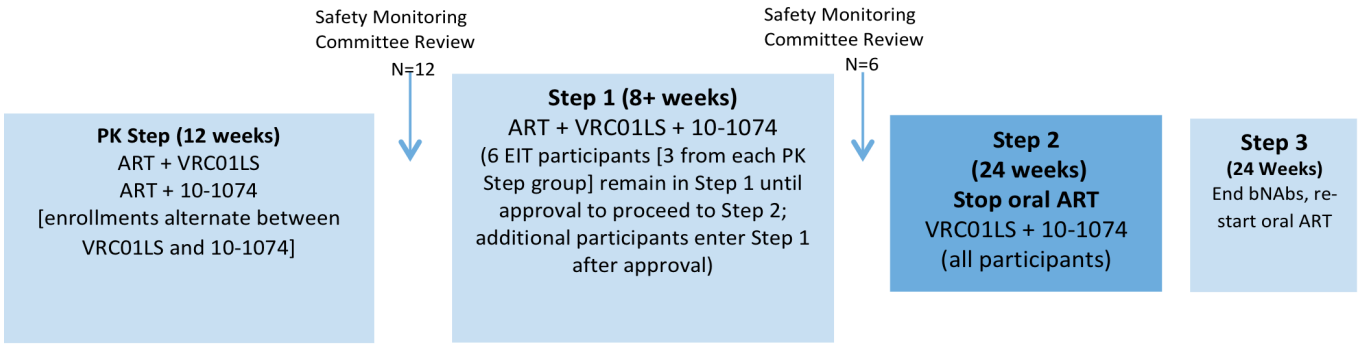
	Step 1: ART + dual bNAbs					Possible additional visits for first 6 participants in Step 1[$]											
Study week	0	1	4	5	8[$]	10*	12*	14*	16*	18*	20*	22*	24*	26*	28*	30*	32*
VRC01LS	X		X		X		X		X		X		X		X		X
10-1074	X		X		X		X		X		X		X		X		X
Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline Characteristics (if required)	X																
Adherence/ Acceptability Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA[∞]	X		X		X		X		X		X		X		X		X
CBC^	X	X		X		X		X		X		X		X		X	
CD4	X					X		X		X		X		X		X	
Chem / LFTs^	X	X[#]		X[#]		X[#]		X[#]		X[#]		X[#]		X[#]		X[#]	
Stored Plasma	X		X		X		X		X		X		X		X		X
Stored PBMC	X		X		X		X		X		X		X		X		X
HIV-1 Qualitative DNA	X	X	X		X		X		X		X		X		X		X
Proviral Genome Sequencing**	X				X												
HIV-1 gag DNA Analysis by ddPCR[%]	X				X				X				X				X
Immune Profiling	X		(X)		X				X		(X)		X				X
ELISA	X				X				X				X				X
PK Testing[&]	X[&]	X[&]	X[&]		X		X		X		X		X				
Blood Volume (mL)	12	5	10	3	12	3	10	3	10	3	10	3	10	3	10	3	10

Study Schema: Intervention (Step 2,3)

- Step 2: stop ART, dual bNAbs up to 24 wks
  -- ART re-started if VL > 400 copies/mL
- Step 3: ART re-started at 24 wks or if viral rebound, bNAbs end

	Step 2: Dual bNAbs alone															Step 3: ART alone		
Study week	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24#	4	12	24
VRC01LS	X				X		X		X		X		X		X			
10-1074	X				X		X		X		X		X		X			
Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence/ Acceptability Assessments	X	X	x	x	X	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	X	X	X	X
CBC^		X				X		X		X		X		X		X		X
CD4	X	X				X		X		X		X		X	X	X	X	X
LFTs		X				X		X		X		X		X		X		
Stored Plasma	X		X		X	X	X		X		X		X		X		X	X
Stored PBMC	X		X		X	X	X		X		X		X		X		X	X
HIV-1 Qualitative DNA*	X	X	X	x	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Proviral Genome Sequencing**															X			
HIV-1 DNA Analysis by ddPCR%	X				X		X				X				X			X
Immune Profiling	X		(X)		X				(X)		X		(X)		X			X
ELISA	X				X		X				X				X			
PK Testing	X				X$		X$		X$		X$		X$		X$			
ADA Testing																		X
Discontinue ART	X																	
Re-start ART															X			
Blood Volume (mL)	12	8	10	5	12	12	8	8	10	8	10	8	12	8	12	8	8	10

Safety Monitoring



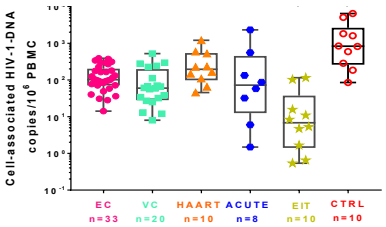
- Safety, PK data reviewed after PK Step, and after first 6 children reach 8 weeks of Step 1
  - SMC, study sponsor will approve continuation of protocol or need for modifications
- Stopping guidelines developed based on at least 30% of participants remaining suppressed
  - CHER: <6% remained virally suppressed at 6 months off ART

Risks and Benefits of bNAb Study

- Benefits
  - Less ART exposure (less toxicity)
  - bNAbs may further reduce viral reservoir
  - Break for children / caregivers from daily ART
  - Potential adjunct to ART if viral failure or poor adherence (limited ART regimens for children)
  - Proof-of-concept scientific trial
    - Better and better antibodies may become available, may allow infrequent dosing and less monitoring in future
    - Close monitoring in a clinical trial will help us understand which children are likely to benefit from antibody treatment

Risks and Benefits of bNAb Study

- Risks
  - No/minimal prior data in children
  - Both bNAbs need to be given as IV infusions because of formulation and dosing
    - Inconvenience of IV infusions, but fewer injection reactions
  - Some children will experience viral rebound
    - Rapid re-suppression expected
    - Likely to have minimal reservoir impact (CROI 2018, EIT)



Conclusions

- New strategies are needed to treat pediatric HIV
  - Early treatment helps but isn't enough
- Broadly neutralizing antibodies have promise as a new treatment for HIV
  - As with ART, combined therapy likely required
  - Early-treated children are an ideal group to benefit from clinical trials of this new treatment strategy

Thanks!

- *Thanks to EIT team and participants, soon to become the bNAb team….*

It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way