Antiretroviral Therapy: Where are we now? Where are we going?

Carl J. Fichtenbaum, MD
Gregory W. Rouan Professor of Education in Internal Medicine
University of Cincinnati College of Medicine
March 19, 2022

AETC AIDS Education & Training Center Program Midwest
UNIVERSITY OF Cincinnati
MIDWEST AIDS TRAINING + EDUCATION CENTER

Disclosures – All Research Grants

Covid Trials

- Ansun Pharmaceuticals
- Atea Pharmaceuticals
- Regeneron Pharmaceuticals
- Moderna
- NIH
- Lilly

HIV Trials

- Gilead Sciences
- ViiV Healthcare
- Janssen
- Cytodyne
- Merck
- Abbvie
- NIH

Disclaimer

This program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $4,198,345 with 50 % financed with nongovernmental sources. The contents are those of the author and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.

AETC AIDS Education & Training Center Program Midwest

Objectives

- Discuss the clinical need for new ART options and paradigms.

- Describe the mechanism of action of new/investigational ARTs.

- Select the appropriate newly approved ART to use in certain clinical situations.

Available ARV Classes and Medications

NRTI
Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Tenofovir DF (TDF)
Tenofovir alafenamide (TAF)
Zidovudine (AZT, ZDV)

Long-acting injectables
Cabotegravir (CAB)
Rilpivirine (RPV)

NNRTI
Delavirdine (DLV)
Doravirine (DOR)
Efavirenz (EFV)
Etravirine (ETR)
Nevirapine (NVP)
Rilpivirine (RPV)

Integrase Inhibitor (INSTI)
Bictegravir (BIC)
Dolutegravir (DTG)
Elvitegravir (EVG)
Raltegravir (RAL)

PI
Atazanavir (ATV)
Darunavir (DRV)
Fosamprenavir (FPV)
Indinavir (IDV)
Lopinavir (LPV)
Nelfinavir (NFV)
Saquinavir (SQV)
Tipranavir (TPV)

Fusion Inhibitor
Enfuvirtide (ENF, T-20)

CCR5 Antagonist
Maraviroc (MVC)

Entry Inhibitor
Fostemsavir (FOS)
Ibalizumab (IBA)

Pharmacokinetic (PK) Booster
Ritonavir (RTV, /r)
Cobicistat (COBI, /c)

71 FDA approved compounds and formulations
(32 unique compounds)

In 2022 Where Are We At With Antiretroviral Therapy for Newly Diagnosed Individuals?

- Test & Treat is the current paradigm for initiating therapy.
  - Rapid start (Same day and/or w/in 2 weeks of Dx)
- Utilizing single-pill combination therapy is a best practice to encourage adherence.
  - There are 12 STRs that are FDA approved
- So, are there any controversies?

Single Pill Regimens

Complete Regi

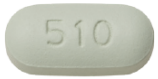
efavirenz + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

bictegravir + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 50 mg bictegravir + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with or without food.

rilpivirine + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 25 mg rilpivirine + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with a meal.

doravirine + tenofovir disoproxil fumarate + lamivudine
One tablet once a day. Each tablet contains 100 mg doravirine + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take with or without food.

dolutegravir + lamivudine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 300 mg lamivudine. Take with or without food.



elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 10 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.

dolutegravir + rilpivirine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 25 mg rilpivirine. Take with a meal.

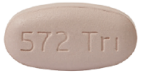
rilpivirine + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 25 mg rilpivirine + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with a meal.

Complete Regimens

elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with food.

efavirenz + tenofovir disoproxil fumarate + lamivudine
One tablet of either Symfi or Symfi Lo once a day. Each tablet of Symfi contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Each tablet of Symfi Lo (above) contains 400 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

darunavir + cobicistat + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 800 mg darunavir + 150 mg cobicistat + 10 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.



dolutegravir + abacavir + lamivudine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 600 mg abacavir + 300 mg lamivudine. Take with or without food. Should be used only by individuals who are HLA-B*5701 negative.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	A higher rate of virologic failure has been observed in those with low pretreatment CD4 counts.
	HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL)	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels
	HIV RNA >500,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL • DTG/3TC	For DTG/3TC, limited data are available in patients above this viral load threshold.
	HLA-B*5701 positive or result unknown	**Do not use ABC-containing regimens.**	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
	ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly.	**Avoid NNRTI-based regimens and DTG/3TC.** **Avoid ABC.** **Recommended ART Regimens:** • BIC/TAF/FTC • DTG plus (TAF or TDF)[a] plus (3TC or FTC) • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance.

Guidelines have complicated provisos:
-CD4 counts
-HIV viral load limits
-HLA testing
-Start before HIV genotype

Other Considerations:
-Food intake and PK
-Hepatitis B
-Kidney Function
-Pregnancy

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive?view=full

Recommended ART Regimens

- BIC/TAF/FTC (Single Pill)

- DTG plus (TAF or TDF) plus (3TC or FTC)
  - Two pill option
- (DRV/r or DRV/c) plus (TAF or TDF) plus (3TC or FTC)
  - Single Pill (DRV/c/TAF/FTC)
  - Two pill option

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive?view=full

DHHS Recommended Single Pill Regimens

Complete Regimens

efavirenz + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.

bictegravir + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 50 mg bictegravir + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with or without food.

rilpivirine + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 25 mg rilpivirine + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with a meal.

doravirine + tenofovir disoproxil fumarate + lamivudine
One tablet once a day. Each tablet contains 100 mg doravirine + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take with or without food.

dolutegravir + lamivudine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 300 mg lamivudine. Take with or without food.

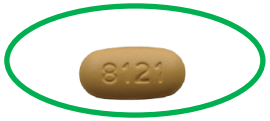
elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 10 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.

dolutegravir + rilpivirine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 25 mg rilpivirine. Take with a meal.

rilpivirine + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 25 mg rilpivirine + 25 mg tenofovir alafenamide + 200 mg emtricitabine. Take with a meal.

elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine
One tablet once a day. Each tablet contains 150 mg elvitegravir + 150 mg cobicistat + 300 mg tenofovir disoproxil fumarate + 200 mg emtricitabine. Take with food.

efavirenz + tenofovir disoproxil fumarate + lamivudine
One tablet of either Symfi or Symfi Lo once a day. Each tablet of Symfi contains 600 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Each tablet of Symfi Lo (above) contains 400 mg efavirenz + 300 mg tenofovir disoproxil fumarate + 300 mg lamivudine. Take on an empty stomach. Dose should be taken at bedtime to minimize dizziness, drowsiness and impaired concentration.



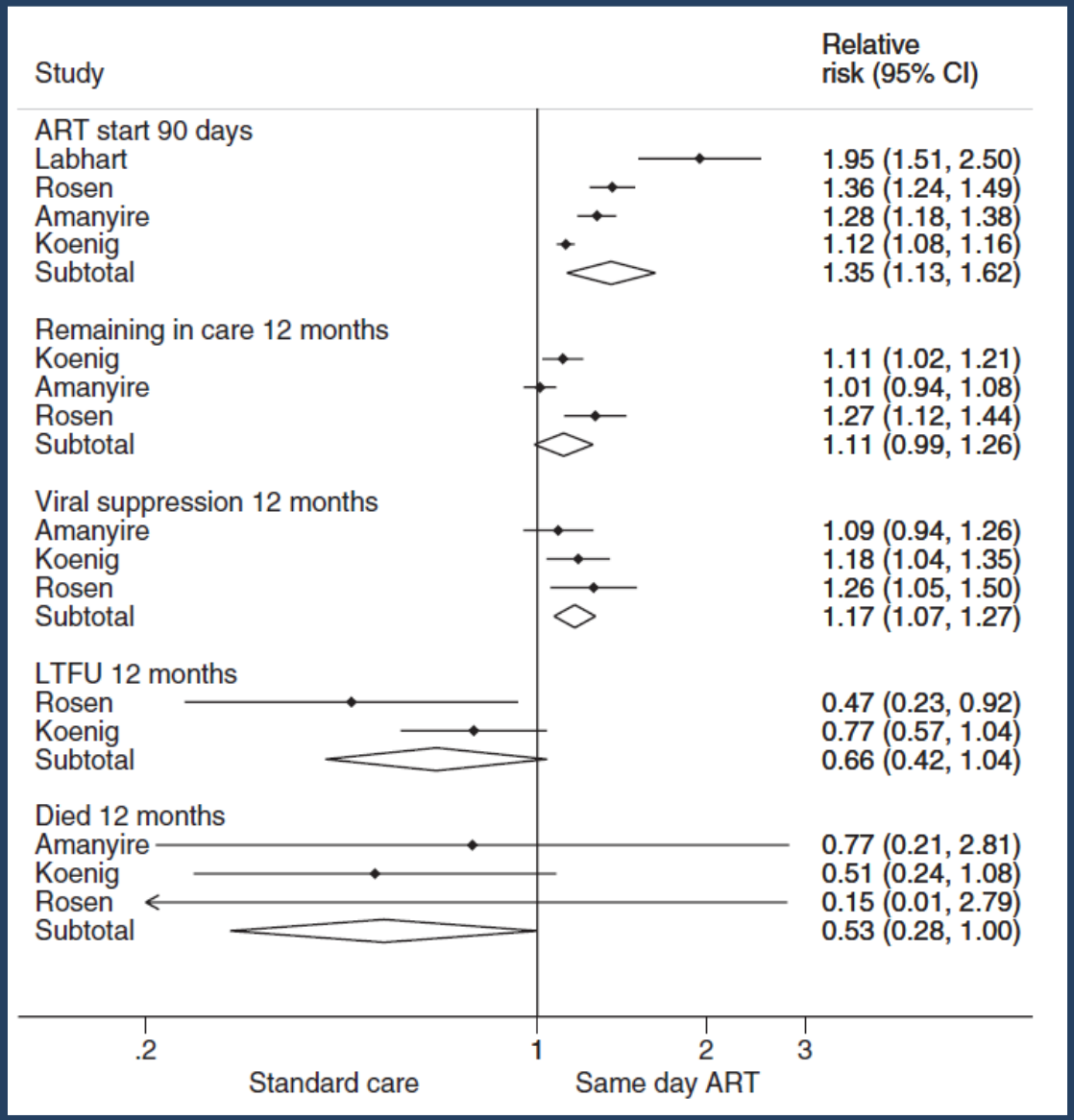
darunavir + cobicistat + tenofovir alafenamide + emtricitabine
One tablet once a day. Each tablet contains 800 mg darunavir + 150 mg cobicistat + 10 mg tenofovir alafenamide + 200 mg emtricitabine. Take with food.

dolutegravir + abacavir + lamivudine
One tablet once a day. Each tablet contains 50 mg dolutegravir + 600 mg abacavir + 300 mg lamivudine. Take with or without food. Should be used only by individuals who are HLA-B*5701 negative.

So, is it really so simple?

- You have 2 Single Pill Choices for Test & Treat Paradigm.
- So, is there data to support both options in the Test & Treat paradigm?
- Are there any comparative trials of these two or other agents?

Rapid Start RCTs is Better than SOC



AIDS 2018, 32:17–23

Rapid Start Data

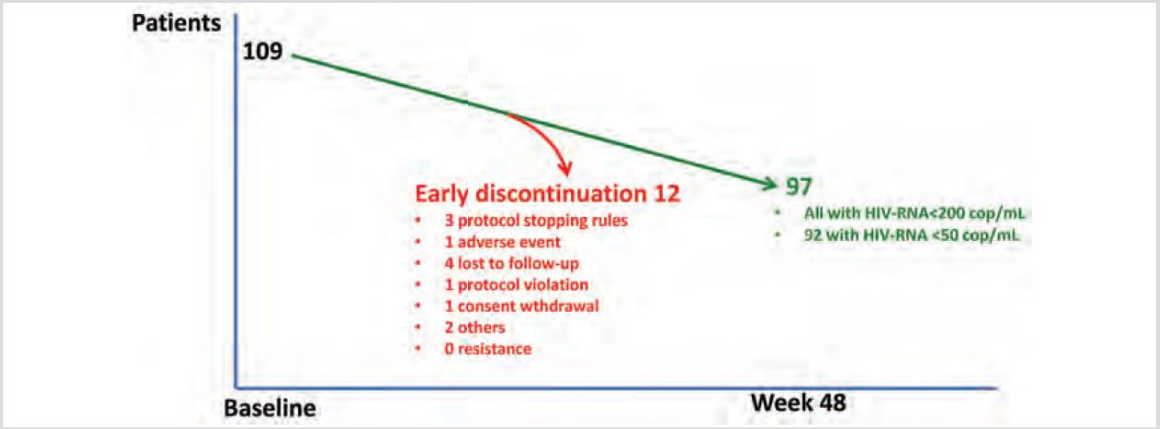
Table 3. Major studies evaluating "test-and-treat" ART approaches

Study	Region	ART initiation (Rapid arm)	Results (at 12 months)		
				Rapid arm	Standard arm
RapIT[18]	South Africa	<90 days	n	187	190
			VL suppression (%)	64	51
			In care (%)	81	64
START ART[19]	Uganda	<4 days	n	347	356
			VL (%)	53	44
			In care (%)	80	72
Koenig, et al.[20]	Haiti	Same day	n	206	208
			VL suppression (%)	66	58
			In care (%)	84	84
Labhardt, et al.[21]	Leshoto	Same day	n	137	137
			VL suppression (%)	50	34
			In care (%)	67	43

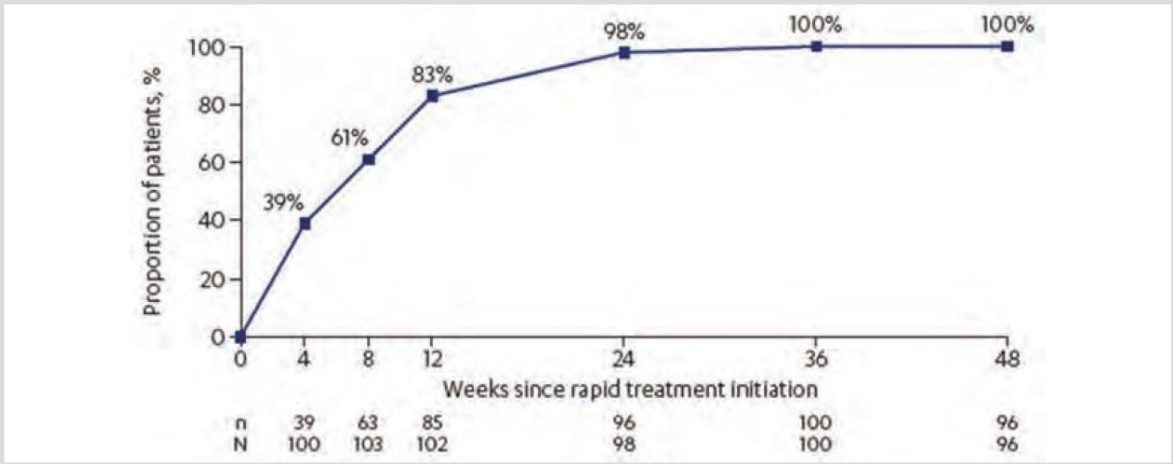
ART: Antiretroviral therapy

AIDS Rev. 2019;21:55-64

DIAMOND Study



Intervention:
HIV Dx w/in 2 weeks
Same Day Initiation
DRV/Cobi/TAF/FTC



Key Characteristics:
Men – 87%
Black/Afr-American – 32%
HIV ≥100K cpm – 25%
CD4 <200 – 21%.

