The Contributions of Clinical Pharmacology to HIV Cure Research

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Lines of Evidence for a Cure or Remission

- Myeloablative allogeneic hematopoietic stem cell transplantation (HSCT)
  - HSCT using cells from a donor homozygous for the delta 32 mutation in gene encoding CCR5; the “Berlin Patient”.
    Hutter G, et al. NEJM 2009;360:692-98.
    Yukl S, et al. PLOS Pathogens May 2013
- Elite Controllers
  - HIV infected persons who can maintain high CD4 cell counts and undetectable HIV RNA in the absence of ART.
    Mendoza D, et al. Blood 2012;119:4645-55.
- Post Treatment Controllers
  - ART initiated in acute/early infection and control of infection sustained after discontinuation of ART (VISCONTI), or sustained for a period of time (27 months, Mississippi Baby).
    Saez-Cirion A, et al. PLOS Pathogens March 2013
    Persaud D, et al. NEJM 2013;369:1828-35.

Viral Reservoirs in HIV Infection

- Evidence supports two distinct, and not mutually exclusive, viral reservoirs and sanctuaries that persist during effective, prolonged suppression of HIV.

- Latent Reservoir
  - Comprised of infected lymphocytes in a quiescent state
  - Perpetuated through cellular expansion and/or cellular longevity; estimated to decay with a half-life of > 44 months
  - A major obstacle to complete clearance of HIV infection

- Sanctuary or Active Reservoir (of Low-Level Replication)
  - A tissue or cell shielded from the effects of ART which permits some low-level of ongoing and complete virus replication cycle.
  - The secondary LN and GALT continue to produce low levels of HIV, and have an HIV burden > PBMCs, despite plasma HIV-RNA < 50cpm.

Rose R, Nolan D, Maidji E, Stoddart C, Singer E, Lamers S, McGrath MS. AIDS Res Hum Retro 2018; 34:3-8. Chun TW and Fauci AS. AIDS 2012;1261-68.

Cure – Remission Strategies and Progress

Strategy	Progress
Hematopoietic stem cell transplantation	N=1 cure (Berlin patient).
Early treatment	Early ART can reduce reservoir size, but has not clinically significantly delayed time to rebound after ART is stopped.
Therapeutic vaccines	Have failed to durably control HIV rebound following analytical treatment interruption (ATI).
Shock and kill (ART, LRAs, immune system)	Has not demonstrated a reduction in the size of latent reservoir and a delay in rebound after ATI.
Anti-α4β7 monoclonal antibody + ART	Sustained virologic control in 1 NHP study (Science 2016); No sustained control seen in a repeat NHP study; No effect on viral rebound in humans after ATI using vedolizumab.
Passive Ab transfer: bNAb + TLR7 (innate immune stimulant) + ART	5/11 (45%) of NHPs showed no rebound for > 6 months after ATI.

Pino M et al. Curr Opin HIV/AIDS 2018;13:435-45. Douek D. Topics in Antiviral Med 2018;25:121-25. NIH Strategies for Cure Meeting, Dec 2018.

HIV Cure - Remission

- Goal: to find and diminish the size and achieve long-term control of a replication-competent HIV reservoir.
- Three preeminent challenges:
  - Identify the location of the anatomical reservoir/sanctuary from which the virus repopulates blood after ART discontinuation;
  - Define the mechanism(s) by which virus is maintained at low or undetectable levels in such locations;
  - Develop treatment(s) that will eradicate or silence virus without damaging nearby sensitive or irreplaceable tissues (eg, CNS).

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Mechanisms and Determinants of ARV Penetration into Lymphatic Tissues

- Portal vein vs. lymph blood flow is 500:1.
  - Most absorbed drugs are preferentially diverted to portal blood.
- Physicochemical characteristics associated with greater lymphatic system penetration: hi molecular weight, larger particle size, log P value > 5, hi long chain TG solubility.
  - All ARVs are low MW compounds and few have log P values > 5.
- Pharmacologic characteristics: distribution and expression of membrane transporters and CYPs in lymphatic endothelial cells and along the GI tract, and ARV substrate specificity.
  - P-gp increases from duodenum to ileum; CYP3A4 decreases from duodenum to colon.
- HIV-associated pathology: lymph node fibrosis.
  - Collagen deposition and resulting fibrosis are correlated with progression to AIDS and less immune reconstitution.

