Treatment Challenges of Multi-Drug Resistant HIV-1 Infection

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State of the Art and Future Directions

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Agenda

- Background Review
- UB-421 Clinical Trial
- Patient Discussion Case

Part I
Background Review

Multiple Challenges Remain on the HIV front

- Inflammatory state
- Life-long treatment
- Treatment toxicity
- Patient adherence issues
- Quality of life
- Immune ageing and senescence
- Development of viral resistance

Background

- Rise in antimicrobial resistance (AMR) is one of the greatest threats to global health
- WHO report indicates that an increasing number of countries are reaching the 10% threshold of PDR HIV drug resistance to NNRTI and people who have had previous exposure to antiretroviral drugs are three times more likely to demonstrate resistance to the NNRTI drug class.
- Nearly half of infants newly diagnosed with HIV carry drug-resistant HIV before initiating treatment

MDR HIV is a clinical conundrum

	Genotype prediction	Phenotype		
		Fold change	Cutoff	Interpretation
Nucleoside reverse transcriptase inhibitor*				
Abacavir	Resistant	6·97	4·5–6·5	Resistant
Didanosine	Resistant	2·06	1·3–2·2	Resistant
Emtricitabine	Resistant	>MAX	3·5	Resistant
Lamivudine	Resistant	>MAX	3·5	Resistant
Stavudine	Resistant	1·83	1·7	Resistant
Tenofovir	Reduced sensitivity	0·91	1·4–4	Sensitive
Zidovudine	Resistant	6·39	1·9	Resistant
Non-nucleoside reverse transcriptase inhibitor†				
Delavirdine	NA	>MAX	6·2	Resistant
Doravirine	Reduced sensitivity	6·9	3	Resistant
Efavirenz	Resistant	>MAX	3	Resistant
Etravirine	Resistant	>MAX	2·9–10	Resistant
Nevirapine	Resistant	>MAX	4·5	Resistant
Rilpivirine	Resistant	>MAX	2	Resistant
Protease inhibitor‡				
Atazanavir	Resistant	44	5·2	Resistant
Darunavir	Resistant	323	10–90	Resistant
Fosamprenavir	Resistant	>MAX	4–11	Resistant
Indinavir	Resistant	19	10	Resistant
Lopinavir	Resistant	38	9–55	Reduced sensitivity
Nelfinavir	Resistant	39	3·6	Resistant
Saquinavir	Resistant	26	2·3–12	Resistant
Tipranavir	Reduced sensitivity	17	2–8	Resistant
Integrase strand transfer inhibitor§				
Bictegravir	Reduced sensitivity	27	3·5–10	Resistant
Dolutegravir	Reduced sensitivity	68	4–13	Resistant
Elvitegravir	Resistant	>MAX	3·5	Resistant
Raltegravir	Resistant	>MAX	2·2	Resistant
Entry inhibitor				
Maraviroc¶	NA	DM virus	NA	Activity not anticipated

eBioMedicine
Part of THE LANCET

Articles

eBioMedicine 2022;77: 103906
Published online 4 March 2022

Achieving virological control in pan-resistant HIV-1 infection: A case series

Diana Canetti,[a,1] Camilla Muccini,[a,b,1] Vincenzo Spagnuolo,[b] Laura Galli,[a] Andrea Poli,[a] Nicola Gianotti,[a] Marcello Feasi,[c] and Antonella Castagna[a,b]*

We report findings from heavily treatment-experienced PLWH with a pan-resistant HIV-1 infection, who achieved virological control once introduced injections of ibalizumab, that is free from cross-resistance with all the antiretroviral drugs available and ensures patient adherence due to a close monitoring attributable to the route of administration, combined with recycled enfuvirtide and an optimized background regimen.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

Brinda Emu, M.D., Jeffrey Fessel, M.D., Shannon Schrader, M.D., Princy Kumar, M.D., Gary Richmond, M.D., Sandra Win, M.D., Steven Weinheimer, Ph.D., Christian Marsolais, Ph.D., and Stanley Lewis, M.D.

2018

Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection

Michael Kozal, M.D., Judith Aberg, M.D., Gilles Pialoux, M.D., Pedro Cahn, M.D., Melanie Thompson, M.D., Jean-Michel Molina, M.D., Beatriz Grinsztejn, M.D., Ricardo Diaz, M.D., Antonella Castagna, M.D., Princy Kumar, M.D., Gulam Latiff, M.D., Edwin DeJesus, M.D., Mark Gummel, M.S., Margaret Gartland, M.Sc., Amy Pierce, B.S., Peter Ackerman, M.D., Cyril Llamoso, M.D., and Max Lataillade, D.O., for the BRIGHTE Trial Team*

2020

Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection

Sorana Segal-Maurer, M.D., Edwin DeJesus, M.D., Hans-Jurgen Stellbrink, M.D., Antonella Castagna, M.D., Gary J. Richmond, M.D., Gary I. Sinclair, M.D., Krittaecho Siripassorn, M.D., Peter J. Ruane, M.D., Mezgebe Berhe, M.D., Hui Wang, Ph.D., Nicolas A. Margot, M.A., Hadas Dvory-Sobol, Ph.D., Robert H. Hyland, D.Phil., Diana M. Brainard, M.D., Martin S. Rhee, M.D., Jared M. Baeten, M.D., Ph.D., and Jean-Michel Molina, M.D., Ph.D., for the CAPELLA Study Investigators*

2022

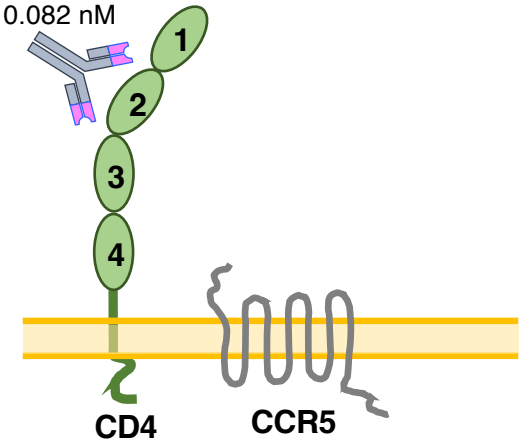
The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Volume 379 August 16, 2018 Number 7

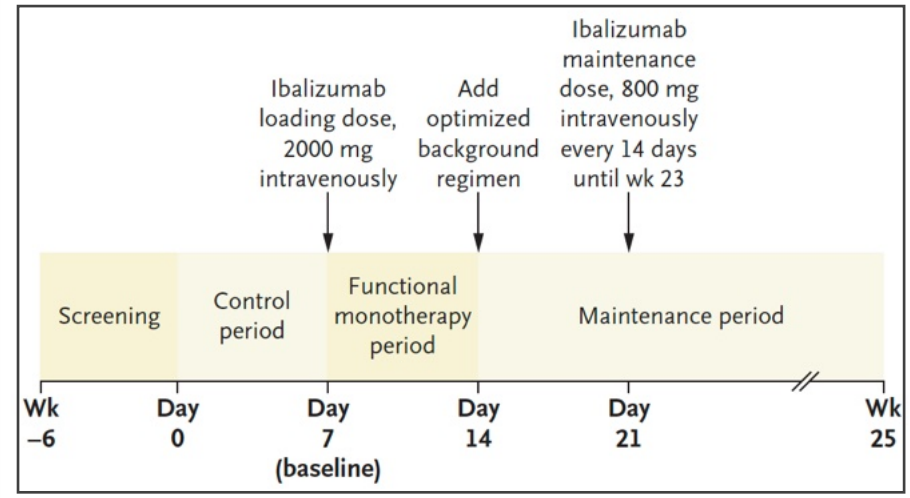
Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

B Emu, J Fessel, S Schrader, P Kumar, G Richmond, S Win, S Weinheimer, C Marsolais, S Lewis

Ibalizumab

- Domain 2-specific
- Affinity 0.082 nM





Summary of Ibalizumab (Trogarzo) Trial

- Humanized IgG4 (does not block binding of HIV to CD4)
- Baseline plasma viremia 4.5 $\log_{10}$ copies/ml and CD4 count 150 cells/μl (n=31 receiving optimized background regimen)
- 43% of the study participants achieved plasma viremia of <50 copies/ml
- 50% of the study participants achieved plasma viremia of <200 copies/ml
- 9/10 who did not respond to the study drug had a lower degree of susceptibility to Ibalizumab (loss of N-linked glycosylation in the V5 loop of HIV gp120)
- Four patients died due to underlying illnesses (1 had IRIS, possibly related to Ibalizumab)

B Emu et al., *N Engl J Med*, 379:645-654, 2018

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Volume 382 March 26, 2020 Number 13

Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection

M Kozal, J Aberg, G Pialoux, P Cahn, M Thompson, J-M Molina, B Grinsztejn, R Diaz, A Castagna, P Kumar, G Latiff, E DeJesus, et al., for the BRIGHTE Trial Team

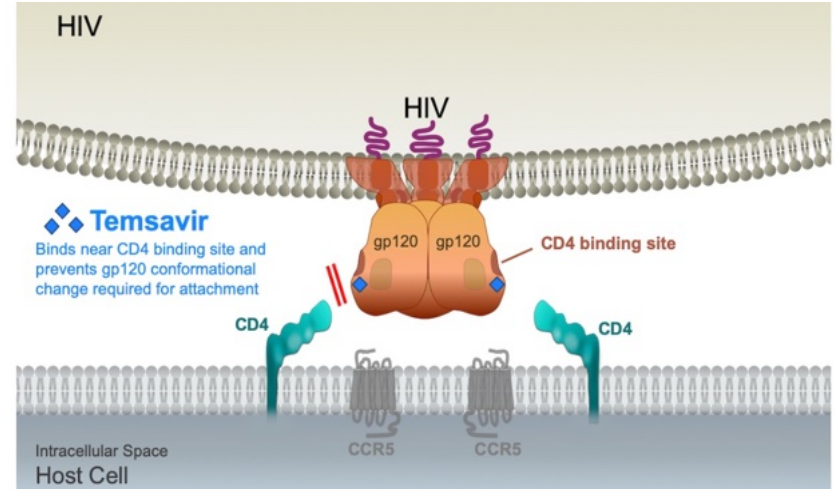
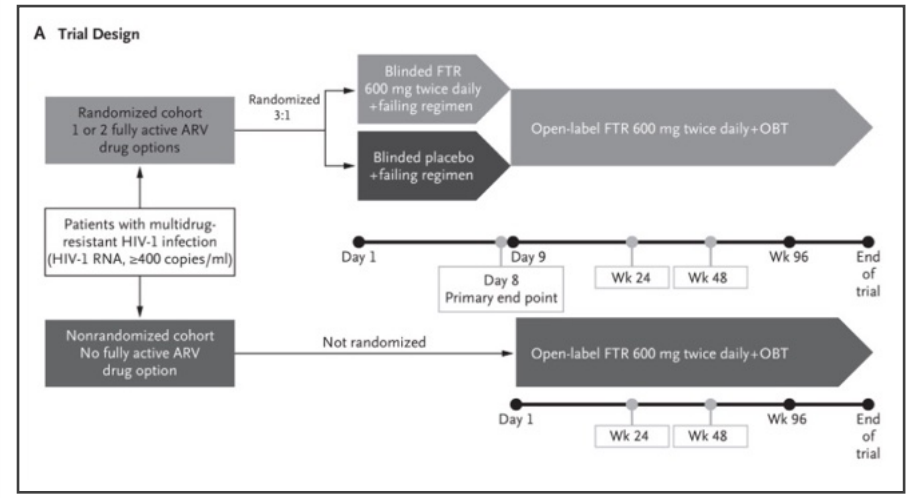


Illustration by David H. Spach, MD



Summary of Fostemsavir Trial

- Temsavir, the active metabolite of fostemsavir, was the first-in-class attachment inhibitor that binds directly to the viral envelope glycoprotein 120 (gp120), close to the $CD4^+$ binding site
- A total of 371 patients were treated, including 272 in the randomized cohort and 99 in the nonrandomized cohort
- At week 48, a virologic response (HIV-1 RNA level, <40 copies per milliliter) had occurred in 54% of the patients in the randomized cohort and in 38% of those in the nonrandomized cohort; the mean increase in the $CD4^+$ T-cell count was 139 cells per cubic millimeter and 64 cells per cubic millimeter, respectively
- In the randomized cohort, glycoprotein 120 (gp120) substitutions were found in 20 of 47 patients (43%) with virologic failure

M Kozal et al., *N Engl J Med*, 382:1232-1243, 2020

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Volume 386 May 12, 2022 Number 19

Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection

S Segal-Maurer, E DeJesus,
H-J Stellbrink, A Castagna,
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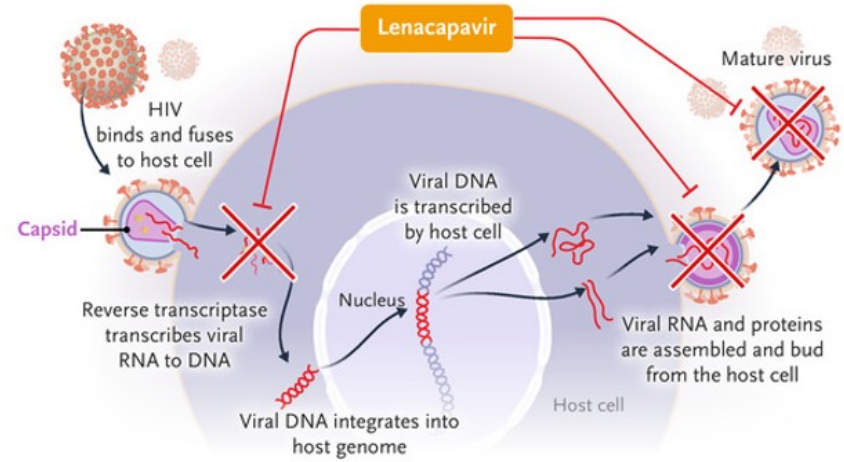
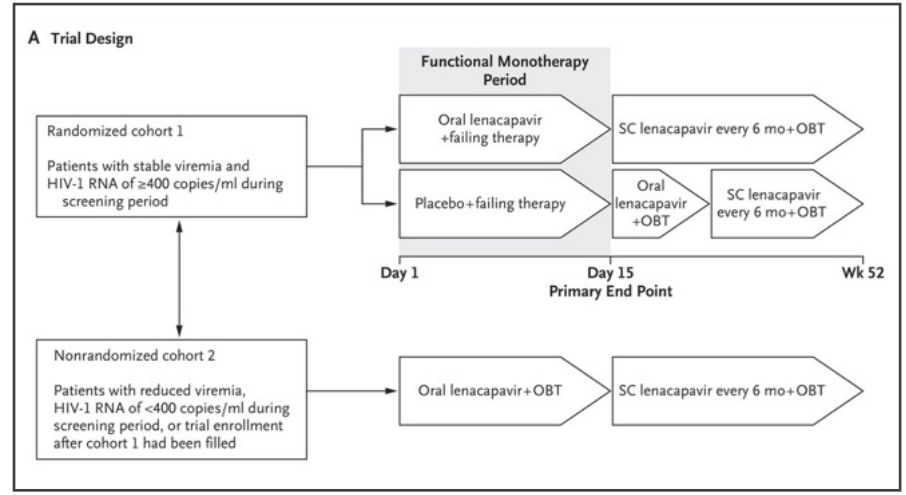
K Siripassorn, PJ Ruane,
M Berhe, H Wang, NA Margot,
H Dvory-Sobol, et al.,
for the CAPELLA Study Team