AIDS Rev. 2019;21:55-64

STAT Study

Intervention:

HIV Dx w/in 2 weeks

Same Day Initiation

DOL/3TC

Key Characteristics:

N=131

Men – 89%

Black/Afr-American – 47%

HIV ≥100K cpm – 40%

CD4 <200 – 28%.

Table 3. Participants who switched from dolutegravir/lamivudine before the Week 24 HIV-1 RNA assessment.

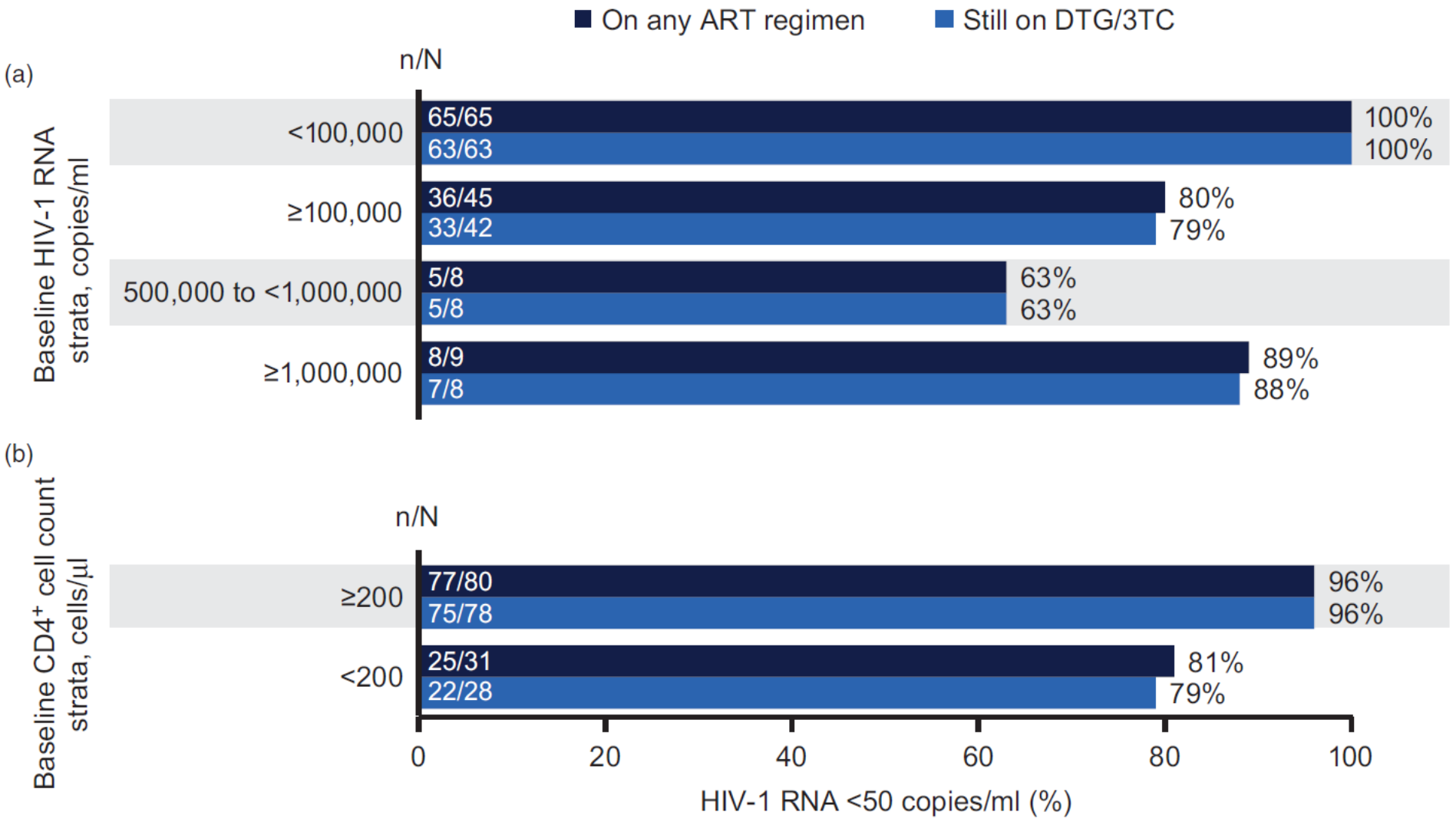
Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at Week 24
Baseline HBV	Week 1	DTG/3TC + TAF	<40 copies/ml
Baseline HBV	Week 1	BIC/FTC/TAF	NA[a]
Baseline HBV	Week 4	DTG + TDF/FTC	<40 copies/ml
Baseline HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	49 copies/ml
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
Baseline HBV	Week 8	DTG/3TC + TAF	<40 copies/ml
Baseline M184V	Week 8	DTG/RPV	NA[d]
Adverse event (rash)	Week 12; Week 12	DRV/COBI/FTC/TAF; BIC/FTC/TAF[e]	<40 copies/ml

Table 4. Adverse events reported under treatment with dolutegravir/lamivudine.

n (%)	DTG/3TC, *N* = 131[a]
Any AE	85 (65)
AEs occurring in >5% of participants	
Headache	10 (8)
Diarrhea	8 (6)
Fatigue	8 (6)
Most common AEs by SOC occurring in >15% of participants	
Infections and infestations	39 (30)
Gastrointestinal disorders	29 (22)
Nervous system disorders	22 (17)
Skin and subcutaneous tissue disorders	21 (16)
Drug-related AEs	9 (7)
Grade 2–5 AEs	2 (2)[b]
AEs leading to discontinuation of DTG/3TC	1 (<1)[c]
Any SAE	2 (2)[d]
AEs of special interest	
Psychiatric disorders	19 (15)

AIDS 2021, 35:1957–1965

STAT Study



AIDS 2021, 35:1957–1965

Bictegravir Rapid Start Studies

B-HASTE

- Prospective Pilot Study of the Efficacy, Safety and Tolerability of Bictegravir-Based HIV ART Same-Day Treatment Evaluations (B-HASTE)
  - Rapid start vs. Standard of Care
  - Planned N=100
  - Enrollment started December 2020.

Barcelona study of B/F/TAF

- Single arm trial of rapid start
  - Planned N=100
  - Enrollment started October 5, 2020

Clinicaltrials.gov - NCT04249037 and NCT04416906

Summary of Rapid Start

- Standard approach is to try to get people started on ART within 2 weeks of diagnosis.
- DHHS guidelines recommend 3 options.
- There are prospective trials to support the use of 2 regimens and plenty of RCTs to support other options.
- Can always tell patient, “Let’s start you on this treatment and when labs come in, we might need to adjust”

Dilemmas for Treatment Naïve Studies

- Do we need more ART studies in newly diagnosed persons?
  - Are there enough choices now?
  - What about long-acting agents?
  - What about novel targets?
  - What about safer compounds?

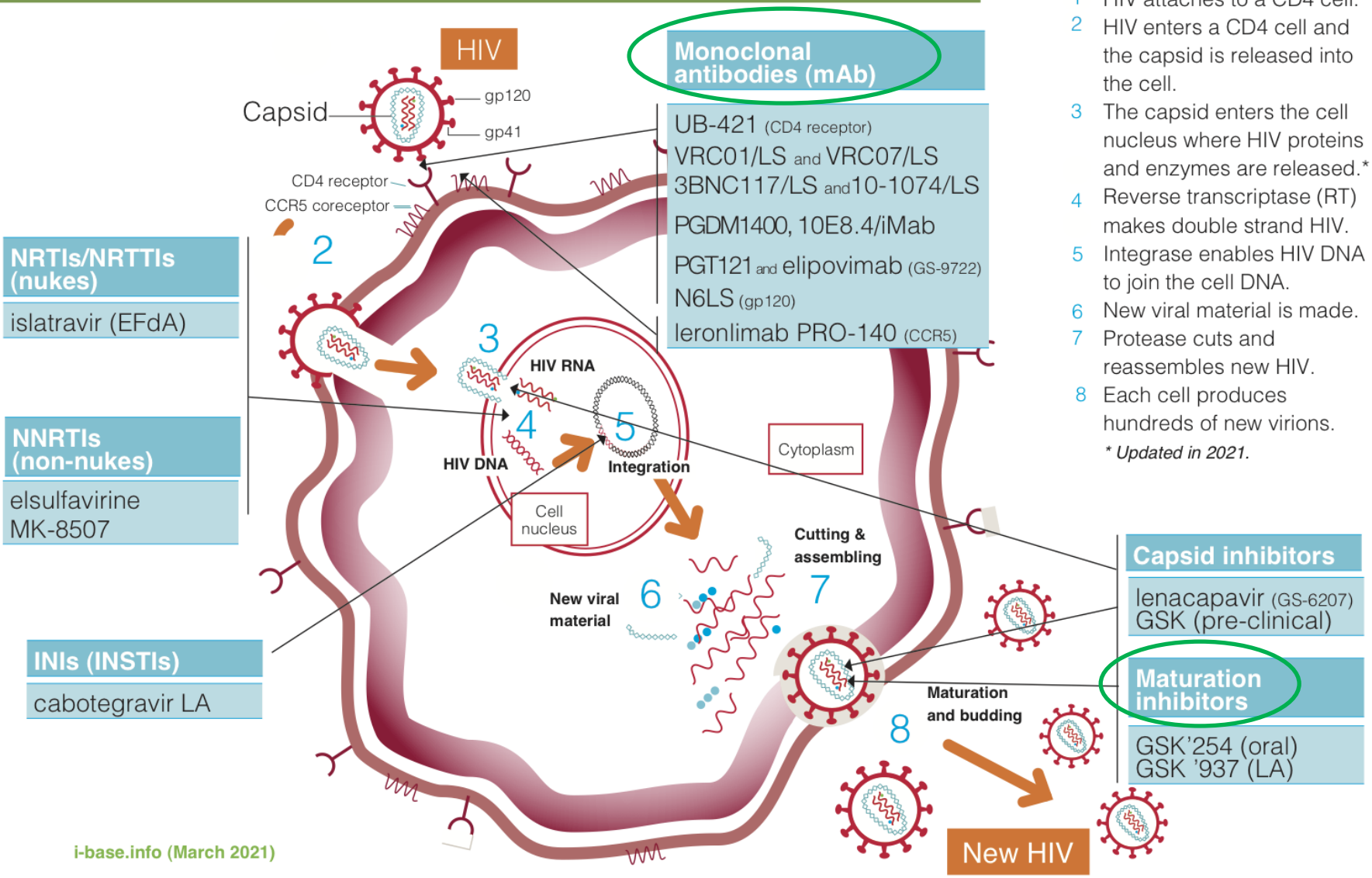
- Should we revise FDA pathway for novel antiretrovirals?
  - Placebo-control for 7-14 days initially
  - Most trials require lab tests to meet INC/EXC criteria prior to randomization/drug initiation.
  - HIV resistance testing is commonplace prior to treatment start.

- What about RAPID start ART; is it ethical to wait for 2-4 weeks?

Proposal: Future Treatment Naïve Studies

- Consent and randomize same day.
- Initiate therapy same day (Step 1).
- Obtain screening labs.
- Bring back participants 2 weeks later for confirmation of participation visit (Step 2).
  - Continue study if meet all INC/EXC criteria
  - “Screen fail” don’t go on to Step 2.
  - Can always fail sooner if safety concerns arise (e.g., Hepatitis B infection, Low GFR)

HIV pipeline 2021: targets in the HIV lifecycle



Stages in the HIV lifecycle

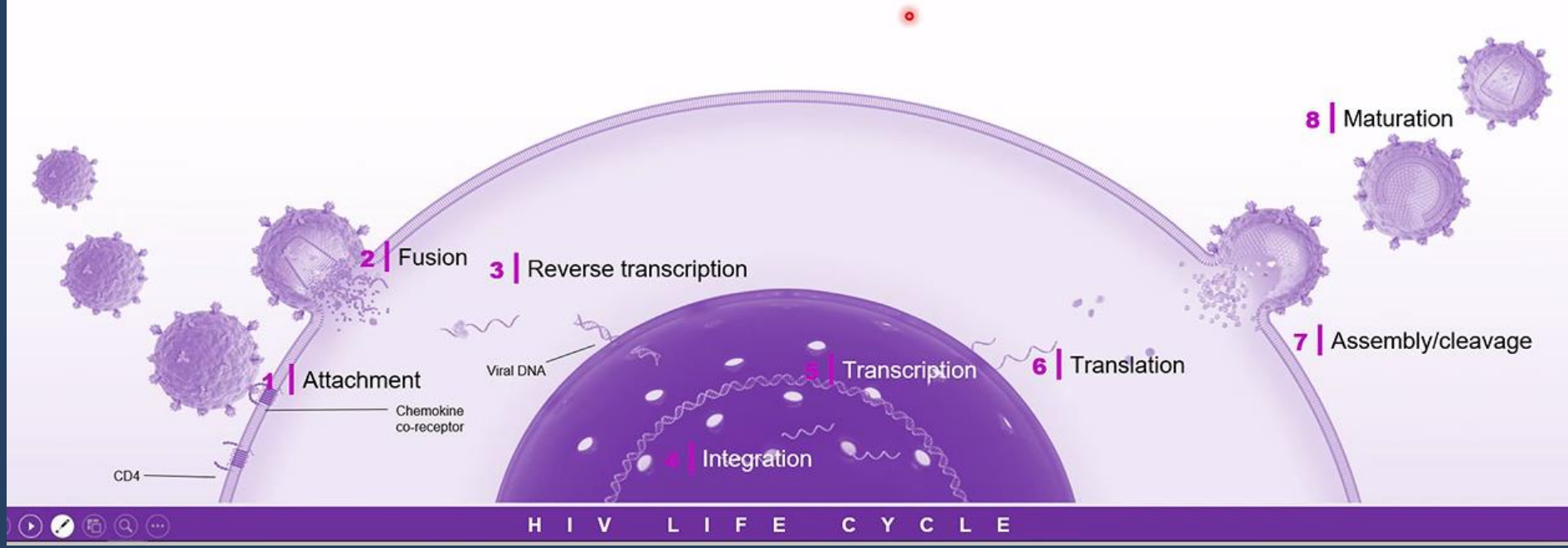
1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and the capsid is released into the cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.*
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

i-base.info (March 2021)