In Vitro Model of LT Bioavailability Using Human Lymphatic Endothelial Cells (hLEC)[1]

Hi (> 67th %ile)	Medium (67->33rd %ile)	Low (<33rd %ile)
RPV	RTV	ATV
EFV	TDF	DRV
EVG	DTG	RAL
Cobi	MVC	FTC
		ABC

Abbreviations

NRTIs: ABC, abacavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate

NNRTIs: EFV, efavirenz; RPV, rilpivirine

PIs: ATV, atazanavir; DRV, darunavir; RTV, ritonavir

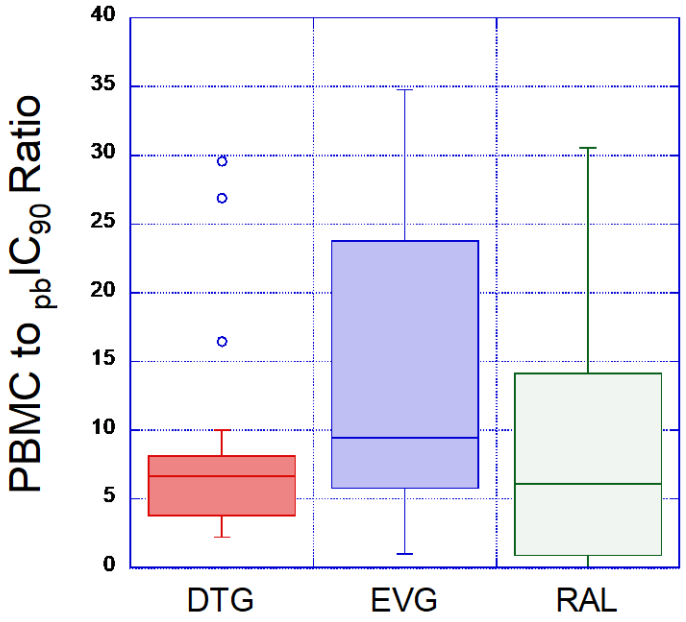
INSTIs: DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir