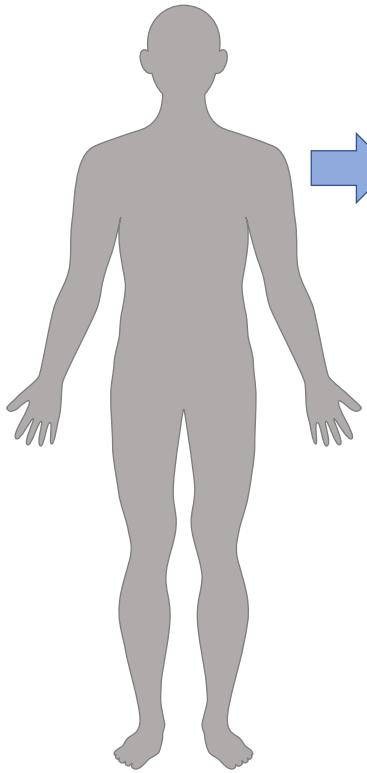


Summary of Lenacapavir (CAPELLA) Trial

- Lenacapavir is a first-in-class inhibitor of HIV-1 capsid function
- A total of 72 patients were enrolled, with 36 in each cohort
- In cohort 1, a decrease of at least 0.5 $\log_{10}$ copies per milliliter in the viral load by day 15 was observed in 21 of 24 patients (88%) in the lenacapavir group and in 2 of 12 patients (17%) in the placebo group
- At week 26, a viral load of less than 50 copies per milliliter was reported in 81% of the patients in cohort 1 and in 83% in cohort 2, with a least-squares mean increase in the $CD4^+$ count of 75 and 104 cells per cubic millimeter, respectively.
- In both cohorts, lenacapavir-related capsid substitutions that were associated with decreased susceptibility developed in 8 patients during the maintenance period (6 with M66I substitutions)

S Segal-Maurer et al., *N Engl J Med*, 386:1793-1803, 2022

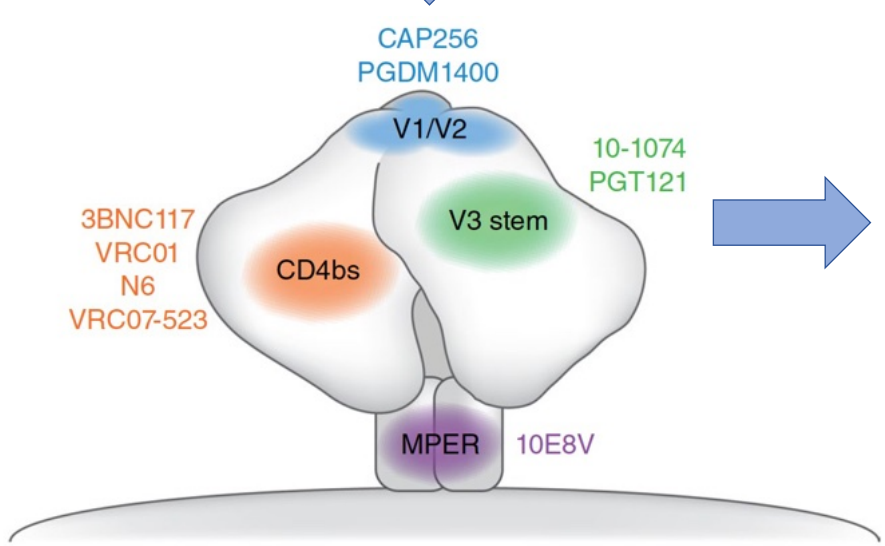
Potential Role of Broadly Neutralizing HIV-Specific Antibodies in the Prevention and Treatment of HIV Infection



HIV-infected individual

Cloning of HIV-specific B cells

Sequencing and production of HIV-specific antibodies (>200 bNAbs)



2nd generation bNAbs that are currently being investigated in clinical trials

Passive transfer of bNAbs in humans

- Prevention of HIV transmission
- Long-term suppression of HIV in the absence of ART
- Clearance of HIV reservoirs and induction of anti-HIV immune responses

Modified from M Caskey et al, *Nat Med*, 25:547-553, 2019

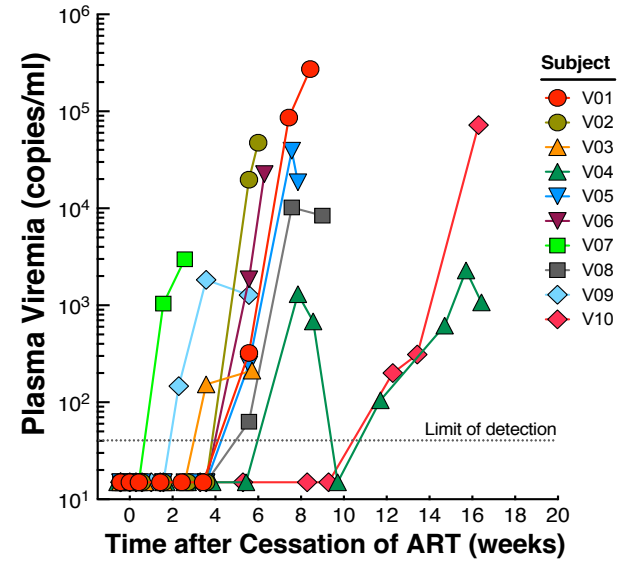
The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 375 November 10, 2016 Number 19

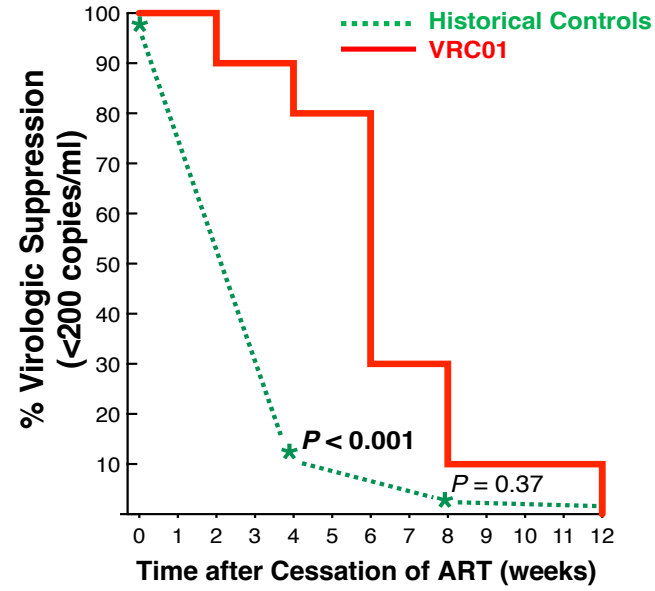
Effect of HIV-Specific Antibody VRC01 on Viral Rebound after Treatment Interruption

K.J. Bar, M.C. Sneller, L.J. Harrison, J.S. Justement, E.T. Overton, M.E. Petrone, D.B. Salantes, C.A. Seamon, B. Scheinfeld, R.W. Kwan, G.H. Learn, M.A. Proschan, E.F. Kreider, J. Blazkova, M. Bardsley, E.W. Refsland, M. Messer, K.E. Clarridge, N.B. Tustin, P.J. Madden, K.S. Oden, S.J. O'Dell, B. Jarocki, A.R. Shiakolas, R.L. Tressler, N.A. Doria-Rose, R.T. Bailer, J.E. Ledgerwood, E.V. Capparelli, R.M. Lynch, B.S. Graham, S. Moir, R.A. Koup, J.R. Mascola, J.A. Hoxie, A.S. Fauci, P. Tebas, and T.-W. Chun



Median time to plasma viral rebound

- Historical controls: 11-28 days
- VRC01: 39 days

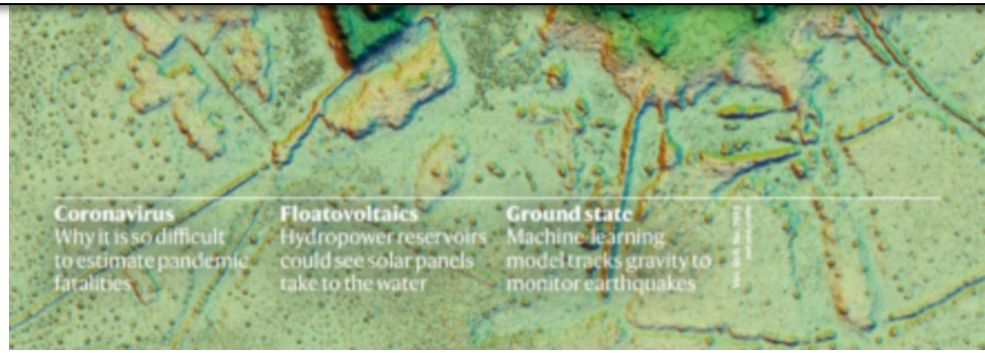


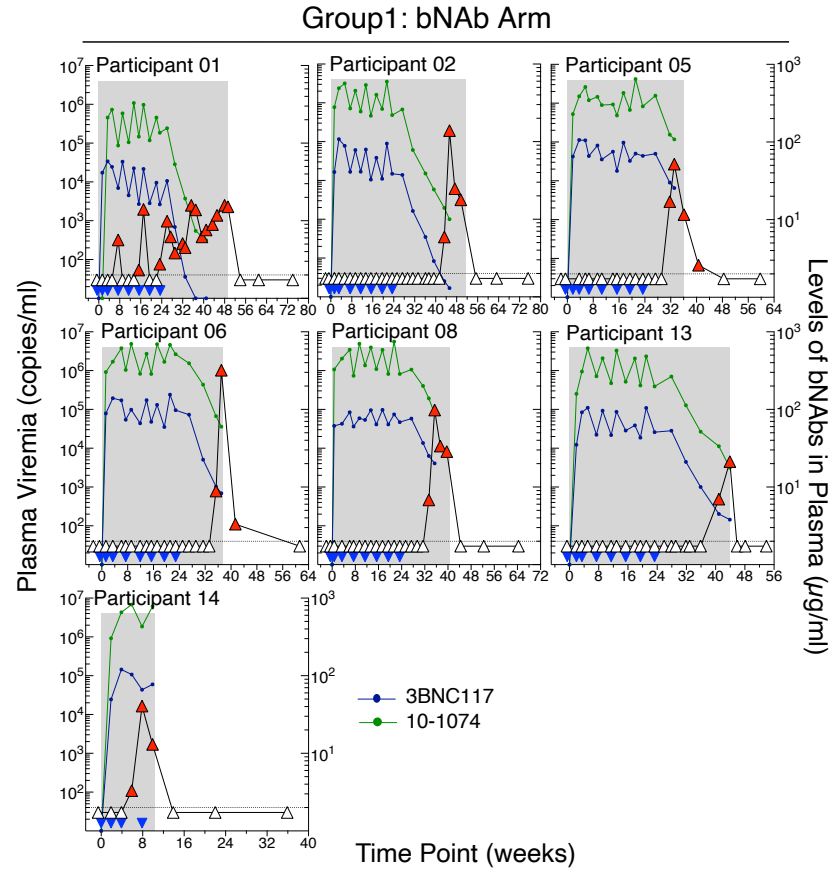
The international journal of science/8 June 2022

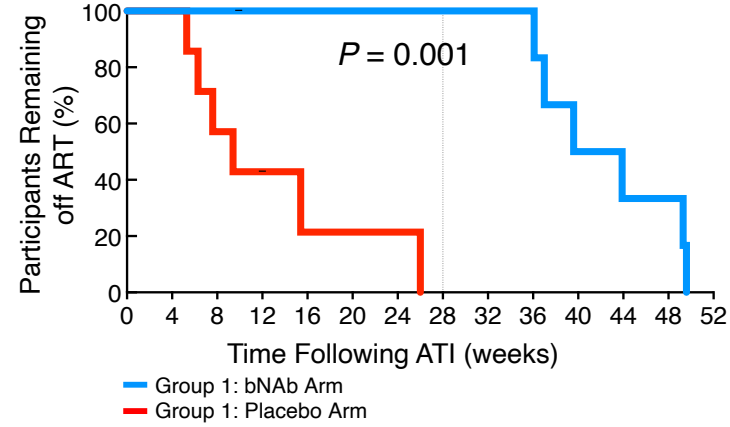
nature

Combination anti-HIV antibodies provide sustained virologic suppression

MC Sneller, J Blazkova, JS Justement, V Shi, BD Kennedy, K Gittens, J Tolstenko, G McCormack, EJ White, RF Schneck, MA Proschan, E Benko, C Kovacs, C Oguz, MS Seaman, M Caskey, MC Nussenzweig, AS Fauci, S Moir, T-W Chun.