Classes in clinical development for treatment and prevention

Entry inhibitors | bNAb | NRTI NRTTI | NNRTI | Integrase inhibitor | Protease inhibitor | Capsid inhibitor | Maturation inhibitor | Topical IVR / MPT



Chloe L. Orkin, CROI 2022

Compounds by modality and indication

Treatment

- Islatravir
- Lenacapavir
- MI 254

ORAL

INJECTABLE
IM, SC, IV

- Albuvirtide
- bNabs
- Lenacapavir
- Elsulfavirine
- Islatravir
- MI 934

Prevention

- Dapivirine IVR
- MIV 150
  PC1005
- TAF/EVG insert
- Tenofovir IVR
- EVO-100 gel
- Dapivirine + C
- MB66 film
- Dual
  prevention pill

IVR/TOPICAL/ MPT

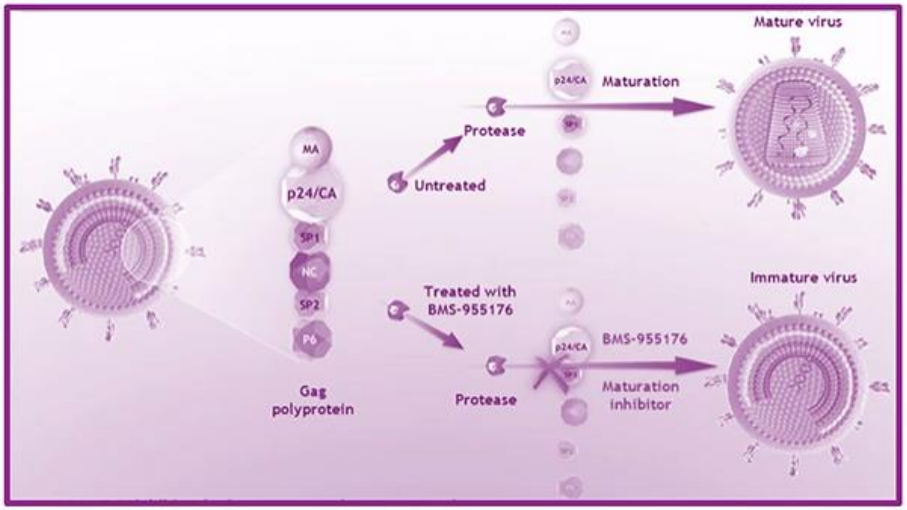
IMPLANTS PATCHES/IM

- Lenacapavir
- Islatravir implant
- INSTI MAP
- TAF implant
- RPV IM

Chloe L. Orkin, CROI 2022

Maturation Inhibitors

- Block protein processing late in life cycle
- MI 254 oral in phase II
  Single entity and with FDC + DTG
  5 studies scheduled
- MI 937 in phase I:
  Long-acting : injectable SC and IM
- 2 monthly or less frequent
- Long-acting MI possible partner for CAB LA



Chloe L. Orkin, CROI 2022

Maturation Inhibitor GSK3640254

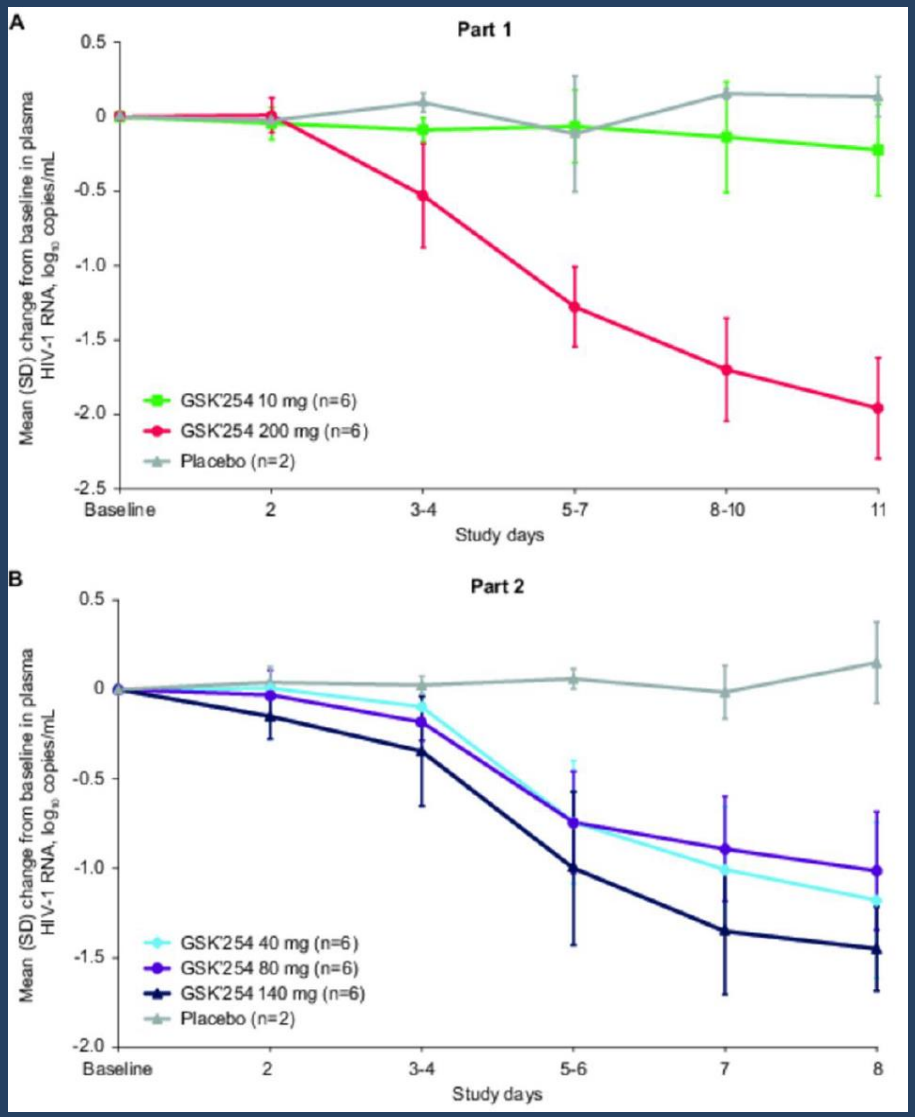
-Phase IIa double-blind placebo-controlled RCT.

-GSK'254 in treatment-naive adults
-Part 1 (10 mg, 200 mg or placebo) daily x 10d
-Part 2 (40, 80, or 140 mg or placebo) daily x 7d
Followed by combination therapy on day 8.

<u>N=34 participants</u>
4 of 12 participants in Part 1 developed the RAM A364A/V at Day 11 (1 w/A364V).

No resistance in 7-day group.

<u>Adverse Events</u>
22 (65%) reported AEs (GSK'254 Arms only)
GI disturbances / Headache most common



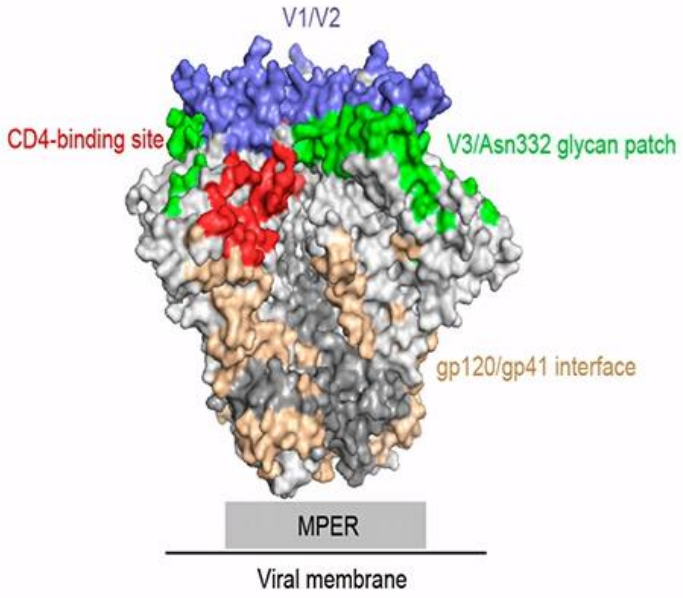
ClinicalTrials.gov: NCT03784079

CID 2022 Jan 6;ciab1065. doi: 10.1093/cid/ciab1065.

Broadly Neutralizing Antibodies

Broadly Neutralizing Antibodies (bNAbs) : treatment & PrEP

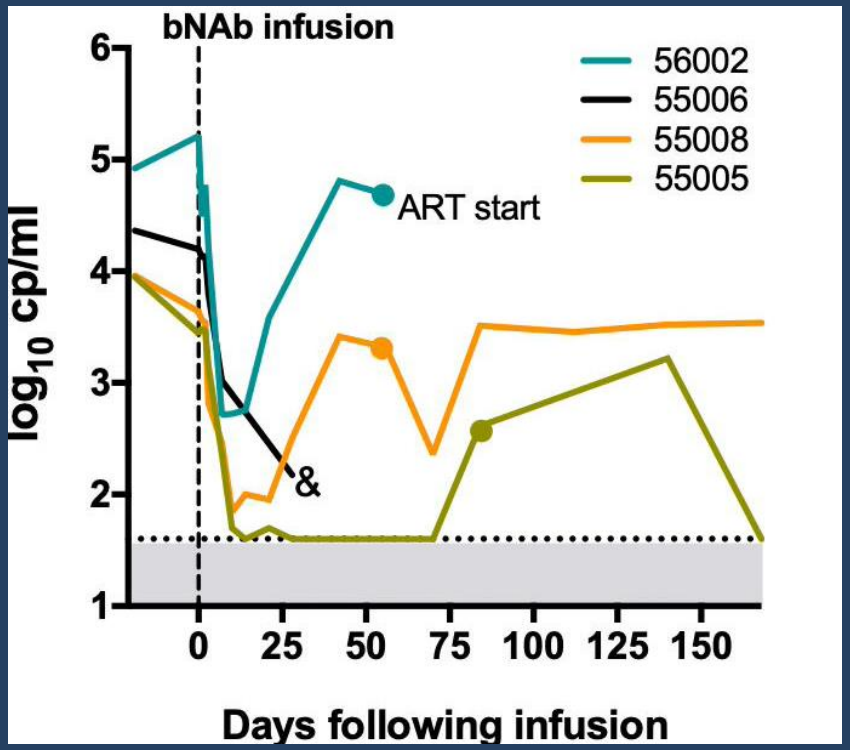
- Delivered as long-acting Q6 infusions
- Resistance: need combination & tri-specific
- Current trials:
  Lenacapavir + GS-5423 + GS-2872 Q6
  CAB: N6LS in phase 2
- PrEP: Antibody Mediated Prevention trials :
  VRC01 did not prevent overall HIV-1 acquisition



Wu X. et al. Science 2010; Mascola JR. Et al. Nat Medicine 2000;
Gautam R. et al. Nature 2016.
Zhang Z et al Int J Mol Sci 2016

BNAB Combination Study

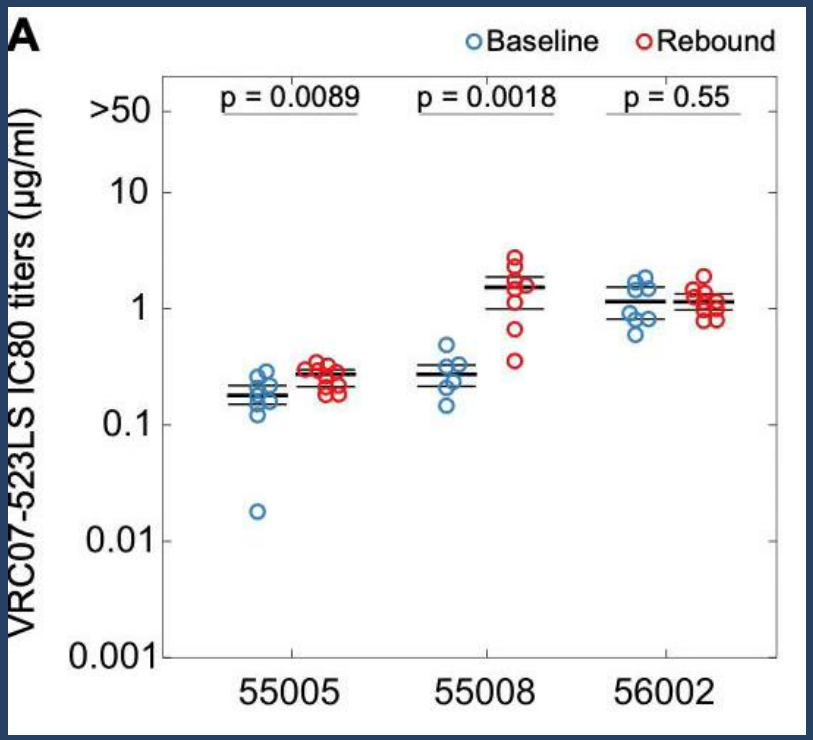
PGDM1400 + PGT121 + VRC07-523LS
20 mg/kg IV infusion (each)



Mean -1.76Log10 HIV RNA drop by day 7

Viral rebound, median 20 days (range 13 – 70)

PGDM1400 – V1/V2 Mab
PGT121 – V3 Mab
VRC07-523LS – CD4 binding site Mab



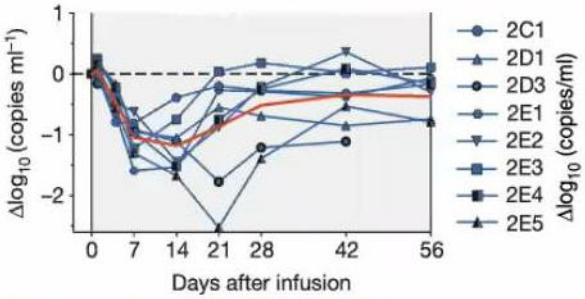
No resistance in VRC07-523LS
Resistance to PGDM1400, PGT121