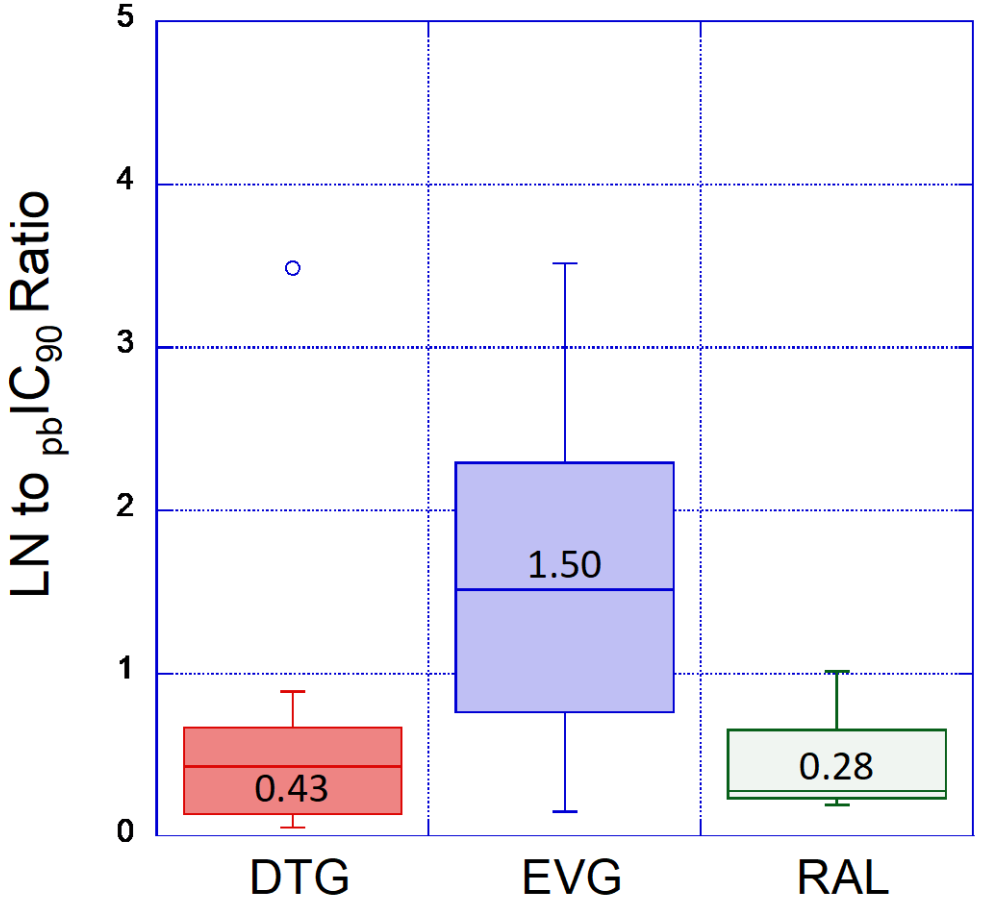
Other: MVC, maraviroc; Cobi, cobicistat

1. Dyavar SR, Podany AT, Gautam N, Winchester L, Mykris T, Weinhold J, Campbell K, Alnouti Y and Fletcher CV. HIV Persistence During Therapy, Miami, FL. December 2017.

Comparative Lymphoid Tissue Pharmacokinetics of Integrase Inhibitors

	IC & IQ Values in Plasma		
	DTG	EVG	RAL
$IC_{90,}$ ng/mL	64	NA	NA
IC_{95}, ng/mL	NA	44.9	14.7
C_{trough}, ng/mL	1100	450	124
IQ	17	10	8