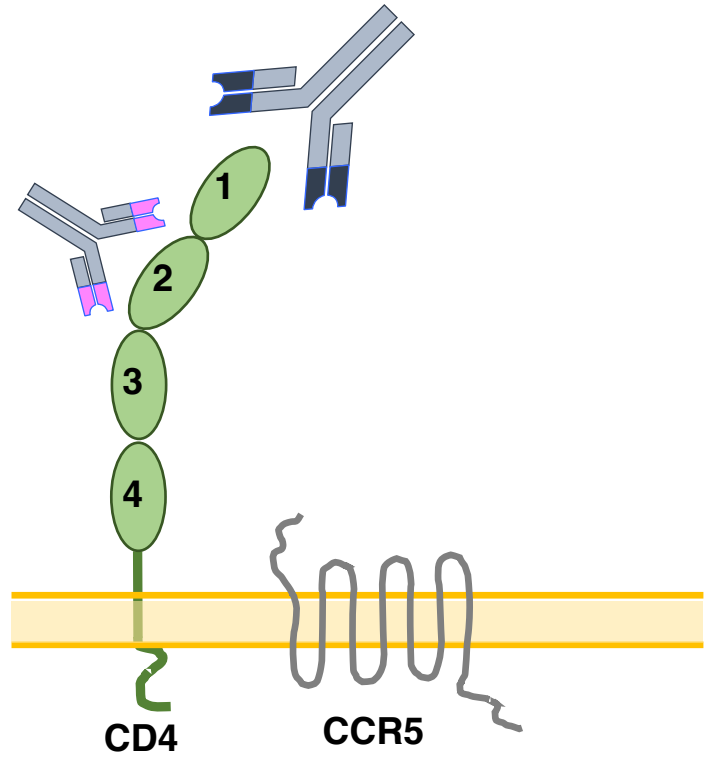




Targeting Human CD4 to Suppress HIV

UB-421
- Domain 1-specific
- Affinity 0.057 nM

Ibalizumab
- Domain 2-specific
- Affinity 0.082 nM
- FDA-approved for MDR HIV



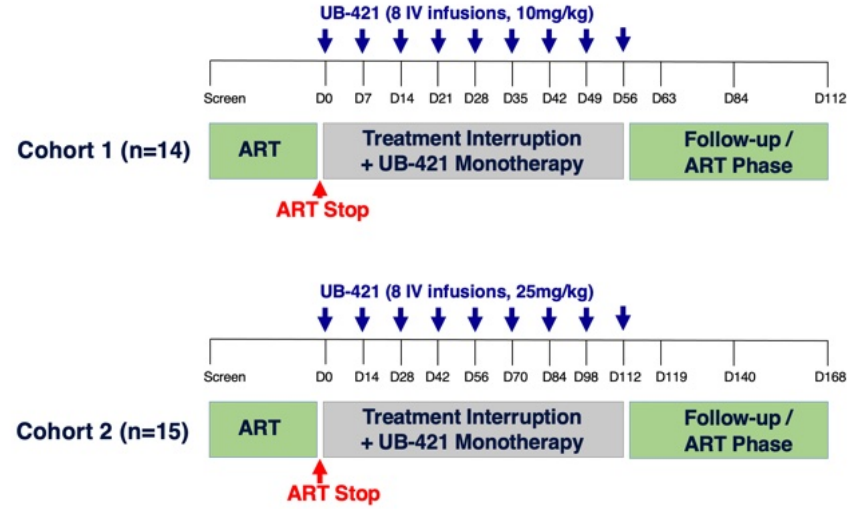
The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 380 April 18, 2019 Number 16

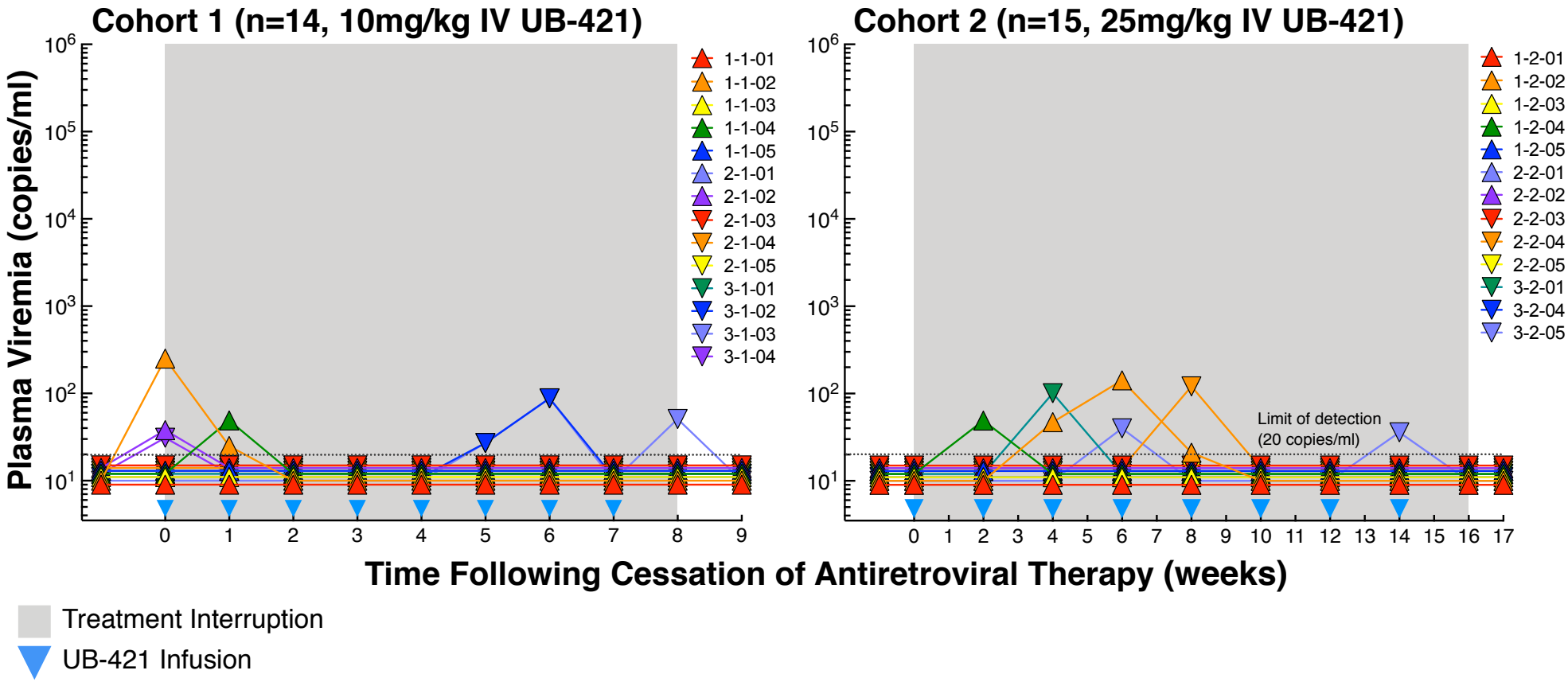
Effect of Anti-CD4 Antibody UB-421 on HIV-1 Rebound after Treatment Interruption

C Wang, W Wong, H Tsai, Y Chen, B Kuo, S Lynn, J Blazkova, K Clarridge, H Su, C Lin, F Tseng, A Lai, F Yang, C Lin, W Tseng, H Lin, C Finstad, F Wong-Staal, C Hanson, T-W Chun, and M Liao



Variable	Cohort 1 (N=14)	Cohort 2 (N=15)
Baseline characteristics		
Asian race — no. (%)†	14 (100)	15 (100)
Male sex — no. (%)	14 (100)	15 (100)
Median age (range) — yr	35 (25–47)	31 (21–56)
Median weight (range) — kg	70.3 (55–97)	62.3 (46–74)
Median height (range) — cm	175 (168–183)	169 (159–178)
Median duration of HIV infection (range) — yr	5.7 (2.9–17.7)	5.8 (1.3–15.7)
Median duration of ART (range) — yr	4.8 (1.7–16.3)	5.2 (1.3–10.9)
Plasma viremia <20 copies of HIV RNA/ml — no. (%)	14 (100)	15 (100)
Median red-cell count (range) — $\times 10^{-6}$/mm^3	4.1 (3.6–5.0)	4.3 (3.4–5.3)
Median CD4+ T-cell count (range) — cells/mm^3	653 (370–951)	640 (394–1087)
Median CD8+ T-cell count (range) — cells/mm^3	721 (392–1145)	831 (379–1511)
Adverse event of grade 2 or higher — no./total no. (%)‡		
Rash	1/14 (7)	2/14 (14)§
Eosinophilia	1/14 (7)	2/14 (14)§
Bilirubin elevation	1/14 (7)¶	0/14
Alkaline phosphatase elevation	1/14 (7)¶	0/14
γ-Glutamyltransferase elevation	1/14 (7)¶	0/14
Alanine aminotransferase elevation	1/14 (7)¶	1/14 (7)§
Aspartate aminotransferase elevation	1/14 (7)¶	2/14 (14)§

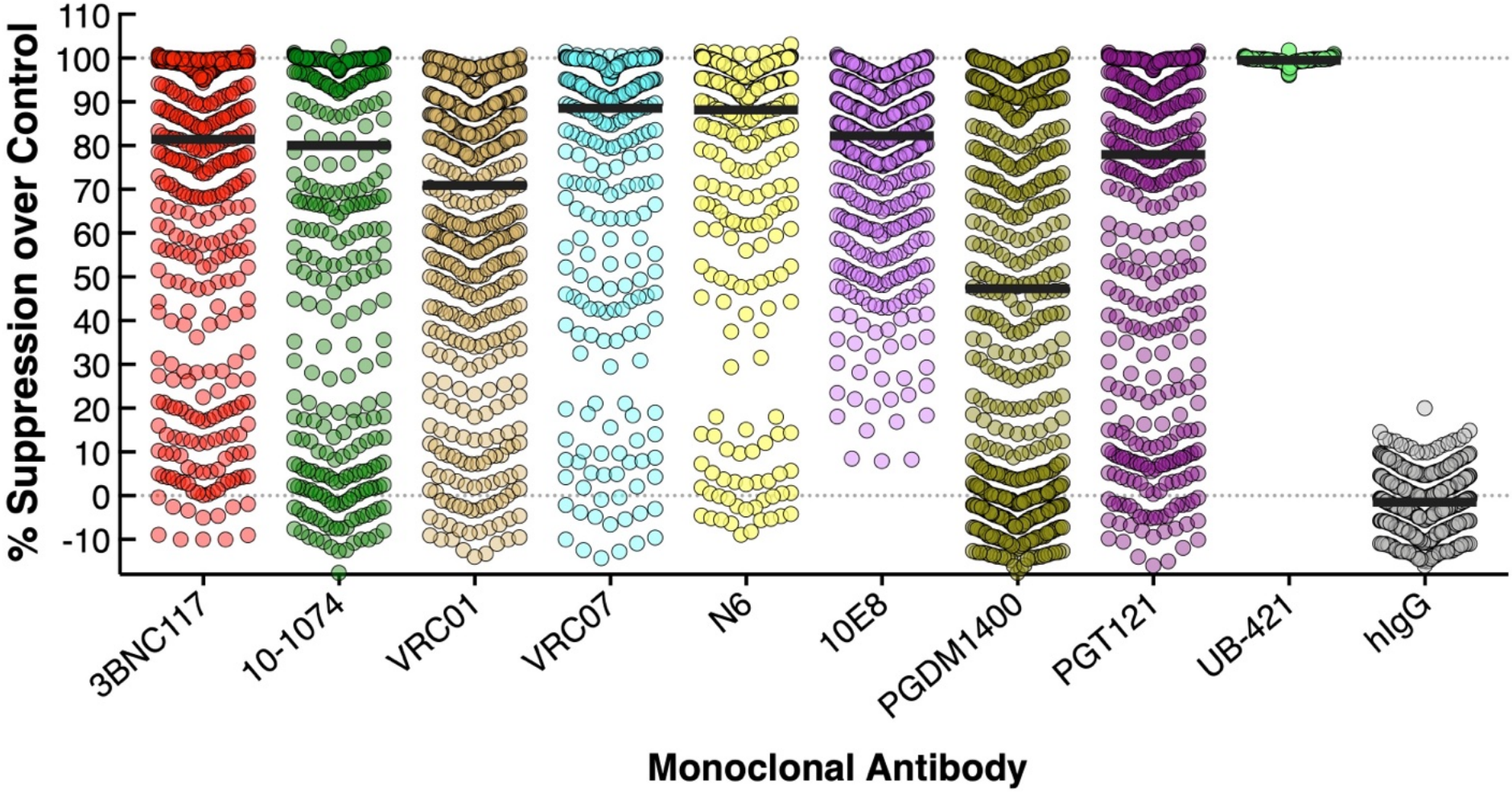
Effect of Anti-CD4 Antibody UB-421 on Plasma Viral Rebound in HIV-Infected Individuals Following Treatment Interruption



C Wang et al., *N Engl J Med,* 380:1535-1545, 2019

Capacity of bNAbs to Suppress Infectious HIV Isolates

(>800 isolates from 90 infected individuals)

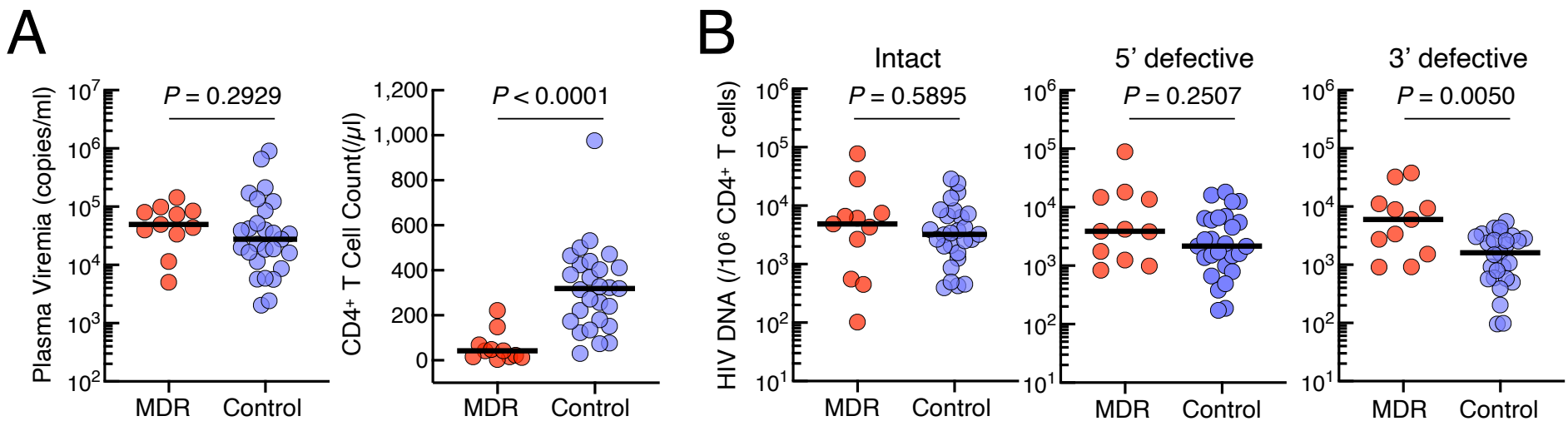


Baseline Characteristics of Study Participants

Study participant	Age	Sex	Race or ethnic group	Plasma Viremia (copies/ml)	$CD4^+$ T cell count (cells/µl)	% $CD4^+$ T cells	$CD8^+$ T cell count (cells/µl)	% $CD8^+$ T cells	Genotype prediction			
									NRTIs	NNRTIs	PIs	INSTIs
1	24	F	African American	84,626	16	2	599	73	R	R	R	S
2	54	M	Caucasian	39,950	23	1	1896	84	R	R	R	R
3	50	M	African American	143,379	222	20	610	55	R	R	R	R
4	42	M	African American	11,464	4	1	197	46	R	R	R	R
5	44	M	African American	80,156	42	4	593	57	R	S	R	R
6	26	F	African American	49,585	69	7	550	56	R	R	R	S
7	52	M	Hispanic	43,873	48	2	1071	45	R	R	R	R
8	50	F	African American	99,051	13	1	403	32	R	S	R	R
9	61	F	African American	33,669	42	5	535	63	R	R	R	S
10	29	M	African American	73,265	16	2	512	64	R	R	R	S
11	52	M	Caucasian	5,053	149	13	655	57	R	R	R	R
Median				**49,585**	**42**	**2**	**593**	**57**				