Julg et al. CROI 2022, Abstract 12

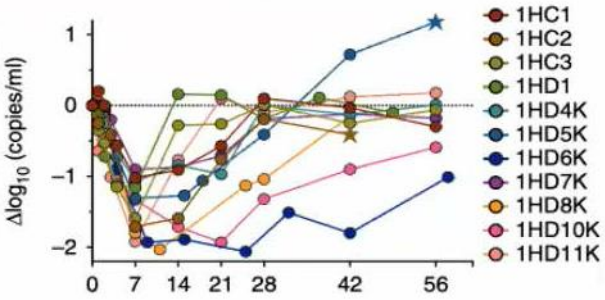
HIV-1 bNAbs: Activity During Viremia

Single bNAb

3BNC117

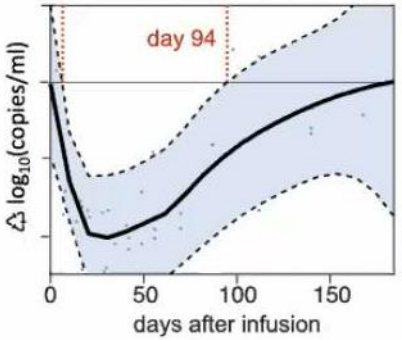


10-1074



Combination two bNAbs

3BNC117 +10-1074



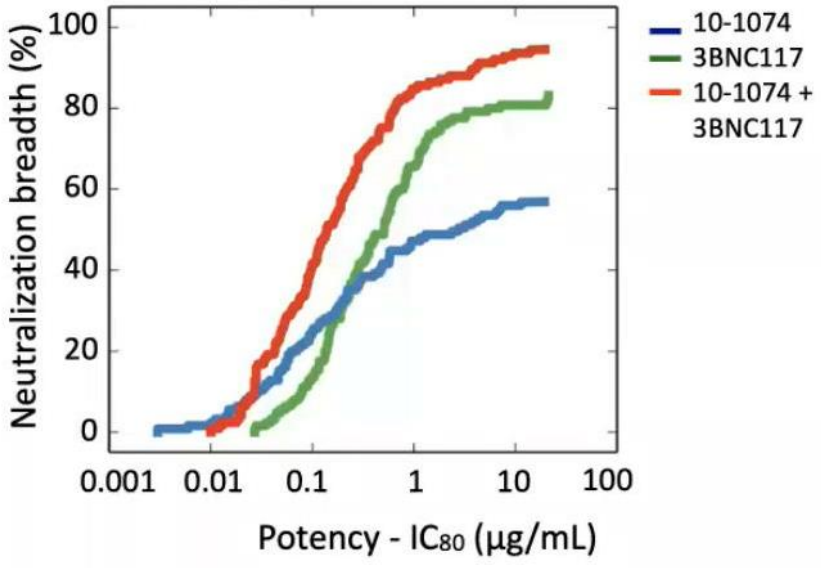
Caskey, Klein et al., Nature 2015
Caskey, Schoofs et al., Nat Med 2017
Bar-On, Nat Med et al. 2018

- Across studies: A subset of participants with baseline bNAb resistance
- **Reduction in plasma viremia** of ~ 1.5 $\log_{10}$ cp/ml.
- Selection of resistant viral strains with monotherapy.
- Viral suppression only achieved with low starting VLs
- *In contrast, the **two-bNAb combination** can maintain viral suppression after ART interruption (Mendoza, Nature et al. 2018)*

Caskey et al. CROI 2022, Abstract 140

3BNC117 (CD4bs) & 10-1074 (V3 loop): *In Vitro* Neutralizing Activity

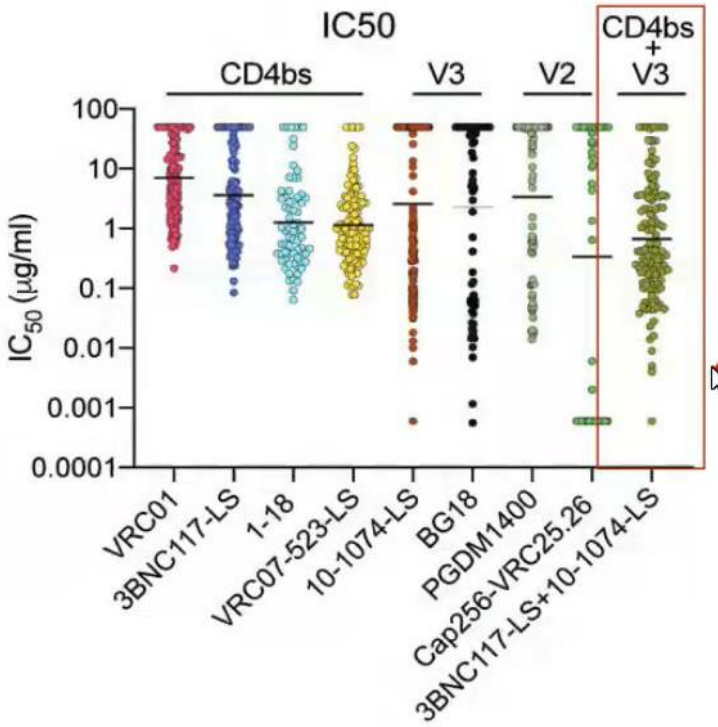
Pseudovirus Panel (Multi-Clade)



Coverage of **96%** - IC_{50} < 10 µg/ml
GeoMean **IC_{50} of 0.04 µg**/ml and **IC_{80} 0.15 µg/ml**.

Kong et al, J Virol 2015

Primary Isolates (Clades A, C, D)



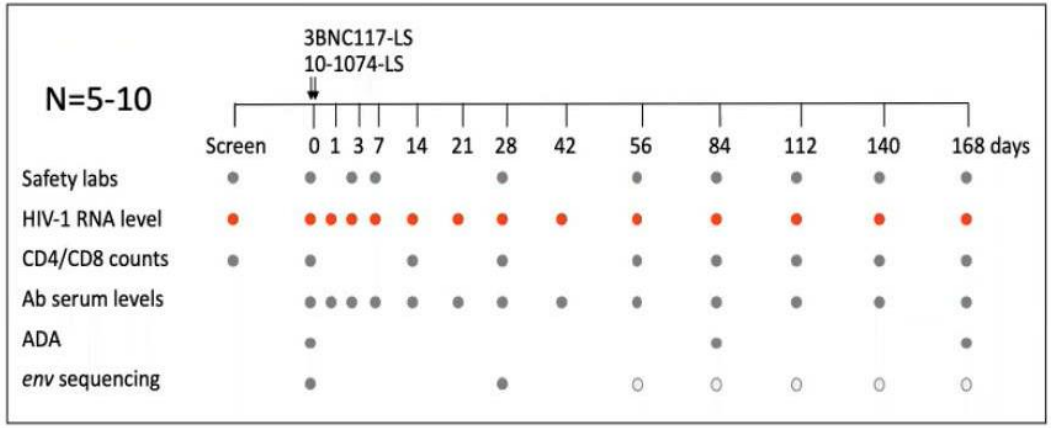
Lorenzi et al, J Virol 2020

Caskey et al. CROI 2022, Abstract 140

LS Variants: Study Design and Endpoints

- ***Design:*** This was a phase 1 open-label, single arm study to evaluate the safety, PK and antiviral activity of the combination of 3BNC117-LS and 10-1074-LS in **viremic PWH not on ART**.

  - Single infusions of 30 mg/kg, each mAb at 30 mg/kg
  - Follow up of 24 weeks.



Study Population:

- Age > 18 yrs
- Off ART for 4 weeks, with HIV-1 RNA 500 – 125,000 cp/ml
- Current CD4 count > 300 cells/ml
- Without hx of AIDS-defining illness within last 3 yrs
- Without chronic HBV or HCV infection

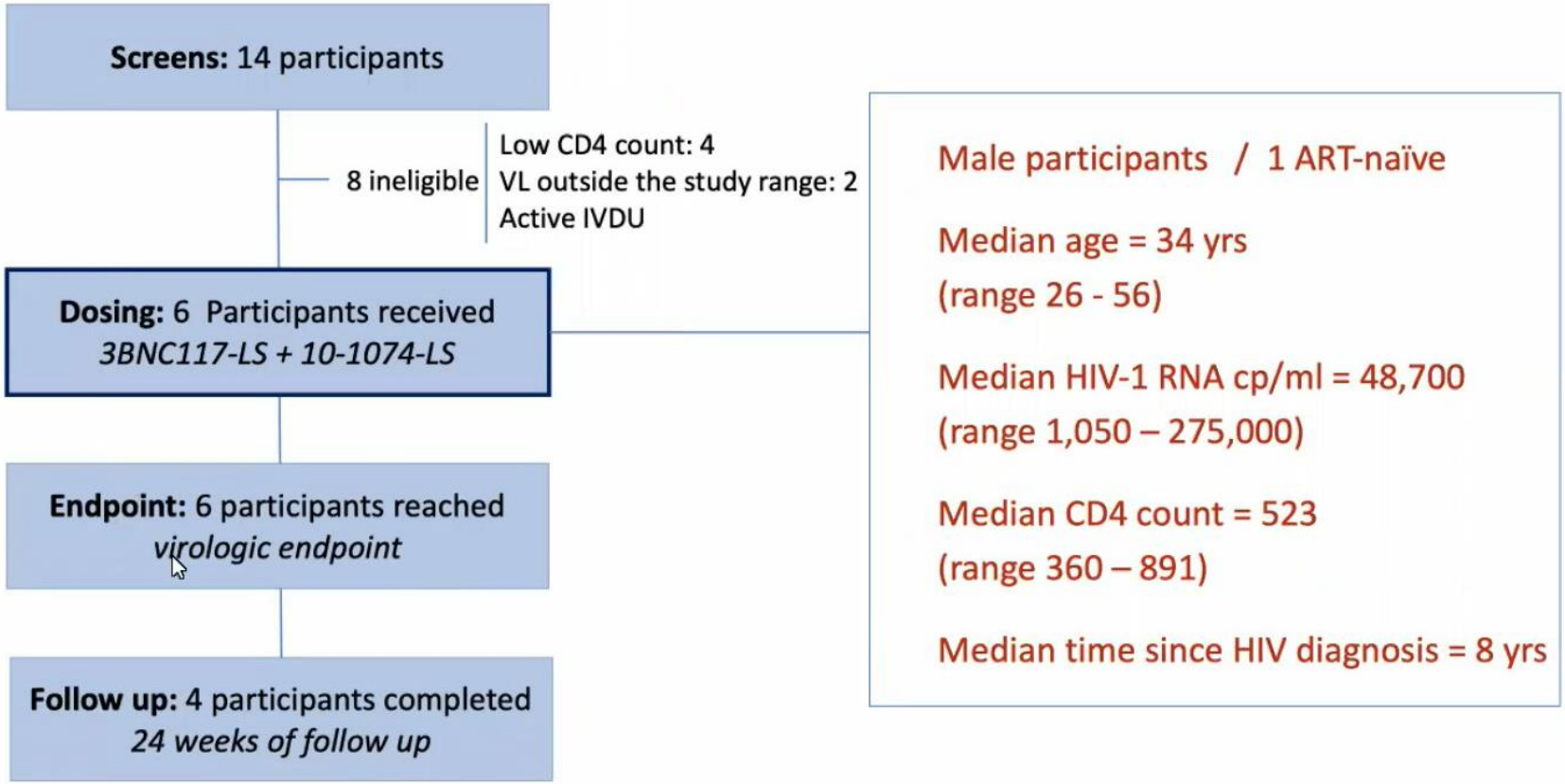
Study Endpoints:

- Safety – treatment related solicited or unsolicited grade 3 AEs and SAEs
- PK parameters
- Decline in plasma viremia through week 4 after bNAb infusions

Note: participants encouraged to initiate ART at study week 8.