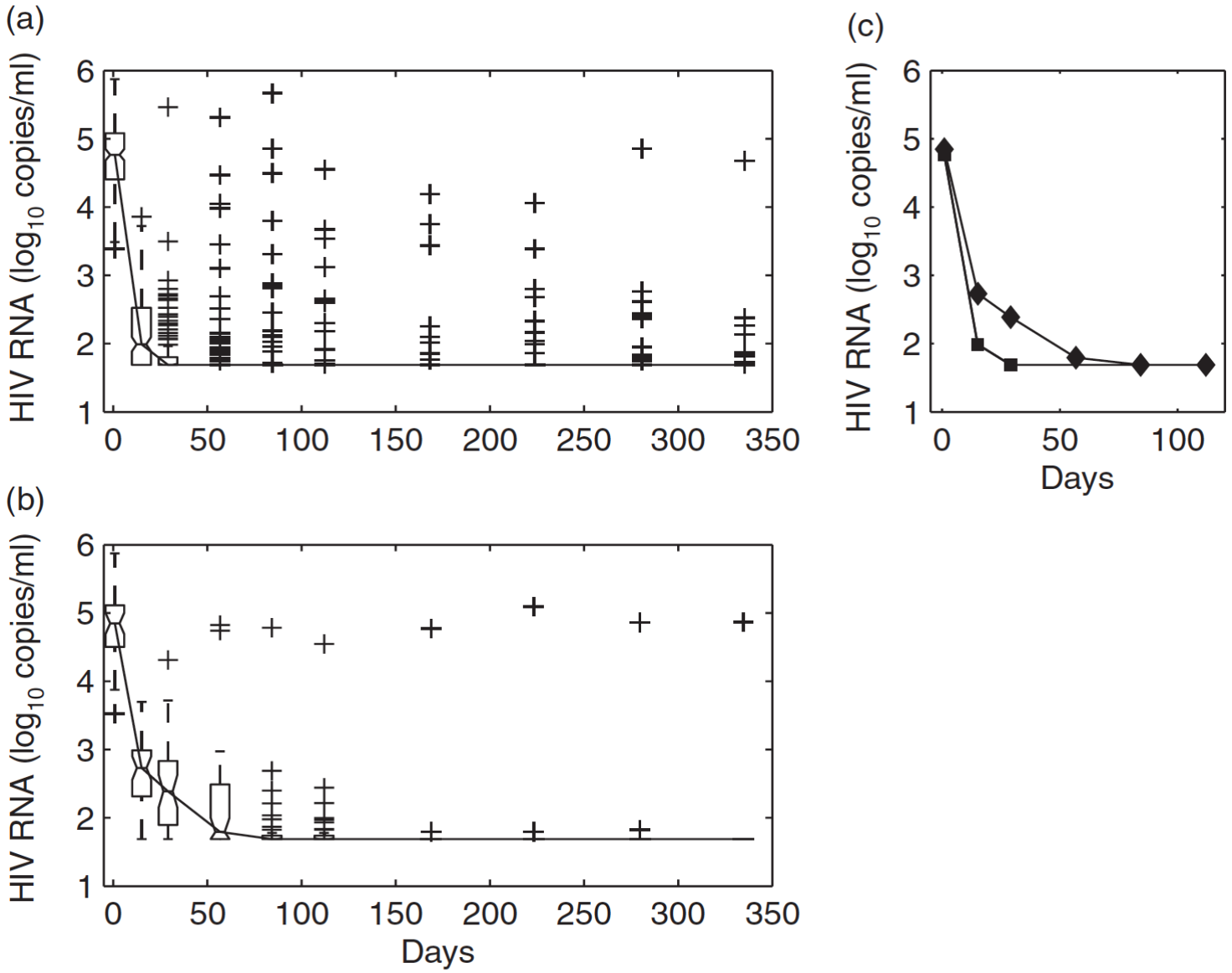
❖ hLEC model: EVG > DTG > RAL

Fletcher CV, Thorkelson A, Winchester L, ... Schacker TW. Abstract, CROI 2018, March 4-7, 2018.

Observations

- Physicochemical properties of ARVs influence lymphoid tissue (LT) penetration. Modification of these characteristics (e.g., prodrugs and nanoformulations) can enhance LT penetration.
- ARV affinity for membrane transporters and CYPs influences tissue distribution. The optimal analytical technique and species differences pose challenge for predictions in humans. (see Thompson CC, et al. AIDS 2017;31:1669-78).