R, resistant; S, sensitive

Comparison of Immunologic and Virologic Parameters Between the MDR HIV and Control Groups



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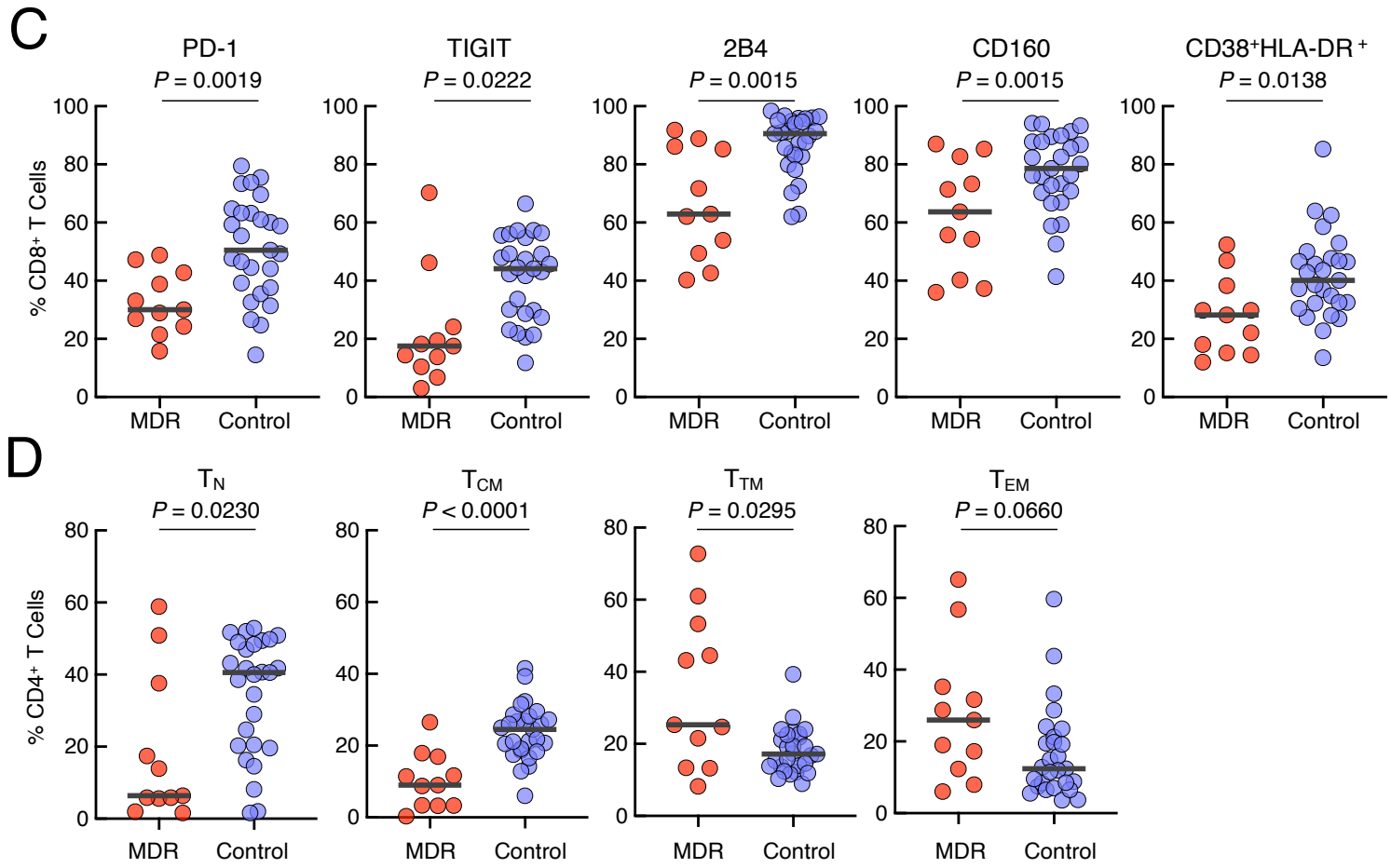
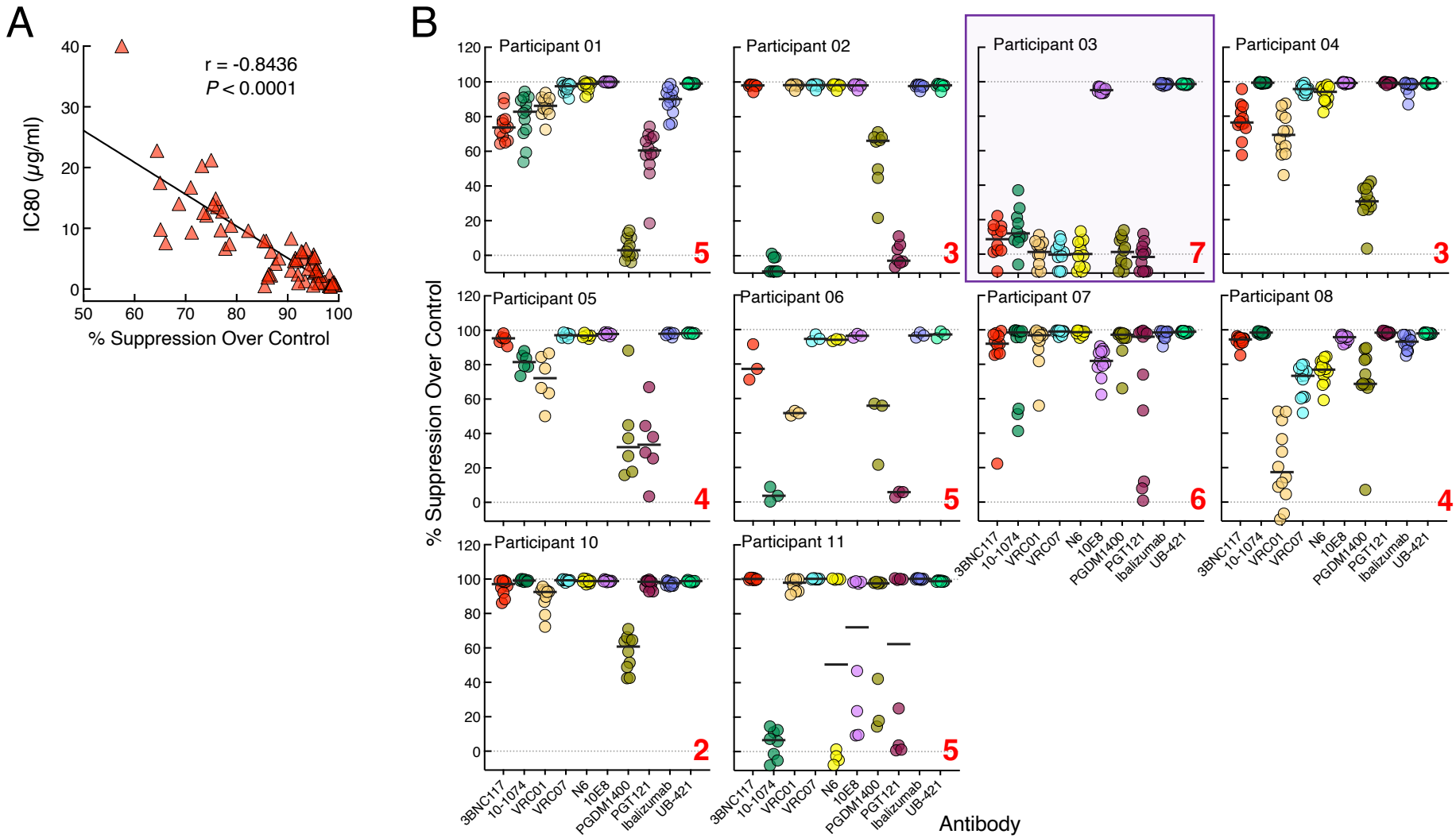


Capacity of bNAbs and Anti-CD4 Antibodies to Suppress Replication-Competent Viral Isolates Derived from Infected Individuals with Multidrug-Resistant HIV



Summary and Conclusions

- Evaluation of the sensitivity of replication-competent HIV to clinically available bNAbs could potentially lead to a new therapeutic avenue for infected individuals with multi-drug resistant (MDR) virus

- Anti-CD4 antibody UB-421 with optimized background therapy may allow sustained suppression of plasma viremia in HIV-infected individuals carrying multi-drug resistant virus

- Drugs in the pipe-line include GSK2838232 (maturation inhibitor) and Albuvirtide (long-acting fusion inhibitor)

Part II
UB-421 Clinical Trial

Study Proposal

- Single arm Open Label Phase 2 trial
- To evaluate the efficacy and safety of UB-421 in conjunction with an existing failing antiretroviral therapy (ART) for 2 weeks followed by optimized background therapy (OBT) in conjunction with UB-421 for 24 weeks
- Study includes infected individuals with Multi-Drug resistant HIV-1 infection

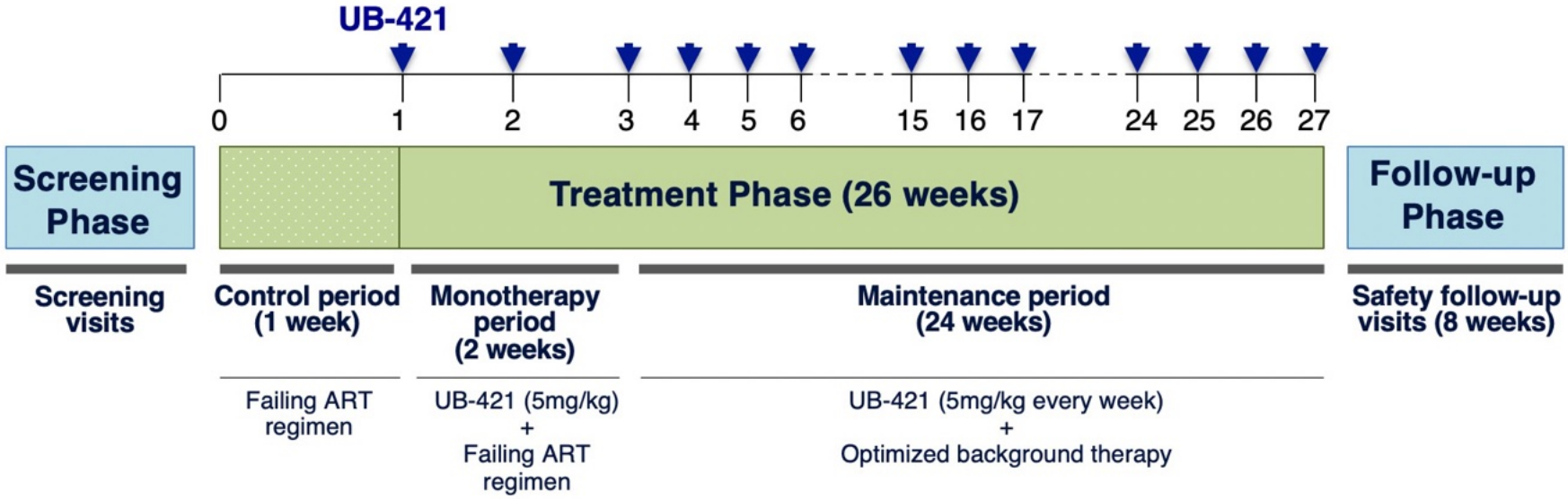
A Single arm Open Label Phase 2 trial of anti-CD4 antibody UB-421 in Patients with Multi-Drug Resistant HIV-1 Infection

Study Population:

- 10 adults with human immunodeficiency virus (HIV) who demonstrate evidence of HIV-1 replication despite ongoing ART with documented genotypic and/or phenotypic resistance to multiple classes of HIV drugs (3 classes or more)

A Single arm Open Label Phase 2 trial of anti-CD4 antibody UB-421 in Patients with Multi-Drug Resistant HIV-1 Infection

Study Design:



A Single arm Open Label Phase 2 trial of anti-CD4 antibody UB-421 in Patients with Multi-Drug Resistant HIV-1 Infection

Primary Objectives:

- To assess the antiviral activity of UB-421 in reducing HIV-1 plasma viremia during the 2-week functional monotherapy treatment period
- To assess the safety of UB-421 during the treatment phase

Secondary Objectives:

- Evaluate the antiviral activity of UB-421 during the 24-week maintenance treatment period
- Evaluate changes from baseline in $CD4^+$ and $CD8^+$ T cell counts during the UB-421 treatment period
- Evaluate Evaluate the pharmacokinetic parameters of UB-421
- Evaluate the immunogenicity of UB-421 by the presence of anti-UB-421 antibodies

A Single arm Open Label Phase 2 trial of anti-CD4 antibody UB-421 in Patients with Multi-Drug Resistant HIV-1 Infection

Primary Efficacy Endpoint:

- Proportion of participants with ≥0.5 $\log_{10}$ reduction in HIV-1 plasma viremia from baseline (Day 7) to Day 21

Primary Safety Endpoint:

- The rate of occurrence of grade 2 or higher adverse events (AEs), including serious adverse events (SAEs), which are probably or definitely related to UB-421

A Single arm Open Label Phase 2 trial of anti-CD4 antibody UB-421 in Patients with Multi-Drug Resistant HIV-1 Infection

Secondary Endpoints:

- Proportion of participants achieving ≥1 $\log_{10}$ reduction in HIV-1 plasma viremia from baseline (Day 7) to Day 21
- Percentage of participants achieving HIV-1 plasma viremia <40 copies/mL at the end of treatment (EOT-Study week 27).
- Percentage of participants achieving HIV-1 RNA <200 copies/mL at the EOT
- Mean change in $CD4^+$ and $CD8^+$ T cell counts from baseline (Day 7) to EOT for all evaluable subjects
- Measured levels of anti-UB-421 antibodies in blood samples
- Measured levels of serum UB-421 concentration (pharmacokinetic parameters) in participant blood samples

Inclusion Criteria

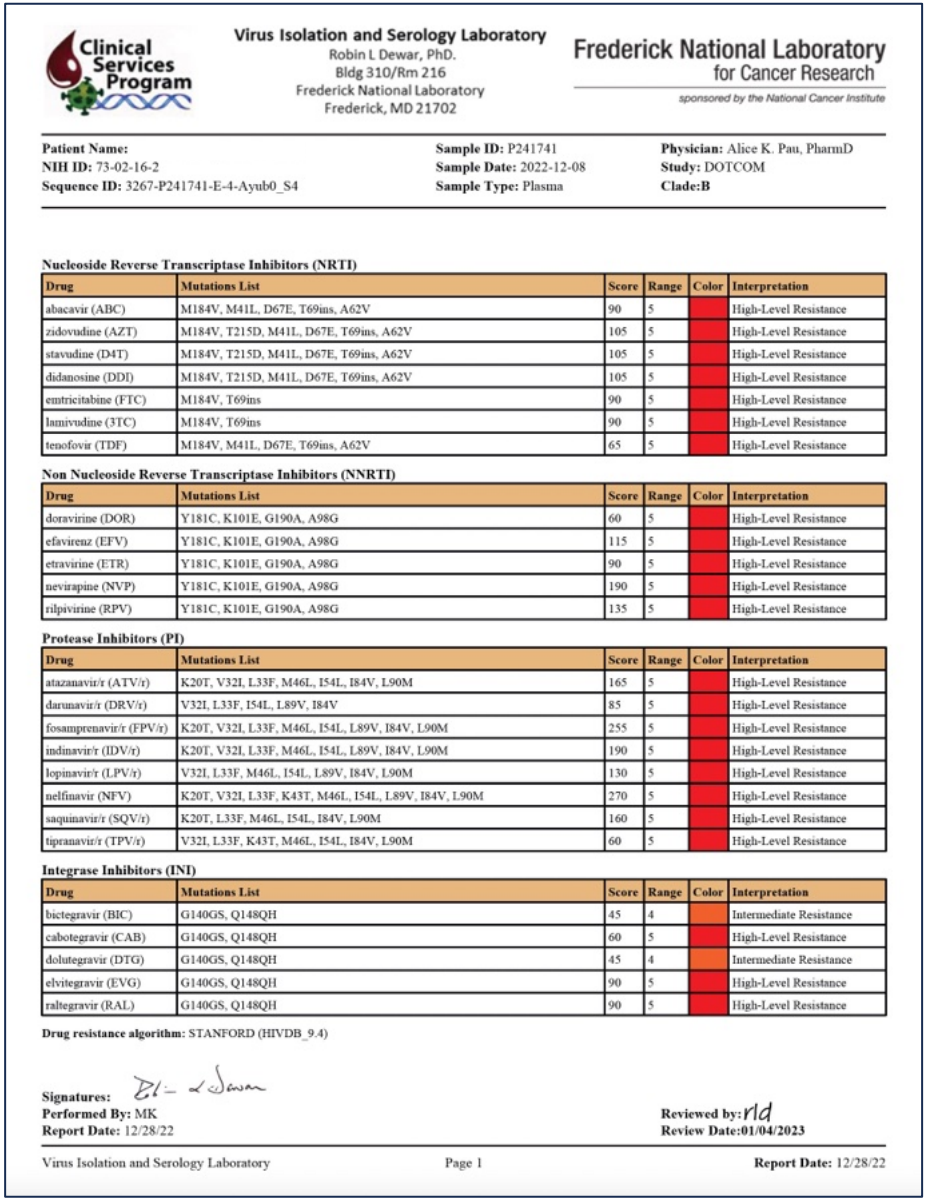
- Ability to provide informed consent
- Age 18 years or older
- Have a life expectancy that is > 6 months
- HIV-1 seropositive
- Have a history of being treated for at least 6 months with ART
- Plasma HIV-1 RNA ≥ 1,000 copies/mL at the Screening visit
- Baseline $CD4^+$ T cell counts of >350 cells/mm^3
- Documented genotypic or phenotypic resistance to at least one antiretroviral drug within three or more drug classes of antiretroviral medications
- Have viral sensitivity to at least one FDA-approved antiretroviral agent, as determined by genotypic or phenotypic ARV drug resistance testing, and such agent can be used as a component of OBT
- Laboratory values within pre-defined limits at screening:
  - Absolute neutrophil count > 750/mm^3
  - Hemoglobin levels >10.5 g/dL for men and >9.5 g/dL for women
  - Platelet count > 50,000/mm^3
  - Estimated or a measured glomerular filtration rate >60 mL/min/1.73m^2 as determined by the National Institutes of Health (NIH) Clinical Center laboratory
  - AST and ALT levels of <2.5 x upper limit of normal (ULN)
  - Total bilirubin <2.5 x ULN (unless subject is taking atazanavir or has Gilbert's Syndrome)

Exclusion Criteria

- Chronic hepatitis B, as evidenced by a positive test for HBsAg, or chronic hepatitis C virus (HCV) infection, as evidenced by a positive test for HCV RNA
- HIV immunotherapy (including broadly neutralizing HIV antibodies) within 12 weeks prior to screening
- Participation in an experimental drug trial(s) within 4 weeks prior to the Screening visit
- AIDS-defining Stage 3 opportunistic illnesses according to the Centers for Disease Control and Prevention (CDC) Classification System for HIV Infection [7] at or within 3 months of screening
- Pregnancy or lactation
- Any licensed or experimental vaccination (e.g., hepatitis B, influenza, pneumococcal polysaccharide) received within 2 weeks prior to study enrollment (day 0)
- Prior use of UB-421
- Any acute febrile illness within 14 days before initial administration of UB-421
- Treatment with another investigational drug or other intervention within 28 days of Screening
- Any active malignancy that may require systemic chemotherapy or radiation therapy
- Active drug or alcohol use or any other pattern of behavior that, in the opinion of the investigator, would interfere with adherence to study requirements
- Systemic immunosuppressive medications received within 3 months prior to enrollment (Exceptions: [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids administered for non-chronic conditions not expected to recur [length of therapy ≤14 days, with completion in ≥30 days prior to enrollment]);
- History or other clinical evidence of significant or unstable cardiac or cerebrovascular disease (e.g., angina, congestive heart failure, recent stroke or myocardial infarction); severe illness, malignancy, immunodeficiency other than HIV, or any other condition that, in the opinion of the investigator, would make the subject unsuitable for the study

Part III
Patient Discussion Case

DOTCOM MDR Participant



Clinical Services Program

Virus Isolation and Serology Laboratory
Robin L Dewar, PhD.
Bldg 310/Rm 216
Frederick National Laboratory
Frederick, MD 21702

Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute

Patient Name:
NIH ID: 73-02-16-2
Sequence ID: 3267-P241741-E-4-Ayub0_S4

Sample ID: P241741
Sample Date: 2022-12-08
Sample Type: Plasma

Physician: Alice K. Pau, PharmD
Study: DOTCOM
Clade:B

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
abacavir (ABC)	M184V, M41L, D67E, T69ins, A62V	90	5		High-Level Resistance
zidovudine (AZT)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
stavudine (D4T)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
didanosine (DDI)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
emtricitabine (FTC)	M184V, T69ins	90	5		High-Level Resistance
lamivudine (3TC)	M184V, T69ins	90	5		High-Level Resistance
tenofovir (TDF)	M184V, M41L, D67E, T69ins, A62V	65	5		High-Level Resistance

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
doravirine (DOR)	Y181C, K101E, G190A, A98G	60	5		High-Level Resistance
efavirenz (EFV)	Y181C, K101E, G190A, A98G	115	5		High-Level Resistance
etravirine (ETR)	Y181C, K101E, G190A, A98G	90	5		High-Level Resistance
nevirapine (NVP)	Y181C, K101E, G190A, A98G	190	5		High-Level Resistance
rilpivirine (RPV)	Y181C, K101E, G190A, A98G	135	5		High-Level Resistance

Protease Inhibitors (PI)

Drug	Mutations List	Score	Range	Color	Interpretation
atazanavir/r (ATV/r)	K20T, V32I, L33F, M46L, I54L, I84V, L90M	165	5		High-Level Resistance
darunavir/r (DRV/r)	V32I, L33F, I54L, L89V, I84V	85	5		High-Level Resistance
fosamprenavir/r (FPV/r)	K20T, V32I, L33F, M46L, I54L, L89V, I84V, L90M	255	5		High-Level Resistance
indinavir/r (IDV/r)	K20T, V32I, L33F, M46L, I54L, L89V, I84V, L90M	190	5		High-Level Resistance
lopinavir/r (LPV/r)	V32I, L33F, M46L, I54L, L89V, I84V, L90M	130	5		High-Level Resistance
nelfinavir (NFV)	K20T, V32I, L33F, K43T, M46L, I54L, L89V, I84V, L90M	270	5		High-Level Resistance
saquinavir/r (SQV/r)	K20T, L33F, M46L, I54L, I84V, L90M	160	5		High-Level Resistance
tipranavir/r (TPV/r)	V32I, L33F, K43T, M46L, I54L, I84V, L90M	60	5		High-Level Resistance

Integrase Inhibitors (INI)

Drug	Mutations List	Score	Range	Color	Interpretation
bictegravir (BIC)	G140GS, Q148QH	45	4		Intermediate Resistance
cabotegravir (CAB)	G140GS, Q148QH	60	5		High-Level Resistance
dolutegravir (DTG)	G140GS, Q148QH	45	4		Intermediate Resistance
elvitegravir (EVG)	G140GS, Q148QH	90	5		High-Level Resistance
raltegravir (RAL)	G140GS, Q148QH	90	5		High-Level Resistance

Drug resistance algorithm: STANFORD (HIVDB_9.4)

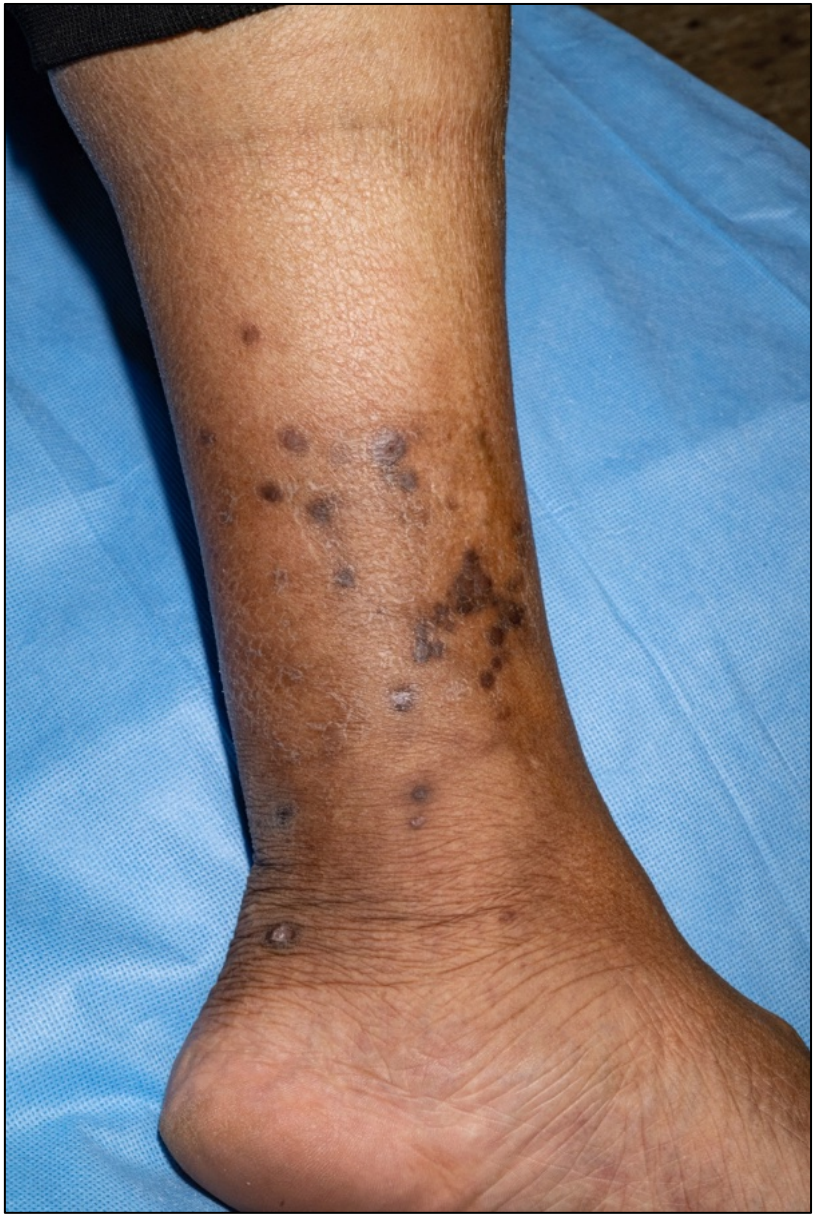
Signatures:
Performed By: MK
Report Date: 12/28/22