Caskey et al. CROI 2022, Abstract 140

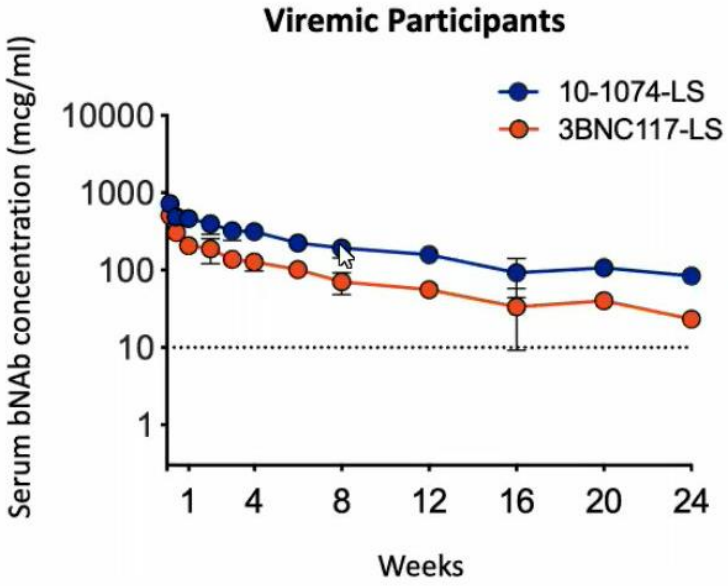
Study Flow

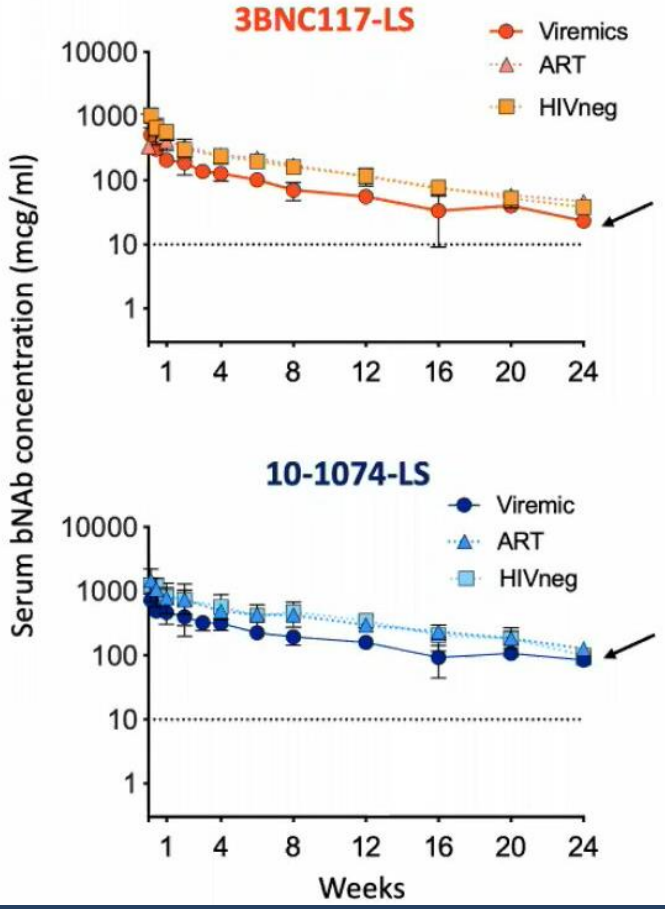


Study Sites: Rockefeller, Weil Cornell, UPenn

Caskey et al. CROI 2022, Abstract 140

Serum Antibody Levels

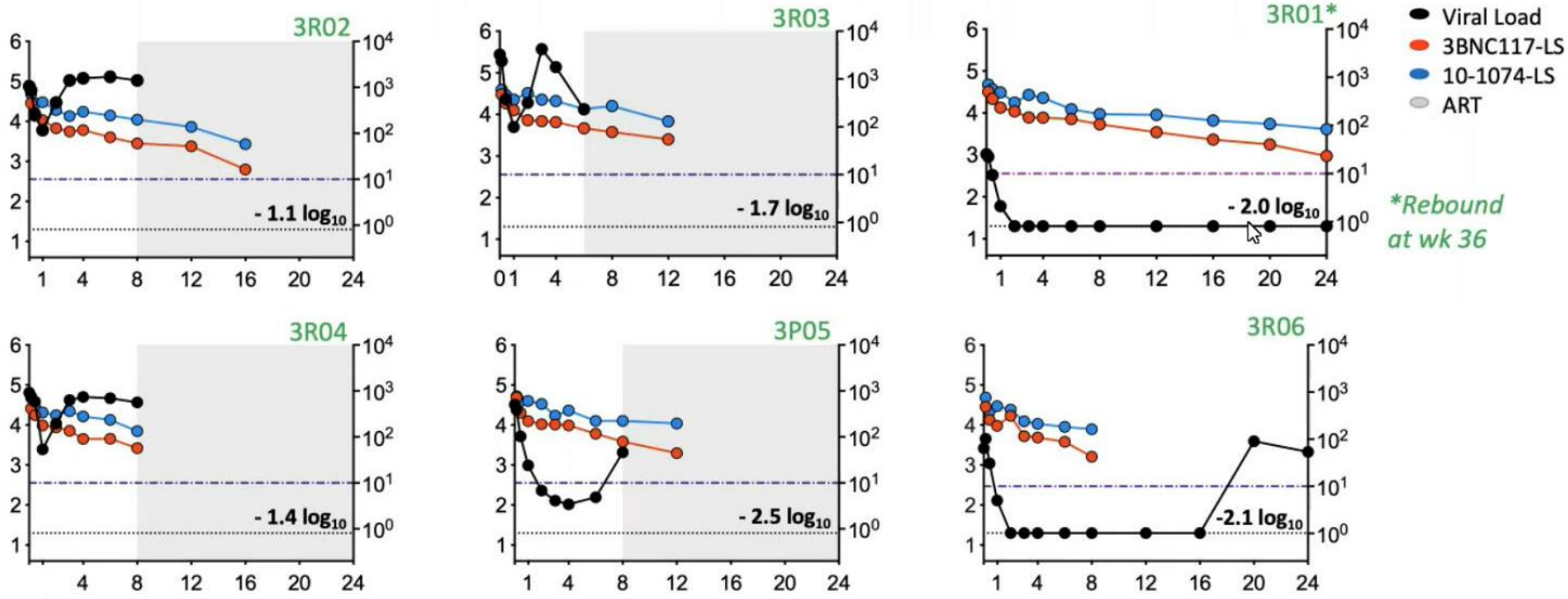




- 10-1074-LS showed slower decay than 3BNC117-LS
- Faster decay of both bNAbs in viremic participants

Caskey et al. CROI 2022, Abstract 140

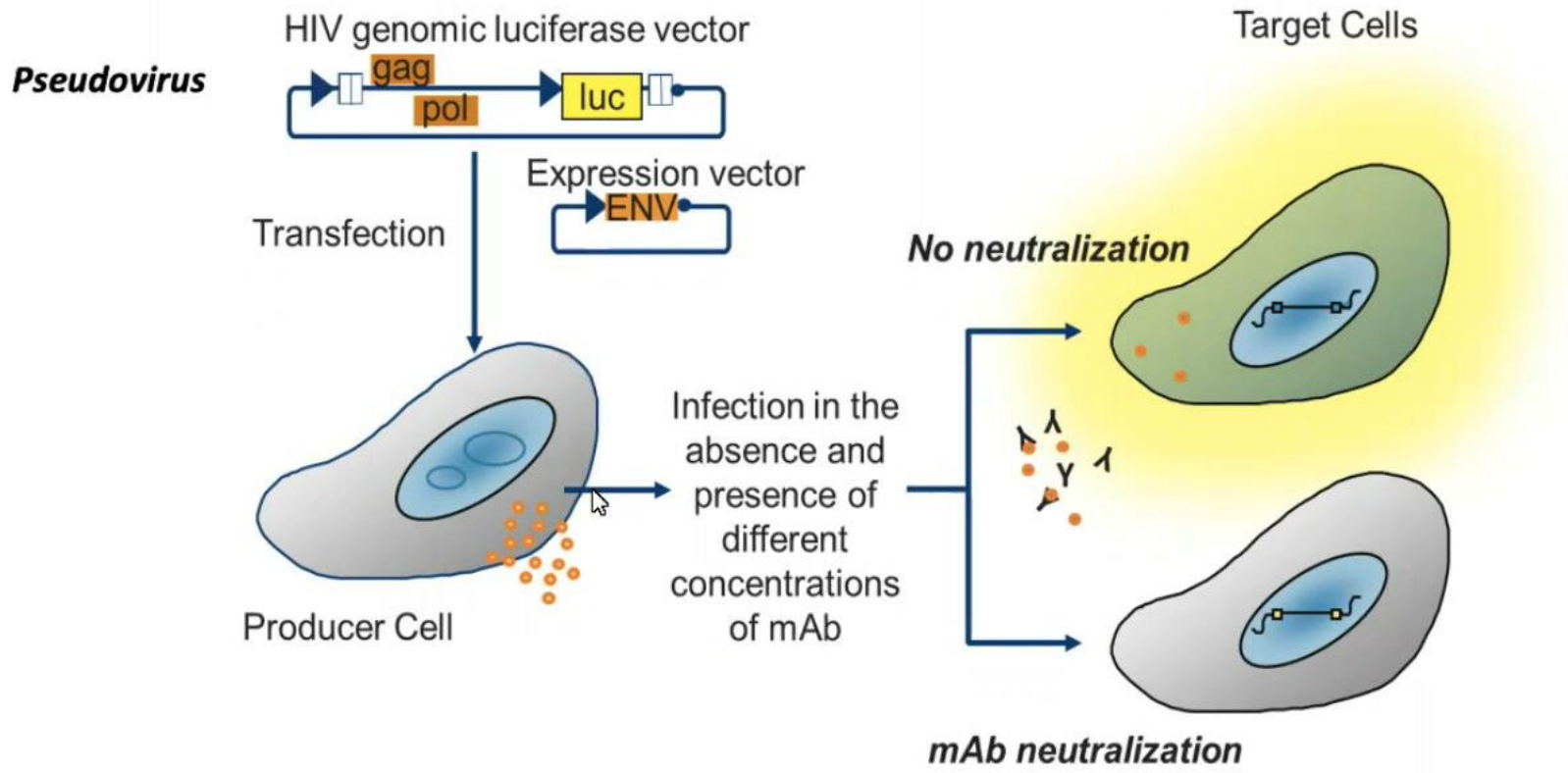
Effects on Plasma Viremia: 3BNC117-LS and 10-1074-LS



➢ **Reduction** in plasma viremia of **~ 1.9 log_{10} cp/ml**.

Caskey et al. CROI 2022, Abstract 140

PhenoSense Monoclonal Antibody (mAb) Assay



Jackie Reeves, Monogram

Caskey et al. CROI 2022, Abstract 140

Viral Responses and Baseline Antibody Sensitivity of Plasma Viruses

PhenoSense Baseline PLASMA

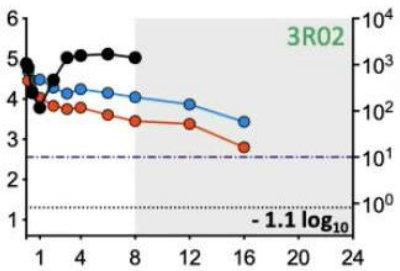
Study ID	3BNC117 IC90	10-1074 IC90
3R02	3.182	>50
3R04	3.615	>50

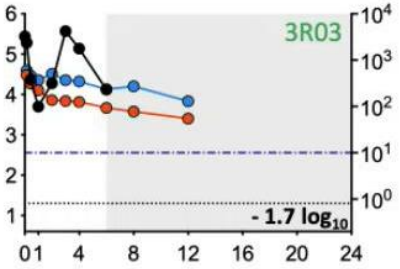
Study ID	3BNC117 IC90	10-1074 IC90
3R03	6.972	0.125
3P05	12.243	0.104

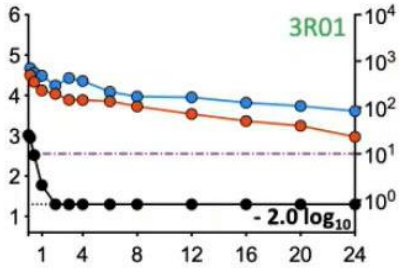
Study ID	3BNC117 IC90	10-1074 IC90
3R01	0.619	0.539
3R06	0.607	0.430

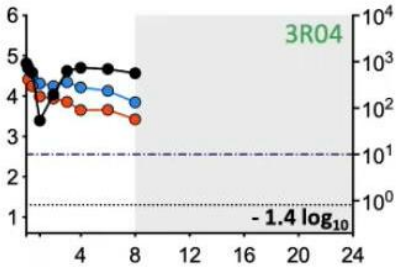
>20 — 0.1

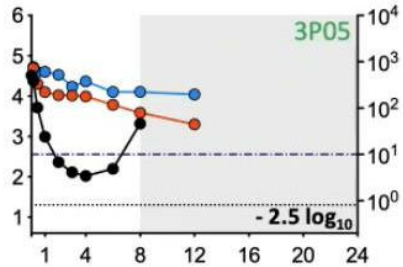
Sensitivity

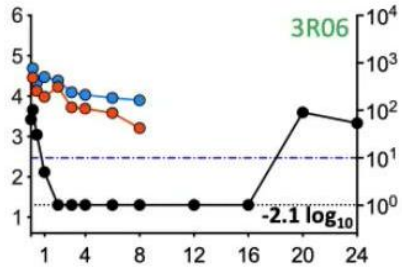










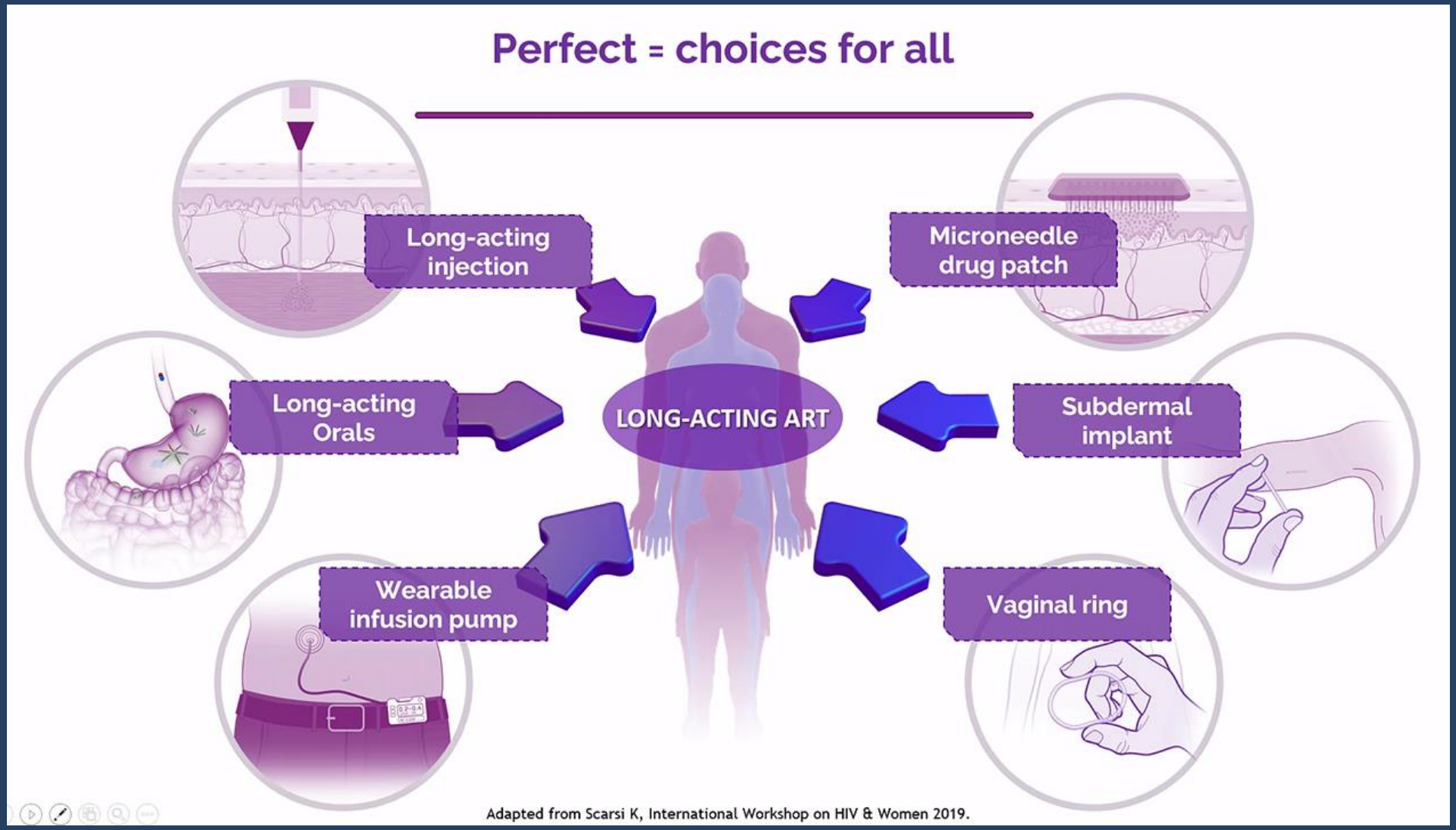


Viral Load
3BNC117-LS
10-1074-LS
ART

Caskey et al. CROI 2022, Abstract 140

Summary of BNABs

- Measure neutralization prior to use
- Combination therapy is better than monotherapy
- Average of 1.5 – 2.5 log decline
- Viral rebound typically occurs in most persons within 3-4 weeks, but some have prolonged viremic control
- Multiple infusions required likely



Chloe L. Orkin, CROI 2022

What about Treatment Experienced Individuals Failing Therapy?