- An in vitro hLEC model predicted LN penetration of EVG > DTG > RAL, which was seen in humans.
- In lymph nodes, TFV-DP concentrations were higher with TAF vs. TDF (104 vs. 22 fmol/10^6 cells).
  - This confirms animal studies showing TFV-DP conc. were 5.7 to 15-fold higher with TAF, depending on the anatomical location of the LN.
  - The TFV-DP concentrations in the LN achieved with TAF are consistent with average PBMC conc. In humans seen with TDF.

Raltegravir Alters Second Phase HIV Decay



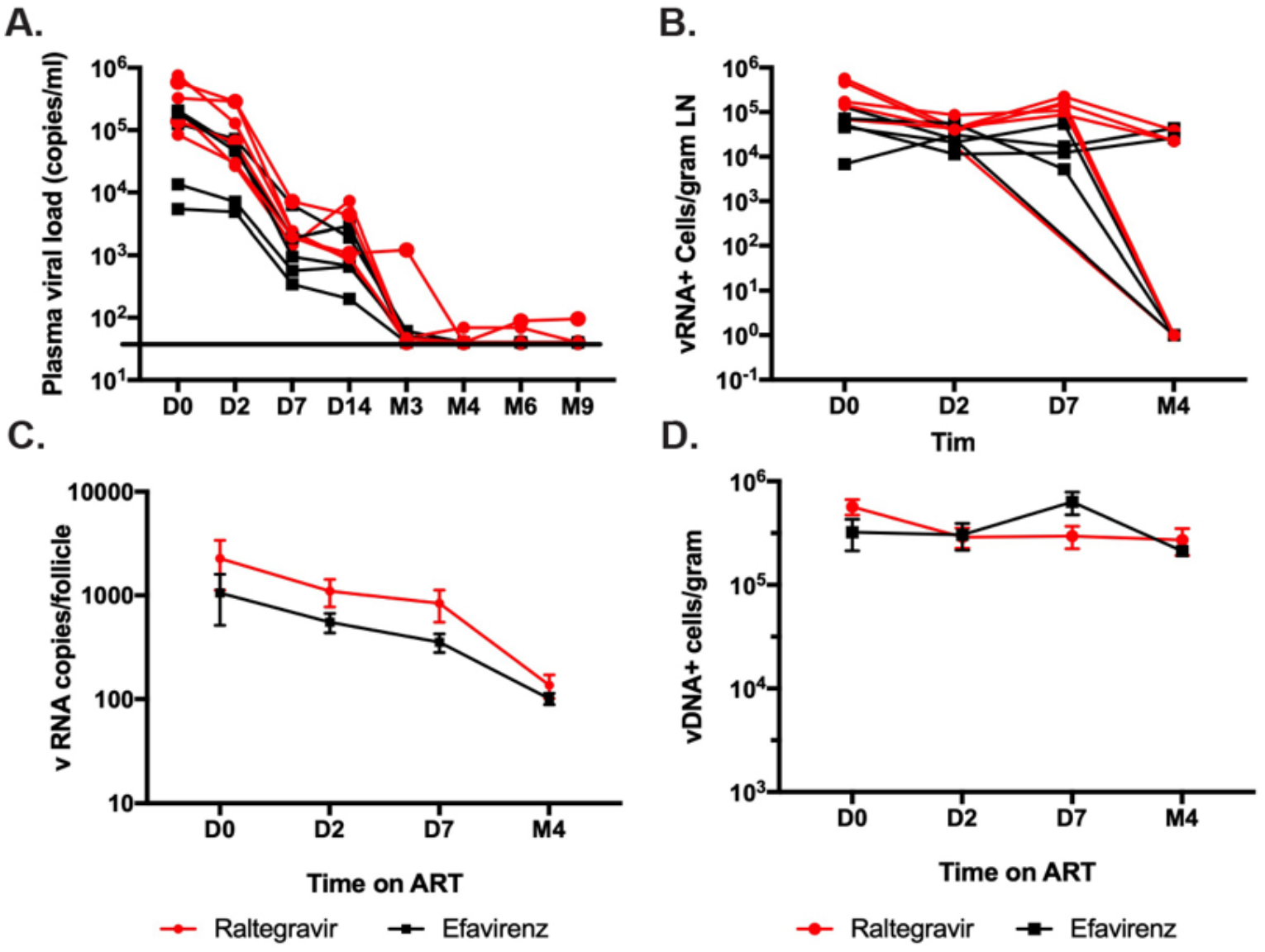
Murry JM et al. AIDS 2007;21:2315-21.