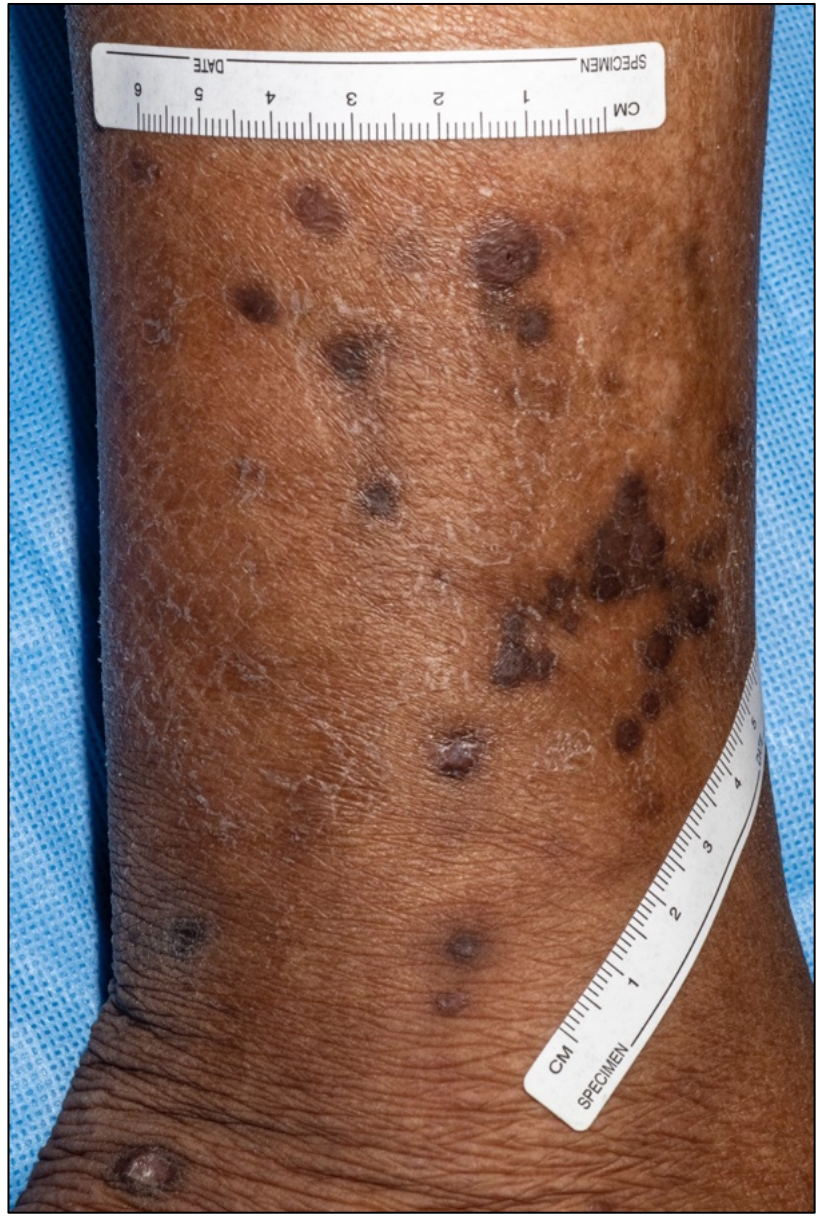
Reviewed by: rld
Review Date: 01/04/2023

Virus Isolation and Serology Laboratory Page 1 **Report Date:** 12/28/22

Timeline (with ART regimen initiation date)	Antiretrovirals
1989-2004*	Zidovudine + Didanosine + Zalcitabine + Stavudine + Indinavir + Saquinavir + Amprenavir + Efavirenz + Nevirapine
06/03/2004**	Abacavir / Azidothymidine / Lamivudine + Tenofovir Disoproxil Fumarate + Lopinavir/Ritonavir
06/22/2004	Abacavir / Azidothymidine/ Lamivudine + Tenofovir Disoproxil Fumarate + Lopinavir/Ritonavir + Atazanavir
09/05/2008	Abacavir + Tenofovir/Emtricitabine + Darunavir/Ritonavir + Raltegravir
Early 2012	Tenofovir/Emtricitabine + Lopinavir/Ritonavir + Atazanavir
10/09/2014***	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Dolutegravir + Maraviroc
10/13/2015	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Maraviroc
08/05/2016	Tenofovir/Emtricitabine + Darunavir/Ritonavir
01/27/2020	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Fostemsavir + Ibalizumab
05/06/2021	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Ibalizumab
06/16/2021	Tenofovir/Emtricitabine + Darunavir/Ritonavir
08/23/2021	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Fostemsavir + Ibalizumab
02/16/2022	Tenofovir/Emtricitabine + Fostemsavir + Ibalizumab
06/23/2022 – 03/2023	Tenofovir/Emtricitabine + Darunavir/Ritonavir + Fostemsavir + Ibalizumab

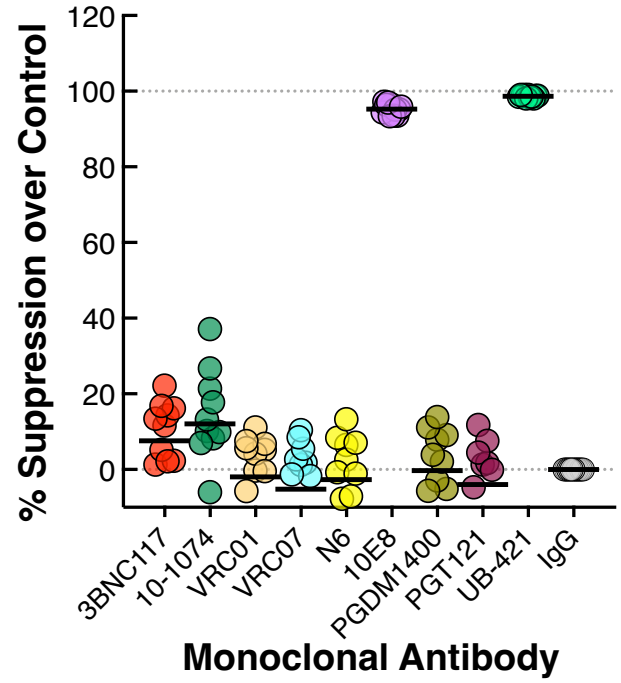
MDR HIV with Kaposi sarcoma: Feb 28, 2023





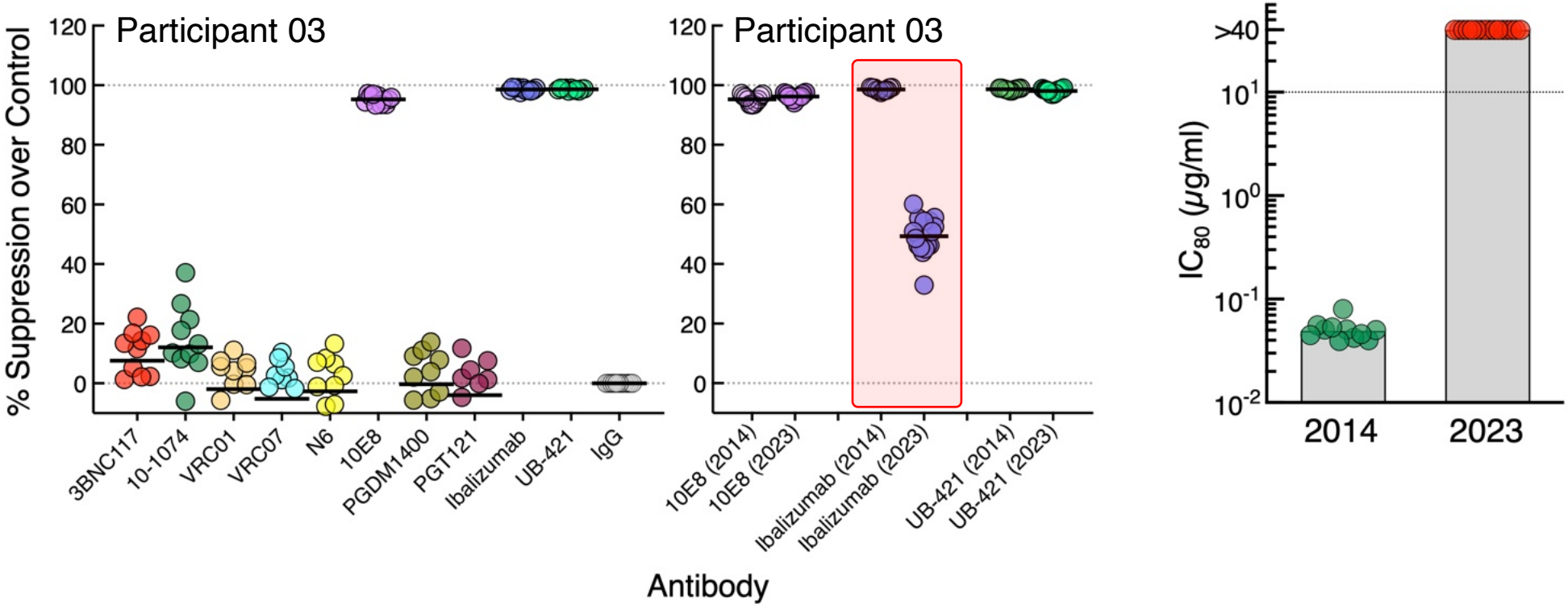
DOTCOM MDR Participant Rx Modalities

The capacity of HIV-specific broadly neutralizing antibody (bNAbs) and UB-421 to suppress infectious HIV isolates derived from the patient

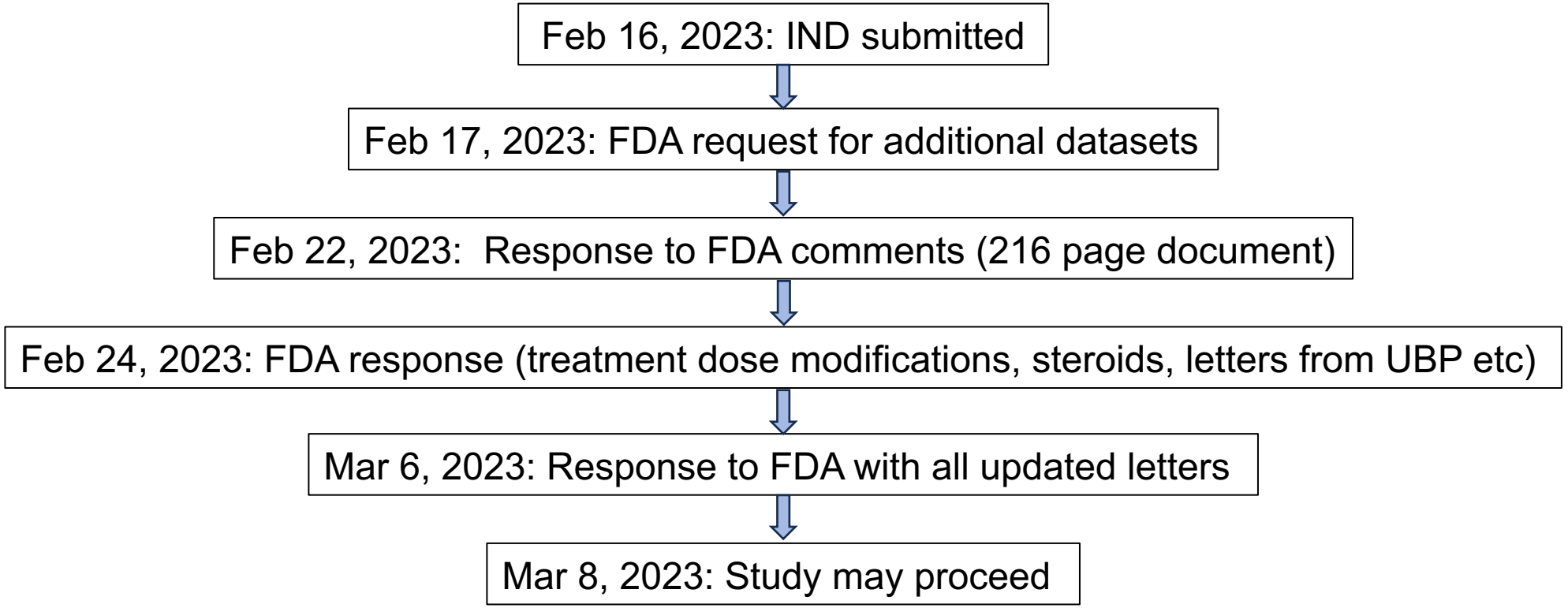


The levels of neutralization of multiple viral isolates isolated from the patient by HIV-specific bNAbs and UB-421 are shown. The y-axis indicates % suppression over control determined by the TZM-bl neutralization assay.

Capacity of bNAbs and Anti-CD4 Antibodies to Suppress Replication-Competent Viral Isolates Derived from an Infected Individual with Multidrug-Resistant HIV



Individual Patient Expanded Access IND

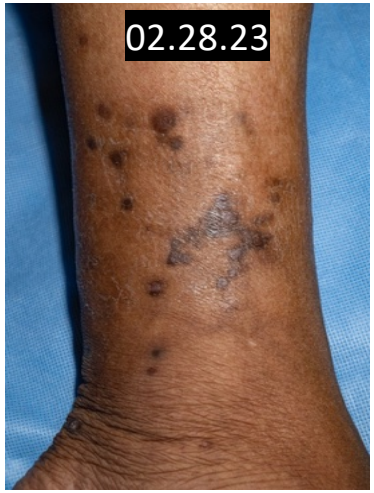


MDR Participant Timeline

- Admitted to the NIH Clinical Center on March 16, 2023
- Received Lenacapavir on March 16 and March 17, 2023
- Received first infusion of UB-421 (5mg/kg) on 3/16

CD4+ T Cell Count and Plasma Viremia of an HIV-Infected Individual with Multidrug-Resistant Virus