- Fostemavir

BRIGHTE STUDY – 96 weeks

Main Entry Criteria

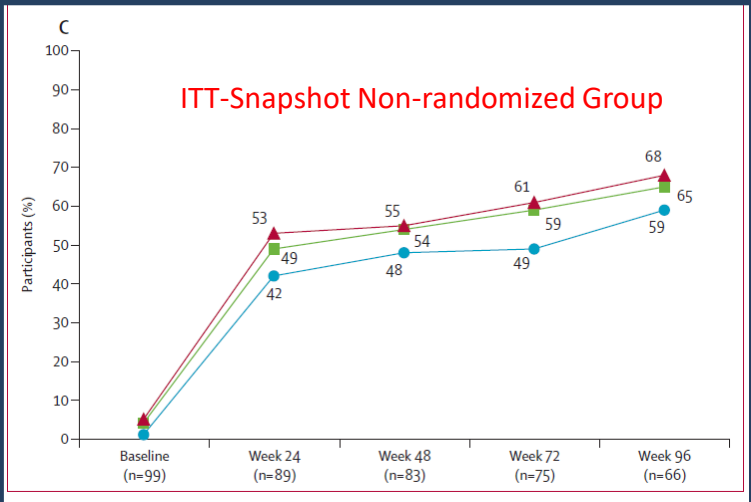
HIV VL > 400 cpm
Currently taking ART (failing)
≤ 2 ART Class Options remaining

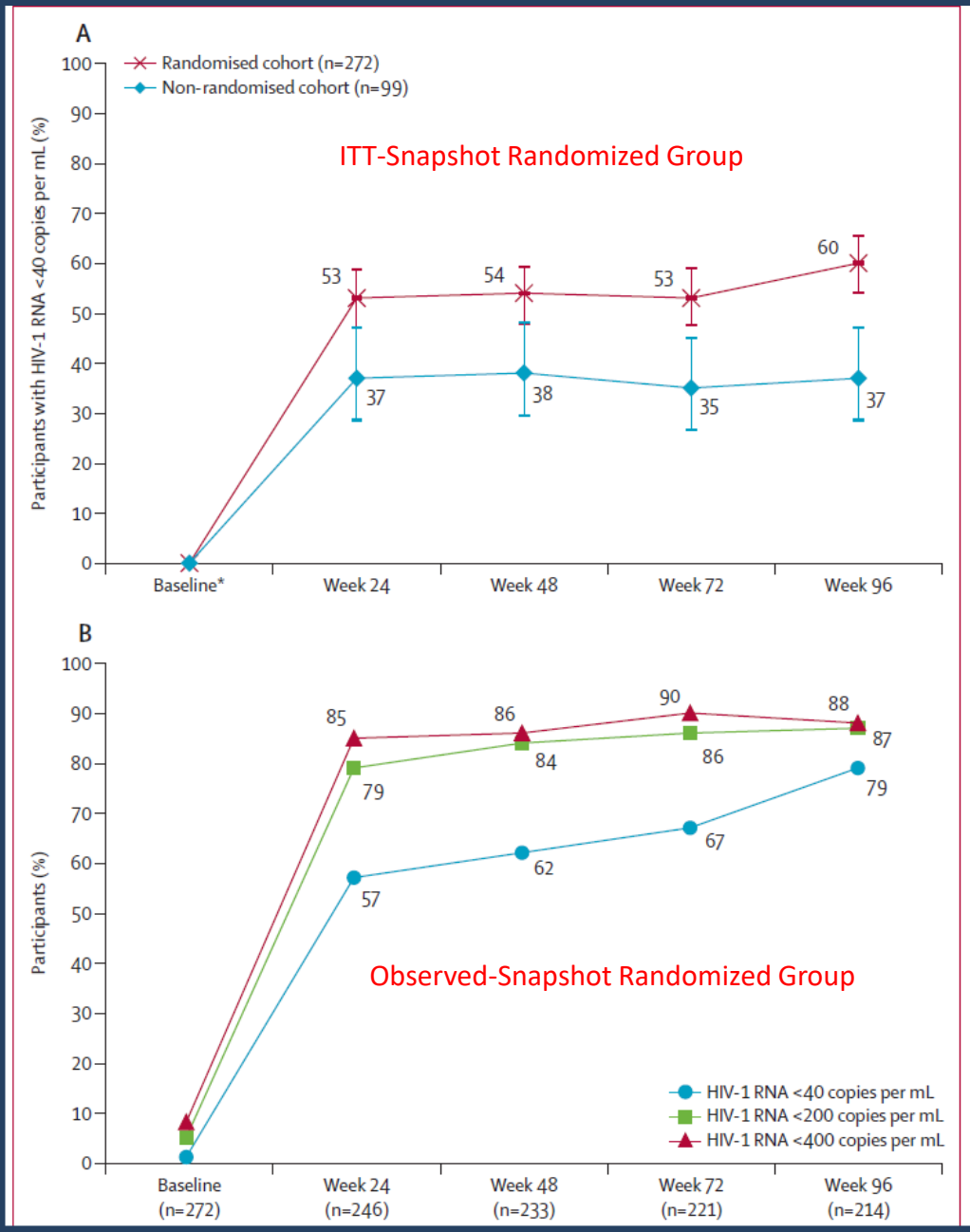
Randomized Cohort

8 days of Fostemavir vs. Placebo
Optimized background, day 8

Non-randomized Cohort

No active treatment options
Fostemavir+optimized background





Lancet HIV 2020; 7: e740–51

Case presentation

- 44 y/o man with HIV since 2004.
- Placed on TDF/FTC/EFV on 2/7/2005 but did not get to VL<200.
- Genotype in 8/12/2005 shows extensive resistance.
- Was off antiretroviral therapy from 2006-2013. (No Insurance)
- Had Presumptive PJP on 2/11/2013.
- Placed on ZDV/3TC+Lopinavir/ritonavir 2013-2015.
- Off treatment for 6 months due to lack of insurance
- On ABC/3TC/Dolutegravir since 3/15/16
- Had CVA on 8/27/2019
- Saw HIV provider 3/5/20 to review ART

Courtesy of Dr. Kelli Williams

8/12/2005

Regimen – TDF/FTC/EFV

HIV VL = 2,900 cpm

5/24/2015

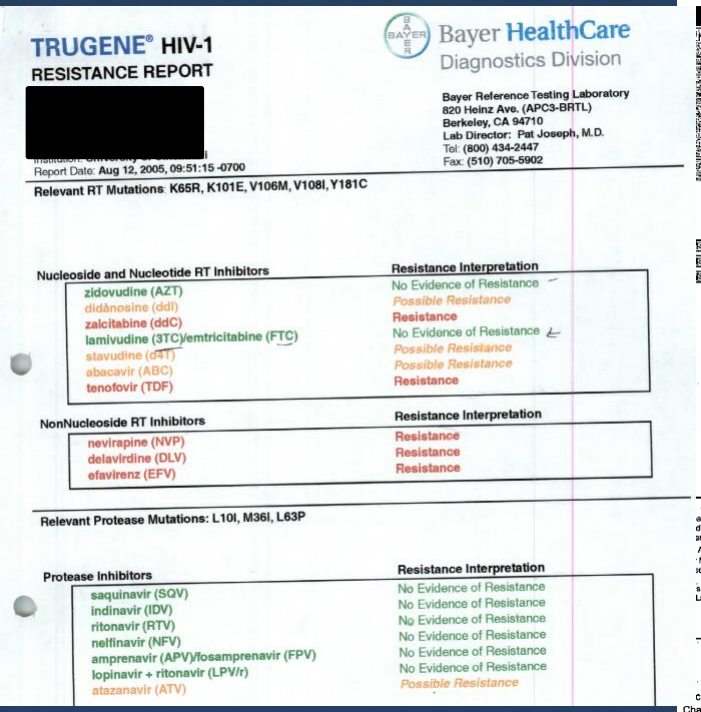
Regimen – No ARVs

HIV VL = 283,218 cpm

2/24/2018

Regimen – ABC/3TC/DOL

HIV VL = 24 cpm



TRUGENE® HIV-1
RESISTANCE REPORT

[redacted]

Report Date: Aug 12, 2005, 09:51:15 -0700

Bayer HealthCare
Diagnostics Division

Bayer Reference Testing Laboratory
820 Heinz Ave. (APC3-BRTL)
Berkeley, CA 94710
Lab Director: Pat Joseph, M.D.
Tel: (800) 434-2447
Fax: (510) 705-5902

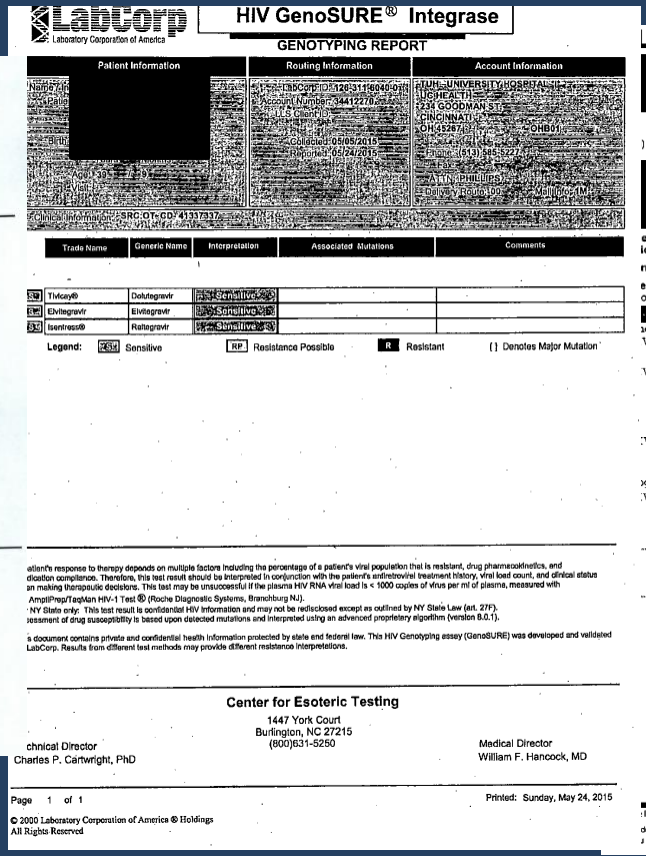
Relevant RT Mutations: K65R, K101E, V106M, V108I, Y181C

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
zidovudine (AZT)	No Evidence of Resistance
didanosine (ddI)	Possible Resistance
zalcitabine (ddC)	Resistance
lamivudine (3TC)/emtricitabine (FTC)	No Evidence of Resistance
stavudine (d4T)	Possible Resistance
abacavir (ABC)	Possible Resistance
tenofovir (TDF)	Resistance

NonNucleoside RT Inhibitors	Resistance Interpretation
nevirapine (NVP)	Resistance
delavirdine (DLV)	Resistance
efavirenz (EFV)	Resistance

Relevant Protease Mutations: L10I, M36I, L63P

Protease Inhibitors	Resistance Interpretation
saquinavir (SQV)	No Evidence of Resistance
indinavir (IDV)	No Evidence of Resistance
ritonavir (RTV)	No Evidence of Resistance
nelfinavir (NFV)	No Evidence of Resistance
amprenavir (APV)/fosamprenavir (FPV)	No Evidence of Resistance
lopinavir + ritonavir (LPV/r)	No Evidence of Resistance
atazanavir (ATV)	Possible Resistance



LabCorp
Laboratory Corporation of America

HIV GenoSURE® Integrase

GENOTYPING REPORT

Patient Information	Routing Information	Account Information
[redacted]	LabCorp ID: 120-311-6040-01 Account Number: 34412270 TLS Client ID: Collected: 05/05/2015 Reported: 05/24/2015	[redacted]

Trade Name	Generic Name	Interpretation	Associated Mutations	Comments
Tivicay®	Dolutegravir	Sensitive		
Elvitegravir	Elvitegravir	Sensitive		
Isentress®	Raltegravir	Sensitive		

Legend: 2SM Sensitive | RP Resistance Possible | R Resistant | { } Denotes Major Mutation

atient's response to therapy depends on multiple factors including the percentage of a patient's viral population that is resistant, drug pharmacokinetics, and dication compliance. Therefore, this test result should be interpreted in conjunction with the patient's antiretroviral treatment history, viral load count, and clinical status n making therapeutic decisions. This test may be unsuccessful if the plasma HIV RNA viral load is < 1000 copies of virus per ml of plasma, measured with

AmpliPrep/TaqMan HIV-1 Test ® (Roche Diagnostic Systems, Branchburg NJ).

NY State only: This test result is confidential HIV information and may not be redisclosed except as outlined by NY State Law (art. 27F).

sessment of drug susceptibility is based upon detected mutations and interpreted using an advanced proprietary algorithm (version 8.0.1).

s document contains private and confidential health information protected by state and federal law. This HIV Genotyping assay (GenoSURE) was developed and validated LabCorp. Results from different test methods may provide different resistance interpretations.

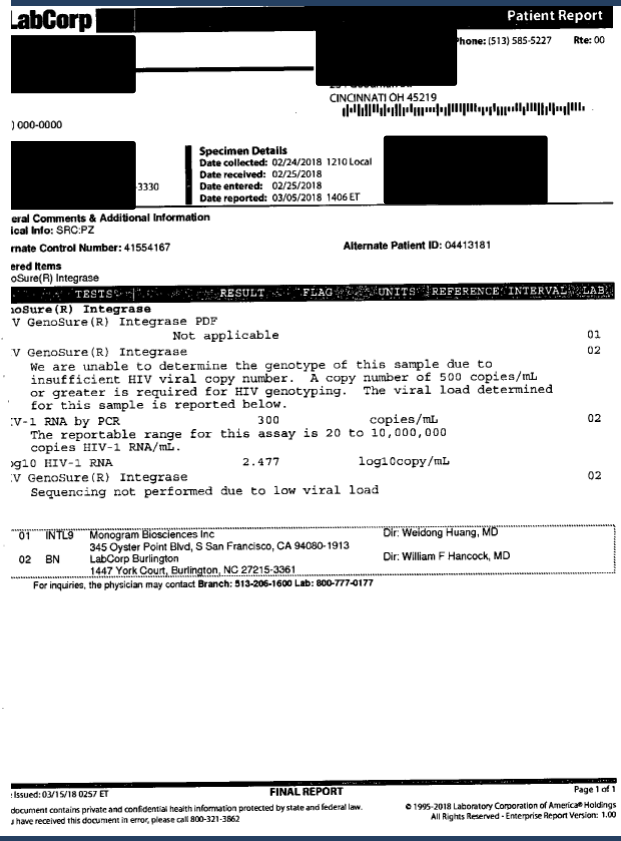
Center for Esoteric Testing
1447 York Court
Burlington, NC 27215
(800)631-5250

chnical Director
Charles P. Cartwright, PhD

Medical Director
William F. Hancock, MD

Page 1 of 1

Printed: Sunday, May 24, 2015



LabCorp

Patient Report

[redacted]

Phone: (513) 585-5227 Rte: 00

CINCINNATI OH 45219

) 000-0000

[redacted]

3330

Specimen Details
Date collected: 02/24/2018 1210 Local
Date received: 02/25/2018
Date entered: 02/25/2018
Date reported: 03/05/2018 1406 ET

[redacted]

eral Comments & Additional Information
ical Info: SRC:PZ

rnate Control Number: 41554167

Alternate Patient ID: 04413181

ered Items
oSure(R) Integrase

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
oSure(R) Integrase					
V GenoSure(R) Integrase PDF					
	Not applicable				01
V GenoSure(R) Integrase					02
We are unable to determine the genotype of this sample due to insufficient HIV viral copy number. A copy number of 500 copies/mL or greater is required for HIV genotyping. The viral load determined for this sample is reported below.					
V-1 RNA by PCR	300		copies/mL		02
The reportable range for this assay is 20 to 10,000,000 copies HIV-1 RNA/mL.					
g10 HIV-1 RNA	2.477		log10copy/mL		
V GenoSure(R) Integrase					02
Sequencing not performed due to low viral load					