Date	UB-421 (5 mg/kg) Infusion date	Plasma Viremia - copies/ml	$CD4^+$ T Cell Count (/µl)	$CD4^+$ T Cell %
03/16/23	Dose 1	186594	26	4
03/22/23	Dose 2	5458	48	4
03/29/23	Dose 3	1488	77	7
04/05/23	Dose 4	477	73	8
04/12/23	Dose 5	380	82	8
04/18/23	Dose 6	275	61	5
04/26/23	Dose 7	477	80	6
05/03/23	Dose 8	342	92	5
05/10/23	Dose 9	265	73	5
05/16/23	Dose 10	267	60	4
05/24/23	Dose 11	250	63	4
05/31/23	Dose 12	252	80	5
06/07/23	Dose 13	67	64	4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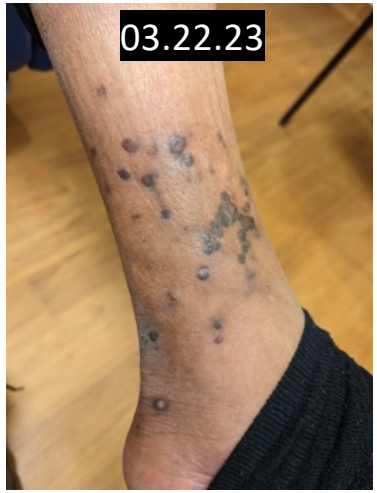
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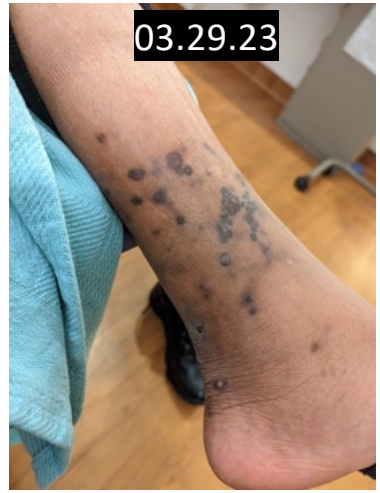
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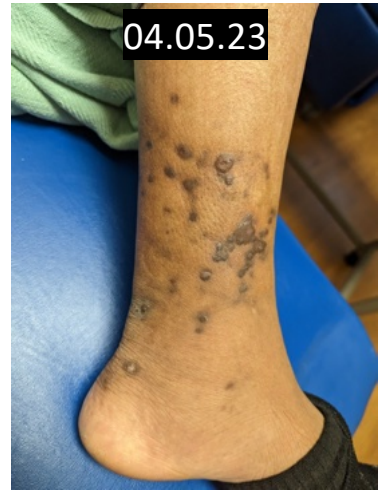
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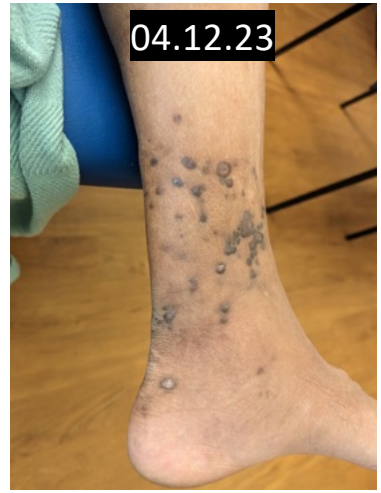
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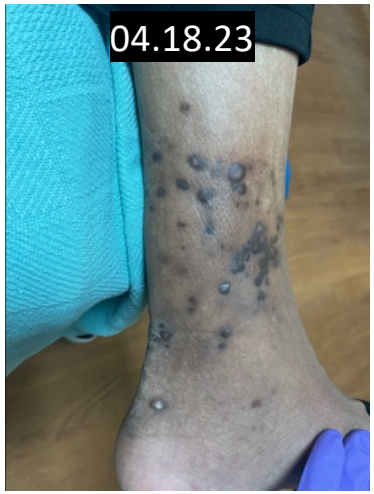
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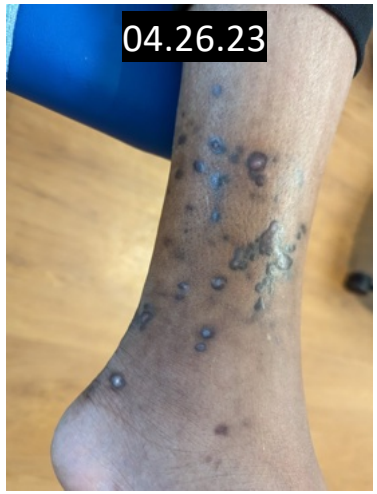
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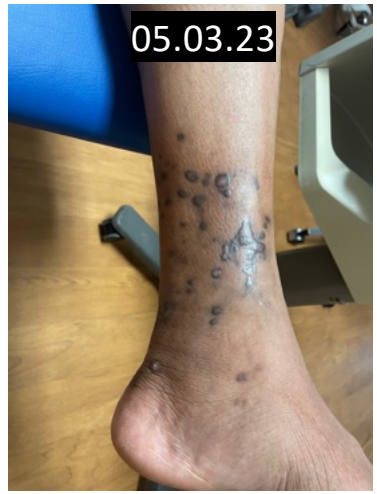
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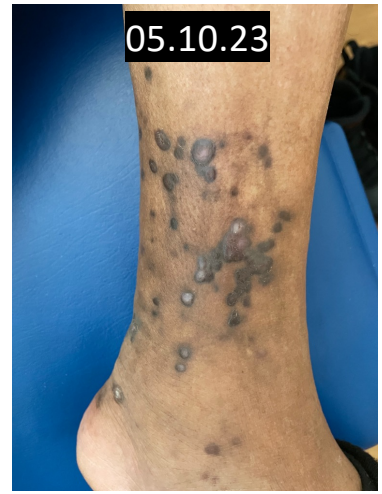
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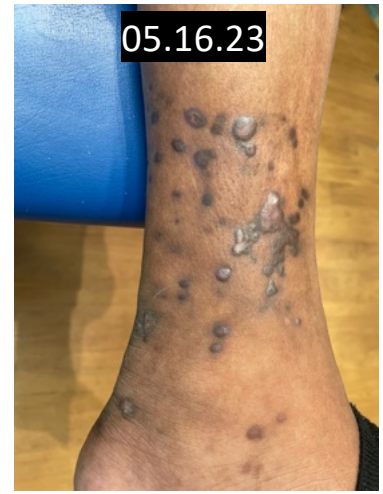
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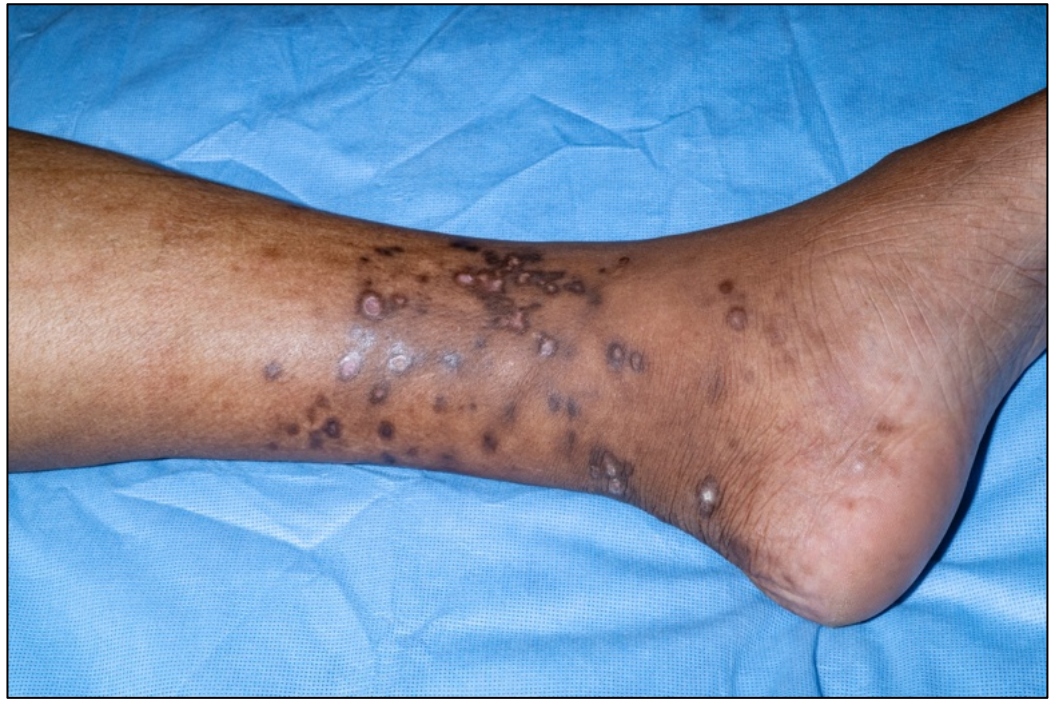
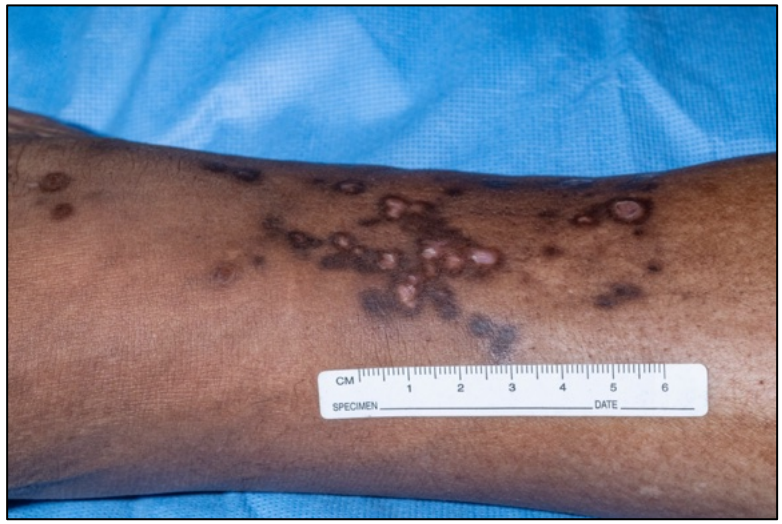
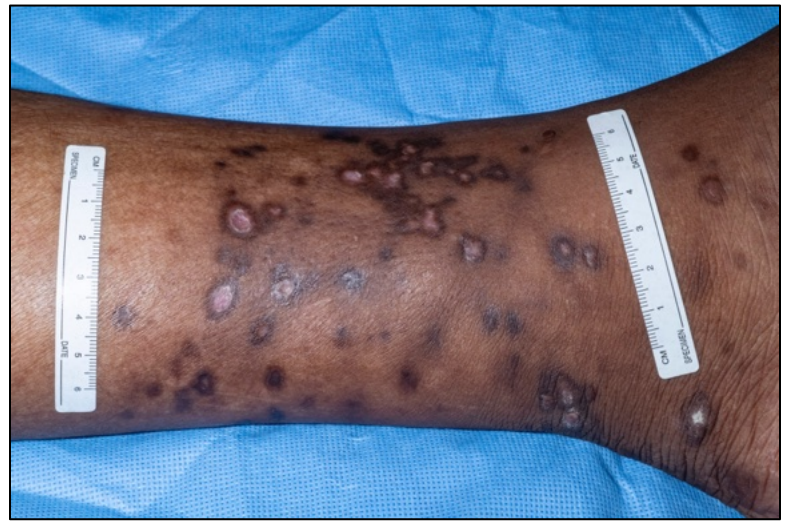
MDR HIV with Kaposi sarcoma

- Re-evaluated by NCI and it was decided to start him on Liposomal Doxorubicin
- Received and tolerated Cycle 1 on June 08, 2023
- Received and tolerated Cycle 2 on June 28, 2023
- Received and tolerated Cycle 3 on July 26, 2023

MDR HIV with Kaposi sarcoma: July 18, 2023







MDR HIV with Kaposi sarcoma AND Norovirus

07/26/2023 13:56 Gastrointestinal Pathogen Panel

Source/Site.
STOOL_

Full Micro Report (with susceptibilities, if applicable)

ORDER#: T5262403 ORDERED BY: RAI, MOHAMMAD
SOURCE: Stool COLLECTED: 07/26/23 13:56
SITE: RECEIVED : 07/26/23 14:09

Microbiology Comment
DETECTED: Norovirus GI/GII
The BioFire Gastrointestinal Pathogen Panel includes
the following targets:
Campylobacter, Clostridium difficile toxin A/B,

Micro Result POSITIVE

07/12/2023 10:22 Gastrointestinal Pathogen Panel

Source/Site.
STOOL_

Full Micro Report (with susceptibilities, if applicable)

ORDER#: T5120287 ORDERED BY: RAI, MOHAMMAD
SOURCE: Stool COLLECTED: 07/12/23 10:22
SITE: RECEIVED : 07/12/23 10:55

Microbiology Comment
DETECTED: Norovirus GI/GII
The BioFire Gastrointestinal Pathogen Panel includes
the following targets:
Campylobacter, Clostridium difficile toxin A/B,

Micro Result POSITIVE

07/03/2023 10:58 Gastrointestinal Pathogen Panel

Source/Site.
STOOL_

Full Micro Report (with susceptibilities, if applicable)

ORDER#: T5030143 ORDERED BY: RAI, MOHAMMAD
SOURCE: Stool COLLECTED: 07/03/23 10:58
SITE: RECEIVED : 07/03/23 11:53

Microbiology Comment
DETECTED: Norovirus GI/GII
The BioFire Gastrointestinal Pathogen Panel includes
the following targets:
Campylobacter, Clostridium difficile toxin A/B,

Micro Result POSITIVE

Journal of Clinical Virology 49 (2010) 219–222

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Chronic norovirus infection in an HIV-positive patient with persistent diarrhoea: A novel cause

Tom Wingfield[a,*], Chris I. Gallimore[b], Jacqueline Xerry[b], Jim J. Gray[b], Paul Klapper[c], Malcolm Guiver[d], Tom J. Blanchard[a]

[a] The Monsall Unit, Infectious Diseases and Tropical Medicine Department, North Manchester General Hospital, Manchester, UK
[b] Enteric Virus Unit, Virus Reference Department, Centre for Infections, Health Protection Agency, Colindale, London, UK
[c] Central Manchester Foundation Trust, Department of Virology, Manchester, UK
[d] Molecular Diagnostics Department, Health Protection Agency North West, Manchester Royal Infirmary, Manchester, UK

Table 1
CD4 count and HIV viral load (VL) of our patient 2008–2010.