01	INTL9	Monogram Biosciences Inc 345 Oyster Point Blvd, S San Francisco, CA 94080-1913	Dir: Weidong Huang, MD
02	BN	LabCorp Burlington 1447 York Court, Burlington, NC 27215-3361	Dir: William F Hancock, MD

For inquiries, the physician may contact Branch: 513-206-1600 Lab: 800-777-0177

Issued: 03/15/18 0257 ET

FINAL REPORT

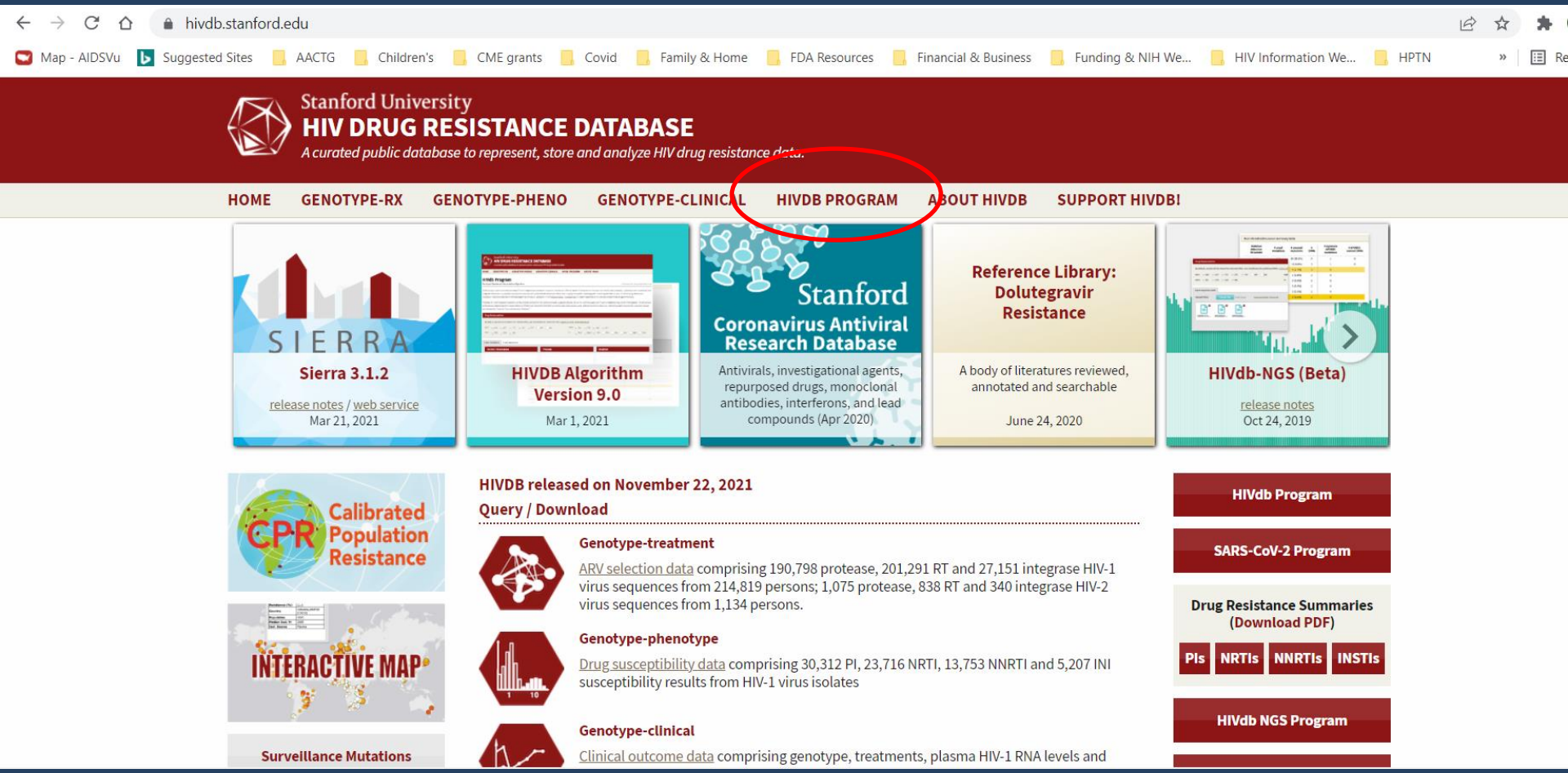
Page 1 of 1

document contains private and confidential health information protected by state and federal law.
have received this document in error, please call 800-321-3862

Key Historical Mutations: K65R, K101E, V106M, V108I, Y181C

What would you do?

- HIV VL = 24 copies/mL
- Recent Stroke on ABC/3TC/DOL
- Failed TDF/FTC/EFV – Resistance
- History of Treatment Failure – ZDV/3TC+LPV/r
- Mostly controlled viremia on ABC/3TC/DOL



https://hivdb.stanford.edu/

Input mutations | Input sequences

Reverse Transcriptase

K65R x K101E x V106M x V108I x Y181C x
Input mutation(s)

Select mutations:

40 ---	41 ---	44 ---	62 ---
65 ---	67 ---	68 ---	69 ---
70 ---	74 ---	75 ---	77 ---
90 ---	98 ---	100 ---	101 ---
103 ---	106 ---	108 ---	115 ---
116 ---	118 ---	138 ---	151 ---
179 ---	181 ---	184 ---	188 ---
190 ---	210 ---	215 ---	219 ---
221 ---	225 ---	227 ---	230 ---
234 ---	236 ---	238 ---	318 ---

Protease

L10I x M36I x L63P x Input mutation(s)

Select mutations:

10 ---	11 ---	13 ---	20 ---
23 ---	24 ---	30 ---	32 ---
33 ---	35 ---	36 ---	43 ---
46 ---	47 ---	48 ---	50 ---
53 ---	54 ---	58 ---	63 ---
71 ---	73 ---	74 ---	76 ---
77 ---	82 ---	83 ---	84 ---
85 ---	88 ---	89 ---	90 ---
93 ---			

Integrase

Input mutation(s)

Select mutations:

51 ---	66 ---	74 ---	92 ---
95 ---	97 ---	114 ---	118 ---
121 ---	128 ---	138 ---	140 ---
143 ---	145 ---	146 ---	147 ---
148 ---	151 ---	153 ---	155 ---
157 ---	163 ---	230 ---	263 ---

https://hivdb.stanford.edu/

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

Drug resistance interpretation: PR

HIVDB 9.0 (2021-02-22)

PI Major Resistance Mutations: None
PI Accessory Resistance Mutations: None
Other Mutations: L10I, M36I, L63P

Protease Inhibitors	
atazanavir/r (ATV/r)	Susceptible
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Susceptible

PR comments

Other

- **L10I/V** are polymorphic, PI-selected accessory mutations that increase the replication of viruses with other PI-resistance mutations.

Mutation scoring: PR

HIVDB 9.0 (2021-02-22)

PI	ATV/r	DRV/r	LPV/r
Total	0	0	0

Drug resistance interpretation: RT

HIVDB 9.0 (2021-02-22)

NRTI Resistance Mutations: **K65R**
NNRTI Resistance Mutations: **K101E**, **V106M**, **V108I**, **Y181C**
Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Intermediate Resistance
lamivudine (3TC)	Intermediate Resistance
tenofovir (TDF)	High-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	High-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	High-Level Resistance

RT comments

NRTI

- **K65R** causes intermediate/high-level resistance to TDF, ddI, ABC and d4T and low/intermediate resistance to 3TC and FTC. **K65R** increases susceptibility to AZT.

NNRTI

- **K101E** is a non-polymorphic primarily accessory mutation that causes intermediate resistance to NVP and RPV, low-level resistance to EFV, and potentially low-level resistance to ETR. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. It is associated with low-level reductions in DOR susceptibility.
- **V106M** is a non-polymorphic mutation that causes high-level resistance to NVP and EFV. It is selected in vitro and in vivo by DOR and preliminary data suggests it is associated with low/intermediate reductions in DOR susceptibility.
- **V108I** is a relatively non-polymorphic accessory mutation selected in vitro and/or in vivo with each of the NNRTIs. It causes low-level reductions in susceptibility to NVP and

https://hivdb.stanford.edu/

Case plan and follow up

- Clinician decided to avoid abacavir given cardiovascular disease
- Changed therapy to dolutegravir/3TC
- History of virologic control

Date:	3/8/2019	9/5/2019	3/10/2020	6/24/2020	2/12/2021	10/13/2021	3/14/2022
HIV-1 RNA	ND	256	ND	ND	ND	ND	ND

Active Clinical Trials

- To learn more about active trials, call Sharon Kohrs, RN, Clinical Research Director at 513-584-6383
- DOMINO – RCT of GSK-254 at varying doses with NRTIs and then combined with DOL for treatment naïve PWH.
- ACTG A5359 – Randomized trial of injectable long-acting treatments for persons failing therapy with minimum antiretroviral resistance.
- ACTG A5391 – Randomized trial of switching to TDF/FTC/DOR in persons with excessive weight gain on TAF and Integrase containing regimens
- ACTG A5386 – IL-15 superagonist with and without BNABs to control HIV with ATI in persons doing well on ART.

Thank You!

- Mary Beth Donica, MD
- T'Keyah Grier, MPH
- Ms. Brenda Miller
- Ms. Mary Ann Schaefer
- Pamposh Kaul, MD
- UC CME Office and College of Pharmacy
- Our sponsors
- Our speakers
- You The Audience
- Slides from Dr. Chloe L. Orkin and other CROI presenters

AETC Resources

- **Clinical Consultation Center**
  - http://nccc.ucsf.edu/
    - HIV management
    - Perinatal HIV
    - HIV PrEP
    - HIV PEP Line
    - HCV Management
    - Substance Use Management
- **AETC National HIV Curriculum**
  - https://aidsetc.org/nhc
- **AETC National HIV-HCV Curriculum**
  - https://aidsetc.org/hivhcv
- **Hepatitis C Online**
  - https://www.hepatitis.uw.edu/
- **AETC National Coordinating Resource Center**
  - https://aidsetc.org/

The End – Iguazu Falls

Back up Slides Only

HIV Cure

2

Cases of HIV-1 Cure

Berlin Patient (2009)

Timothy Ray Brown
(1966-2020)
Caucasian male
Provided proof-of-concept for cure with transplantation of CCR5Δ32/Δ32 cells

Strategy that led to cure

- Chemotherapy for relapsed AML
- Stem cell transplant x2 (chemo & TBI conditioning)
- Graft:**adult donor CCR5Δ32/Δ32 bone marrow cells** (10/10 HLA match)
- Graft versus host disease
- ART stopped immediately after transplant
- HIV-1 remission **20 months; >12 years** (deemed cured)

Hutter G et al, NEJM 2009 . PLoS Pathog 2013; 9: e1003347
Hutter AIDS 2011; 25: 273–74.

London Patient (2019)

Adam Castillejo
(40 years old)
Latino male

Strategy that led to cure

- Chemotherapy for Hodgkin's lymphoma
- Stem cell transplant (chemo conditioning)
- Graft: **adult donor CCR5Δ32/Δ32 homozygous peripheral blood stem cells (9/10 HLA match**)
- Graft versus host disease
- ART stopped 16 months after transplant
- HIV-1 remission **18 months**; **30 months**

Lancet HIV 2020; 7: e340–47
Gupta R et al, Nature 2019

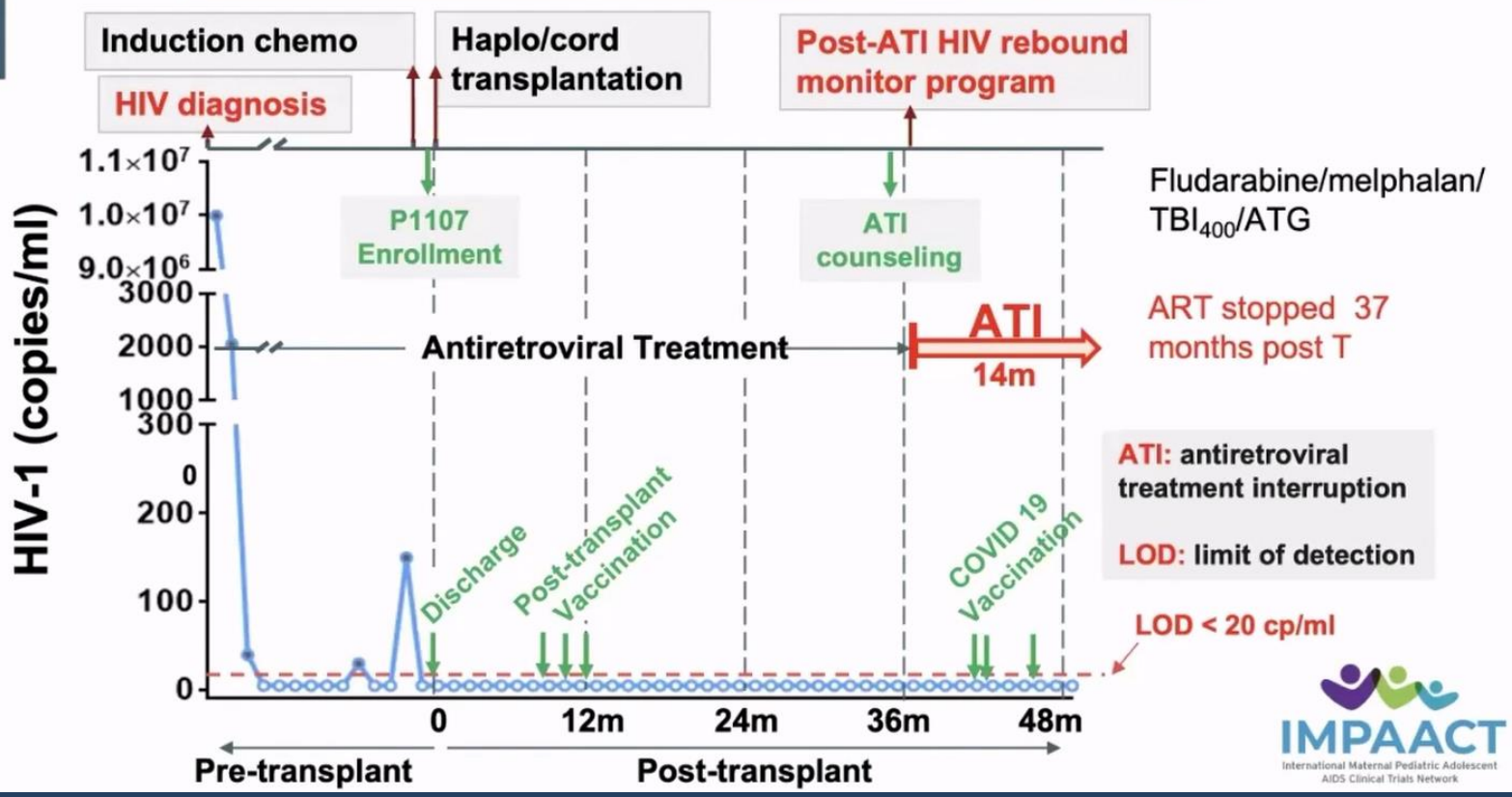
6

CASE REPORT.