Date	Absolute CD4 (cells/μl)	HIV VL (copies/ml)
Oct 08	35	20,033
Dec 08	36	38,362
Mar 09	19	44
May 09	19	44
Jun 09	7	<40
July 09	6	15,202
Oct 09	2	571
Dec 09	16	<40
Jan 10	65	<40
Mar 10	57	223
Jun 10	30	186
July 10	40	57

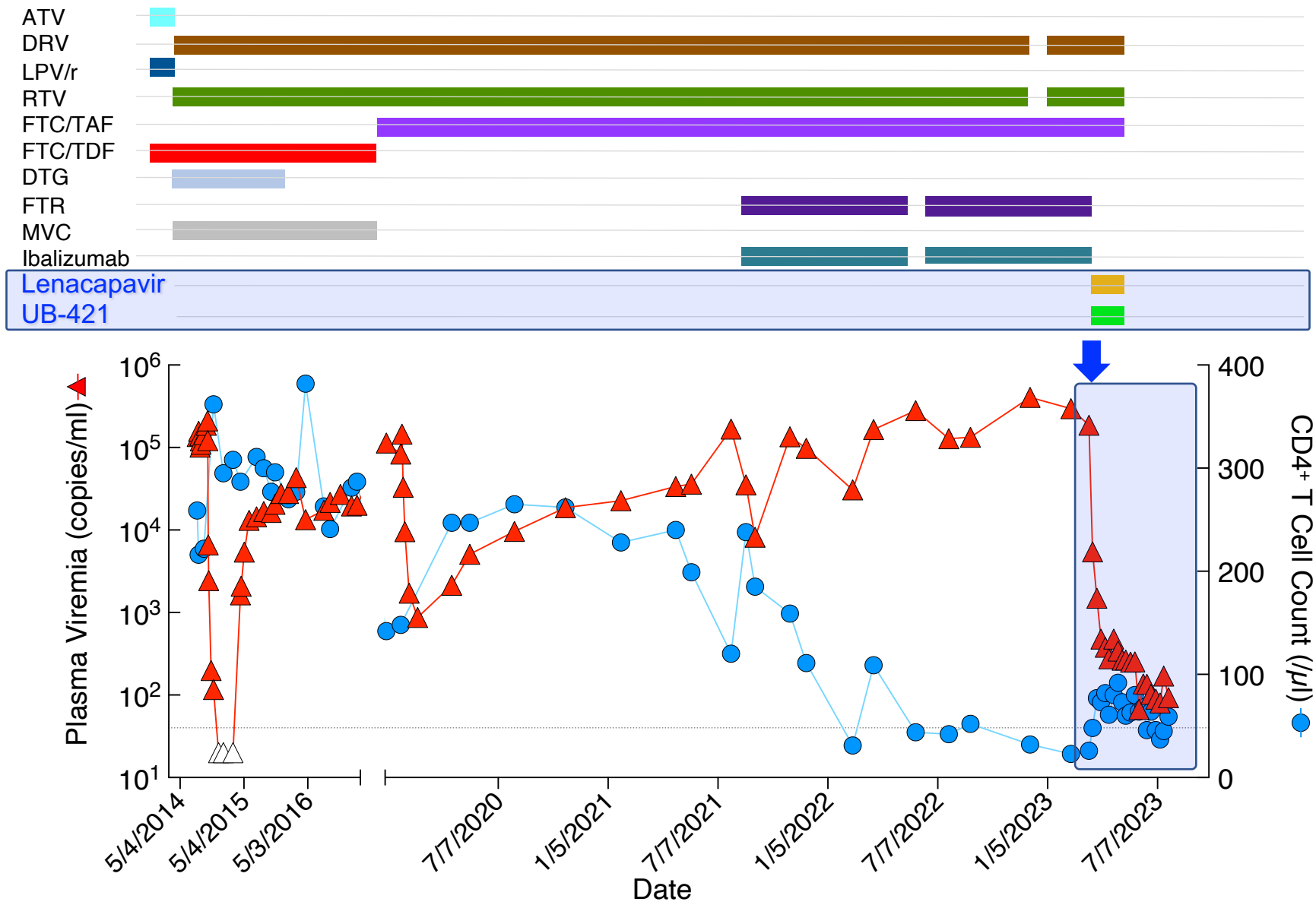
Table 2
Norovirus PCR crossing threshold (CT) and viral burden estimates.

Date	CT	Estimated copies (g)	Log of copies (g)
29/9/5	Negative	0	0
14/11/8	25.4	10,225,000	7.08
15/3/9	25	16,375,000	7.21
6/4/9	24.9	17,605,000	7.25
11/4/9	26	7,934,000	5.89
3/6/9	27	3,843,000	5.58
10/3/10	39.4	50	1.70
12/5/10	Negative	0	0

MDR HIV with Kaposi sarcoma

- Diarrhea continued to worsen
- More frequent usage of Loperamide
- Endorsing increased fatigue, tiredness and lack of appetite
- Re-engaged NCI and re-evaluated on Aug 23, 2023 and plan to hold off additional chemotherapy, with close monitoring

Investigating the Feasibility of Achieving Virologic Suppression by Passive Transfer of Anti-CD4 Antibody



CD4+ T Cell Count and Plasma Viremia of an HIV-Infected Individual with Multidrug-Resistant Virus

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05/16/23	Dose 10	267	60	4
05/24/23	Dose 11	250	63	4
05/31/23	Dose 12	252	80	5
6/7/2023*+1	Dose 13	67	64	4
06/14/23	Dose 14	136	68	6
06/20/23	Dose 15	135	46	4
6/27/2023*+1	Dose 16	102	64	5
07/05/23	Dose 17	89	46	4
07/12/23	Dose 18	80	37	5
07/18/23	Dose 19	170	45	6
7/26/2023*	Dose 20	93	59	6
08/02/23	Dose 21	142	43	5
08/08/23	Dose 22	115	43	5
08/15/23	Dose 23	68	39	7
08/23/23	Dose 24	157	66	8
08/30/23	Dose 25	164	83	7
09/05/23	Dose 26	125	74	8

MDR HIV with Kaposi sarcoma – last Genotype

Clinical Services Program

Virus Isolation and Serology Laboratory
Robin L Dewar, PhD.
Bldg 310/Rm 216
Frederick National Laboratory
Frederick, MD 21702

Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute

Patient Name
NIH ID: 73-02-16-2
Sequence ID: 3267-P241741-E-4-Ayub0_S4

Sample ID: P241741
Sample Date: 2022-12-08
Sample Type: Plasma

Physician: Alice K. Pau, PharmD
Study: DOTCOM
Clade:B

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
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zidovudine (AZT)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
stavudine (D4T)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
didanosine (DDI)	M184V, T215D, M41L, D67E, T69ins, A62V	105	5		High-Level Resistance
emtricitabine (FTC)	M184V, T69ins	90	5		High-Level Resistance
lamivudine (3TC)	M184V, T69ins	90	5		High-Level Resistance
tenofovir (TDF)	M184V, M41L, D67E, T69ins, A62V	65	5		High-Level Resistance

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
doravirine (DOR)	Y181C, K101E, G190A, A98G	60	5		High-Level Resistance
efavirenz (EFV)	Y181C, K101E, G190A, A98G	115	5		High-Level Resistance
etravirine (ETR)	Y181C, K101E, G190A, A98G	90	5		High-Level Resistance
nevirapine (NVP)	Y181C, K101E, G190A, A98G	190	5		High-Level Resistance
rilpivirine (RPV)	Y181C, K101E, G190A, A98G	135	5		High-Level Resistance

Protease Inhibitors (PI)

Drug	Mutations List	Score	Range	Color	Interpretation
atazanavir/r (ATV/r)	K20T, V32I, L33F, M46L, I54L, I84V, L90M	165	5		High-Level Resistance
darunavir/r (DRV/r)	V32I, L33F, I54L, L89V, I84V	85	5		High-Level Resistance
fosamprenavir/r (FPV/r)	K20T, V32I, L33F, M46L, I54L, L89V, I84V, L90M	255	5		High-Level Resistance
indinavir/r (IDV/r)	K20T, V32I, L33F, M46L, I54L, L89V, I84V, L90M	190	5		High-Level Resistance
lopinavir/r (LPV/r)	V32I, L33F, M46L, I54L, L89V, I84V, L90M	130	5		High-Level Resistance
nelfinavir (NFV)	K20T, V32I, L33F, K43T, M46L, I54L, L89V, I84V, L90M	270	5		High-Level Resistance
saquinavir/r (SQV/r)	K20T, L33F, M46L, I54L, I84V, L90M	160	5		High-Level Resistance
tipranavir/r (TPV/r)	V32I, L33F, K43T, M46L, I54L, I84V, L90M	60	5		High-Level Resistance

Integrase Inhibitors (INI)

Drug	Mutations List	Score	Range	Color	Interpretation
bictegravir (BIC)	G140GS, Q148QH	45	4		Intermediate Resistance
cabotegravir (CAB)	G140GS, Q148QH	60	5		High-Level Resistance
dolutegravir (DTG)	G140GS, Q148QH	45	4		Intermediate Resistance
elvitegravir (EVG)	G140GS, Q148QH	90	5		High-Level Resistance
raltegravir (RAL)	G140GS, Q148QH	90	5		High-Level Resistance

Drug resistance algorithm: STANFORD (HIVDB_9.4)

Signatures: Bl – d Dewar
Performed By: MK
Report Date: 12/28/22

Reviewed by: rld
Review Date:01/04/2023

Clinical Services Program

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Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute

Patient Name
NIH ID: 73-02-16-2
Sequence ID: 3505-P242848-E-E5-Lisheng0_S5

Sample ID: P242848
Sample Date: 2023-03-16
Sample Type: Plasma

Physician: Dr. Lane
Study: UB-421 EUA
Clade:B

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
abacavir (ABC)	M184V, M41L, D67E, A62V, T69ins	90	5		High-Level Resistance
zidovudine (AZT)	M184V, T215D, M41L, D67E, A62V, T69ins	105	5		High-Level Resistance
stavudine (D4T)	M184V, T215D, M41L, D67E, A62V, T69ins	105	5		High-Level Resistance
didanosine (DDI)	M184V, T215D, M41L, D67E, A62V, T69ins	105	5		High-Level Resistance
emtricitabine (FTC)	M184V, T69ins	90	5		High-Level Resistance
lamivudine (3TC)	M184V, T69ins	90	5		High-Level Resistance
tenofovir (TDF)	M184V, M41L, D67E, A62V, T69ins	65	5		High-Level Resistance

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Drug	Mutations List	Score	Range	Color	Interpretation
doravirine (DOR)	K101E, G190A, Y181C, A98G	60	5		High-Level Resistance
efavirenz (EFV)	K101E, G190A, Y181C, A98G	115	5		High-Level Resistance
etravirine (ETR)	K101E, G190A, Y181C, A98G	90	5		High-Level Resistance
nevirapine (NVP)	K101E, G190A, Y181C, A98G	190	5		High-Level Resistance
rilpivirine (RPV)	K101E, G190A, Y181C, A98G	135	5		High-Level Resistance

Protease Inhibitors (PI)

Drug	Mutations List	Score	Range	Color	Interpretation
atazanavir/r (ATV/r)	K20T, L33F, V32I, M46L, I54L, I84V, L90M	165	5		High-Level Resistance
darunavir/r (DRV/r)	L33F, V32I, I54L, L89V, I84V	85	5		High-Level Resistance
fosamprenavir/r (FPV/r)	K20T, L33F, V32I, M46L, I54L, L89V, I84V, L90M	255	5		High-Level Resistance
indinavir/r (IDV/r)	K20T, L33F, V32I, M46L, I54L, L89V, I84V, L90M	190	5		High-Level Resistance
lopinavir/r (LPV/r)	L33F, V32I, M46L, I54L, L89V, I84V, L90M	130	5		High-Level Resistance
nelfinavir (NFV)	K20T, L33F, V32I, M46L, K43T, I54L, L89V, I84V, L90M	270	5		High-Level Resistance
saquinavir/r (SQV/r)	K20T, L33F, M46L, I54L, I84V, L90M	160	5		High-Level Resistance
tipranavir/r (TPV/r)	L33F, V32I, M46L, K43T, I54L, I84V, L90M	60	5		High-Level Resistance

Integrase Inhibitors (INI)

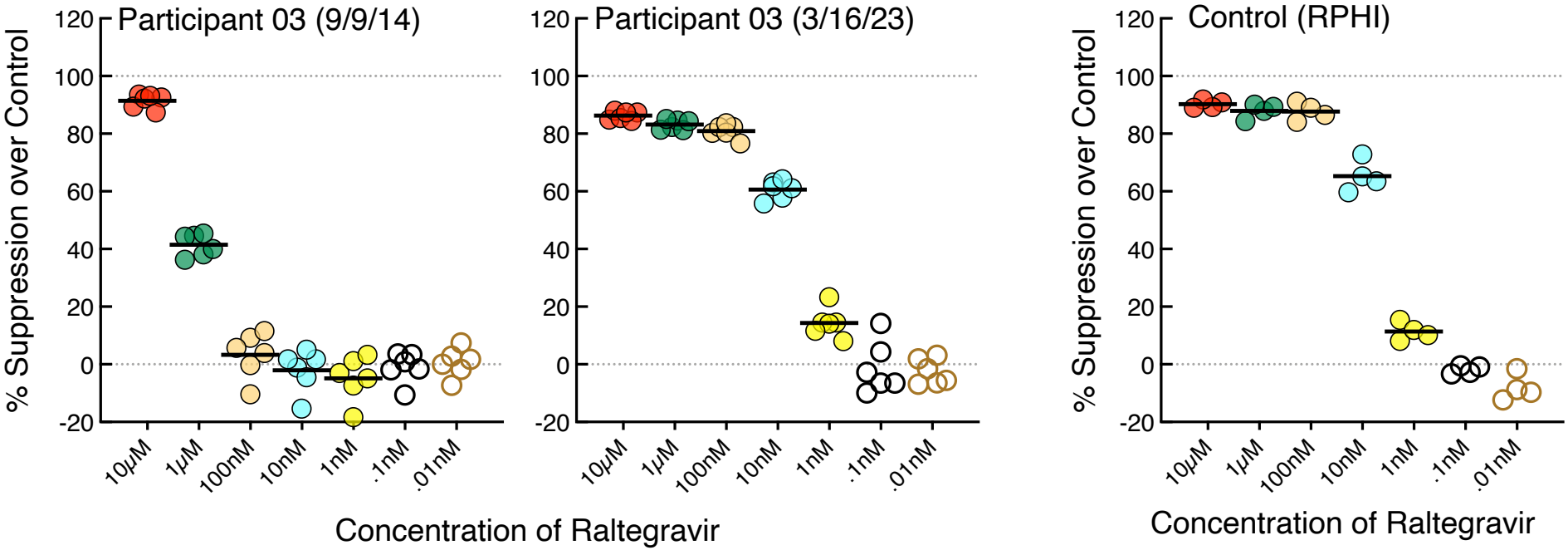
Drug	Mutations List	Score	Range	Color	Interpretation
bictegravir (BIC)		0	1		Susceptible
cabotegravir (CAB)		0	1		Susceptible
dolutegravir (DTG)		0	1		Susceptible
elvitegravir (EVG)		0	1		Susceptible
raltegravir (RAL)		0	1		Susceptible

Drug resistance algorithm: STANFORD (HIVDB_9.4)

Signatures: Bl – d Dewar
Performed By: LD
Report Date: 03/29/23

Reviewed by: rld
Review Date:3/30/23

Sensitivity of Replication-Competent Viral Isolates Derived from an Infected Individual with Multidrug-Resistant HIV to Raltegravir and Lenacapavir



Future Directions and Clinical Concerns

- Why is the patient still viremic?
- Optimization of ART?
- Plan to go to FDA for increasing UB-421 dose and increasing to biweekly frequency

Acknowledgements

TW Research Group

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OP-8 Clinic Staff

Participants

TW Chun

Thank you for your attention and this opportunity


Thank You for Your Attendance!
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