- 59 yr/old female mixed race
- DX acute HIV 2013
- High risk AML monsomy 7, 2017
- 3 partially matched CCR5 delta 32/32 cord units (Stemcyte)
- Haplo/cord transplant :5/8 match CBU & relative's PBMC (2017)

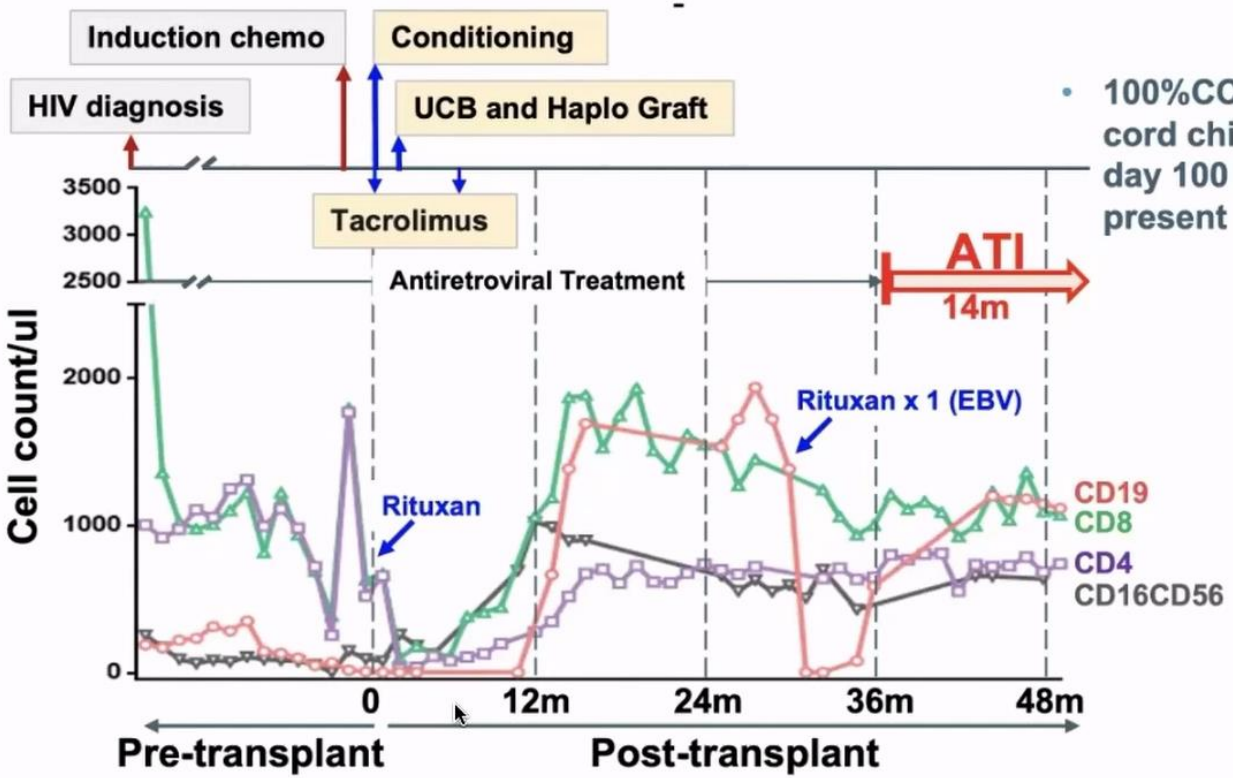
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

HIV and AML Treatment Course



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

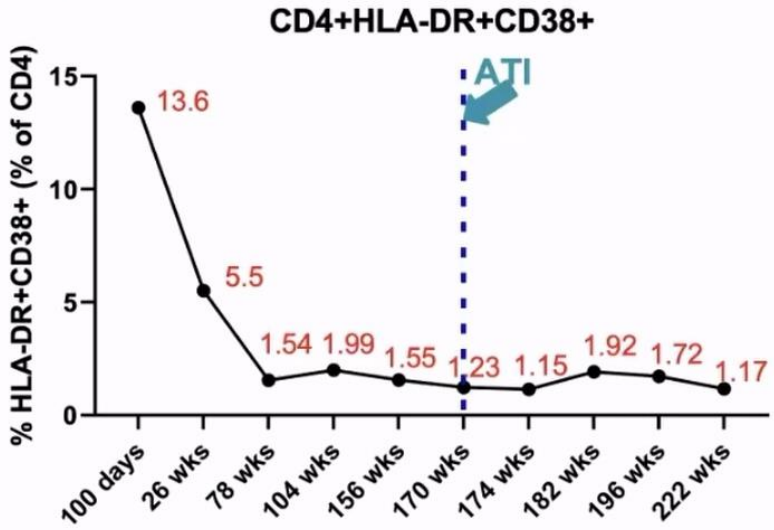
Immune Reconstitution Profiles

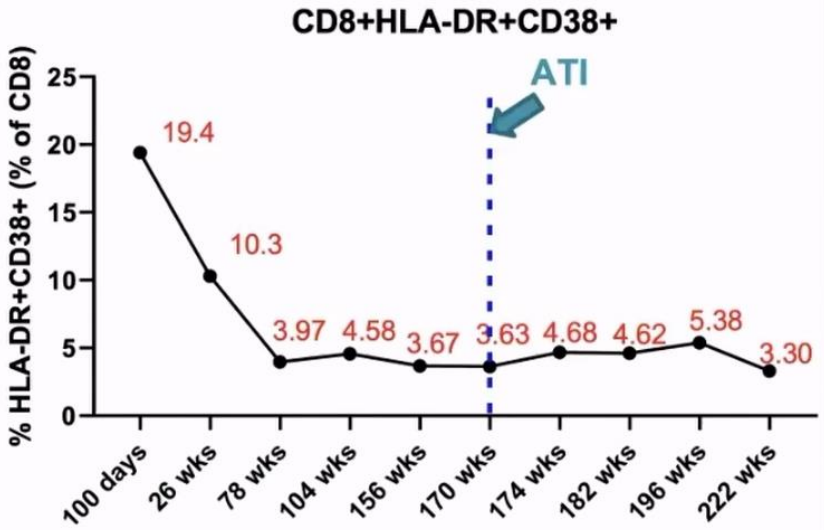


- 100%CCR5Δ32/Δ32 cord chimerism by day 100 until present

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Decrease of Immune activation of CD4 and CD8 T cells

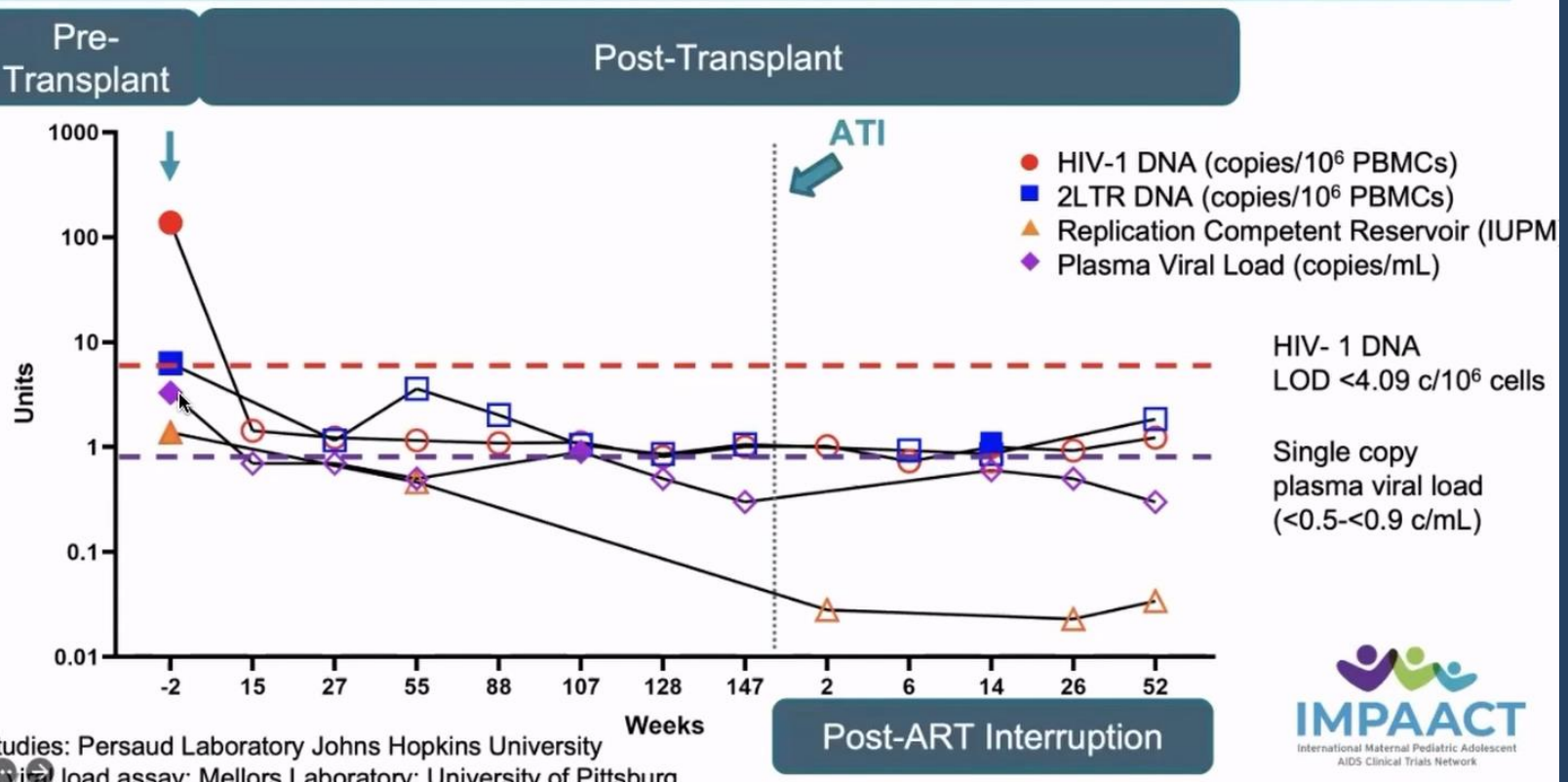




No HIV-1 antigen (HIV-1 gag)- specific T cells were detected, while polyclonal responses (SEB) were intact.- Data not shown

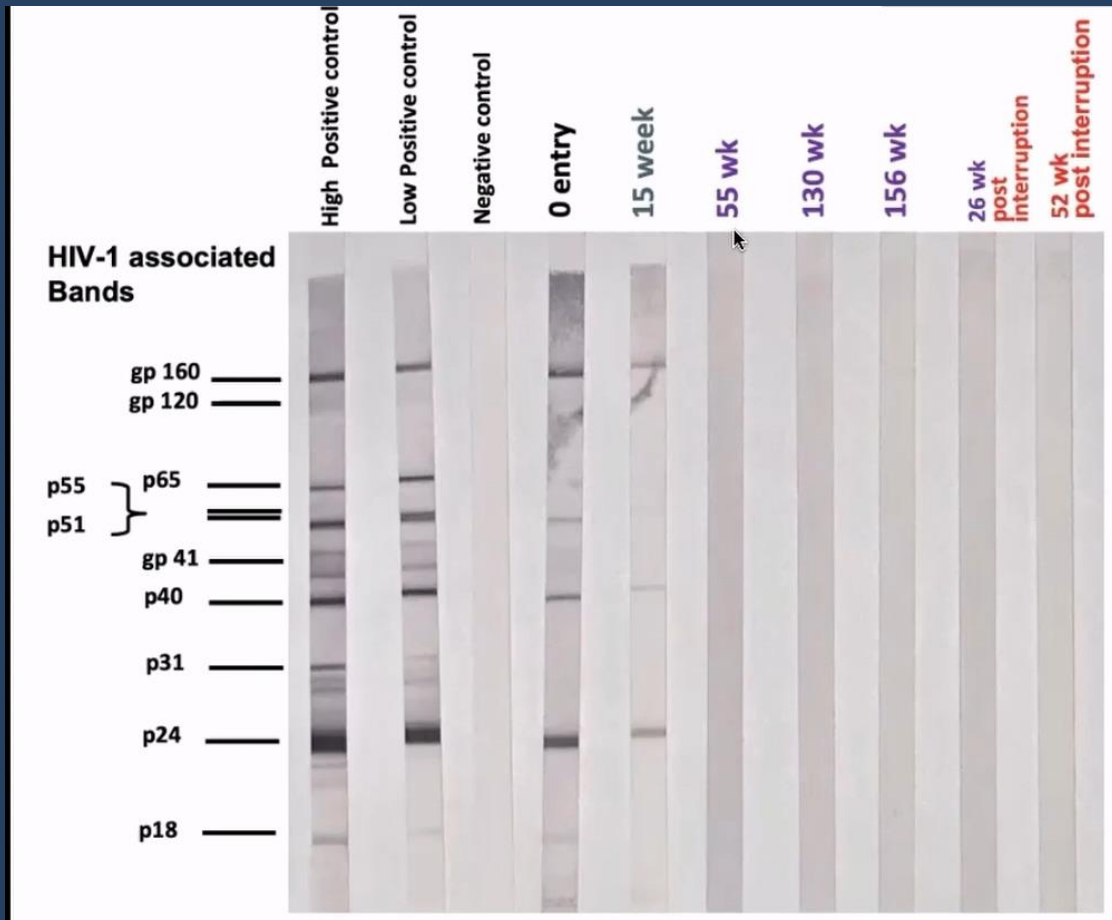
10

Cell-Associated HIV-1 DNA Levels, Latent Reservoir Size and Low-level Viremia Pre-and Post-Transplantation and Following ART Interruption



Reservoir studies: Persaud Laboratory Johns Hopkins University
Single-copy viral load assay: Mellors Laboratory; University of Pittsburg

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network



Loss of HIV-1-specific antibody responses (WB) by Week 55 post-transplant through 52 weeks post ATI

IMPAACT P1107: Conclusions

- **First US woman of mixed race** living with HIV-1 successfully transplanted with CCR5Δ32/Δ32 cord/haplo SCT with 100% sustained engraftment of cord blood and in HIV-1 remission
- Durable remission of AML 4 years 6 months post SCT
- **14 months off ART no viral rebound (no ARV's in plasma)**
- **No detectable replication-competent latent reservoir** (74.5 million CD4T cells)
- **Undetectable HIV-1-specific cellular immune** responses and **HIV antibody negative ,in vitro resistance to lab & autologous virus**
- Negative- (transient trace) HIV DNA by ddPCR
- Remains clinically well with **NO GVHD**

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network