Impact of Raltegravir vs. Efavirenz on Lymphoid Tissue (LT) Reservoirs

- Objective: to compare the kinetics of virus decay in LT and to measure cell-associated ARV concentrations in HIV-infected persons initiating RAL or EFV-based ART in Kampala, Uganda.
- 11 persons randomized to RAL- (n=6) or EFV-based (n=5) ART x 3 months; participants were changed to national standard (EFV+TDF + 3TC or FTC) and followed for another 3 months.
- Peripheral blood was obtained at days 2, 7, 14 and months 3, 4, and 6 on ART. LN biopsies were collected at baseline and days 2 and 7 and month 4. Rectal biopsy was done at mo. 4.
- Plasma VL and CD4 cells were measured in PB; vRNA and vDNA were measured in LT by in situ hybridization and quantitative image analysis; ARV concentrations were measured in PB and tissue MNCs by MS/MS.

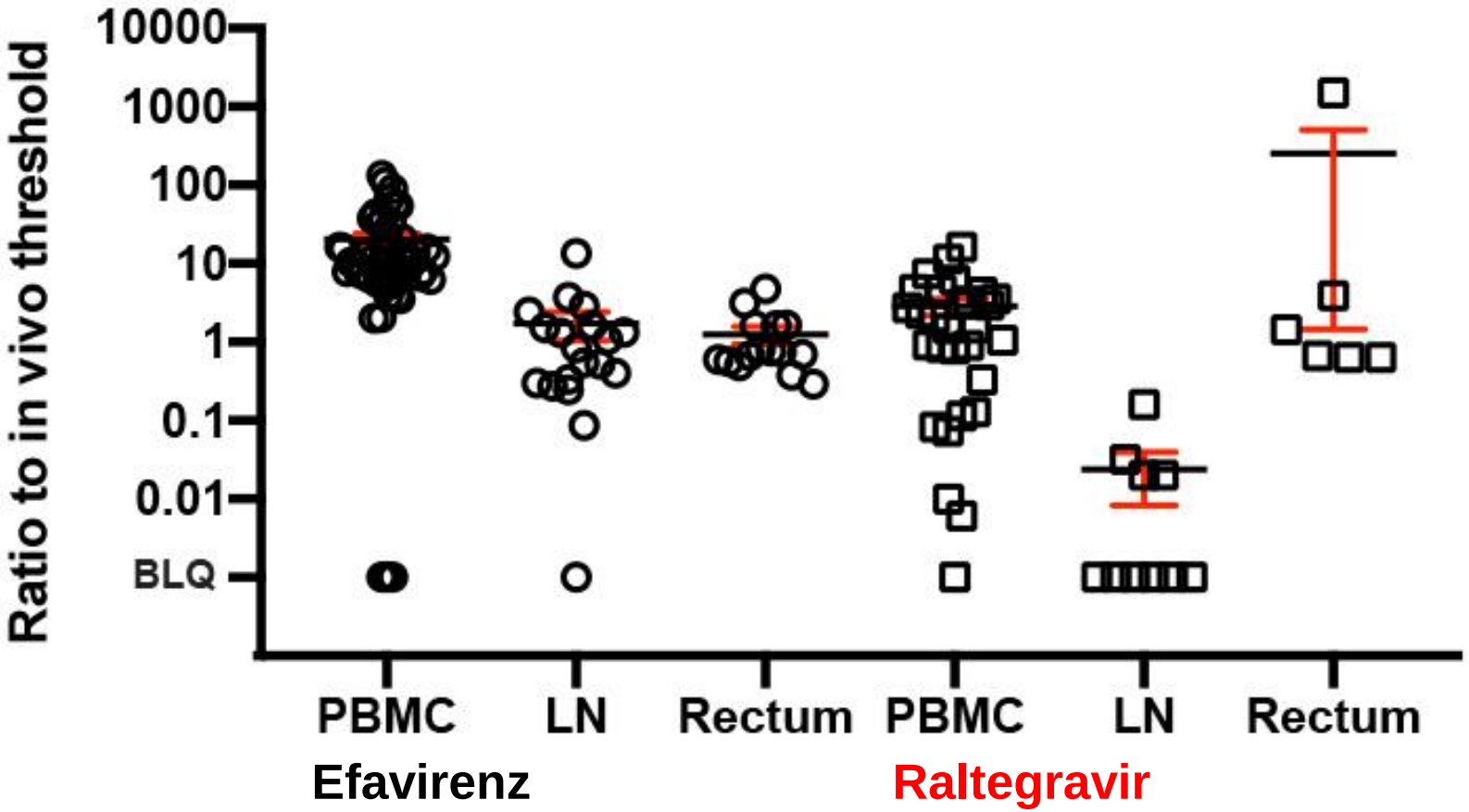
Rothenberger M, … Fletcher CV and Schacker TW. JAIDS 2019; in press.

RAL vs. EFV: Virus Decay in Plasma and LT



Rothenberger M, … Fletcher CV and Schacker TW. JAIDS 2019; in press.

RAL vs. EFV: PBMC and LT IQs (IQ = cell assoc. conc / clinical threshold)



Rothenberger M, … Fletcher CV and Schacker TW. JAIDS 2019; in press.

Impact of Raltegravir vs. Efavirenz on Lymphoid Tissue (LT) Reservoirs

- We found no difference in the rate of virus decay in plasma or in LT in persons randomized to RAL- or EFV-based ART.
- RAL and EFV concentrations in plasma were consistent with expected concentrations. In PBMCs, cell-associated concentrations of RAL and EFV were both greater (1.4x and 10x, respectively) than putative clinical efficacy thresholds (60ng/mL and 700ng/mL, respectively).
- In the LN and rectum, the cell-associated concentrations of RAL and EFV did not exceed these clinical thresholds. The relative, equivalent subtherapeutic LT concentrations of RAL and EFV may explain the lack of difference in LT virus decay.

Rothenberger M, … Fletcher CV and Schacker TW. JAIDS 2019; in press.

Effect of a Switch from PI/r to DTG on Peripheral Blood and Ileal Biopsies

- 42 HIV-infected persons on PI-based ART (median 4yrs) with plasma VL < 50 cpm
- 22 remained on PI-ART and 20 were switched to DTG-ART.
- Residual plasma viremia decreased in the switch group, but after adjustment for multiple comparisons, was NS.
- HIV reservoir was larger in the ileum than peripheral blood; there was no change in reservoir size in the switch group.
- Similarly, there were more activated cells in tissues and the switch did not reduce this activation.

Moron-Lopez S et al. Clinical Infectious Diseases 2019; in press;
https://www.ncbi.nlm.nih.gov/pubmed/30590412

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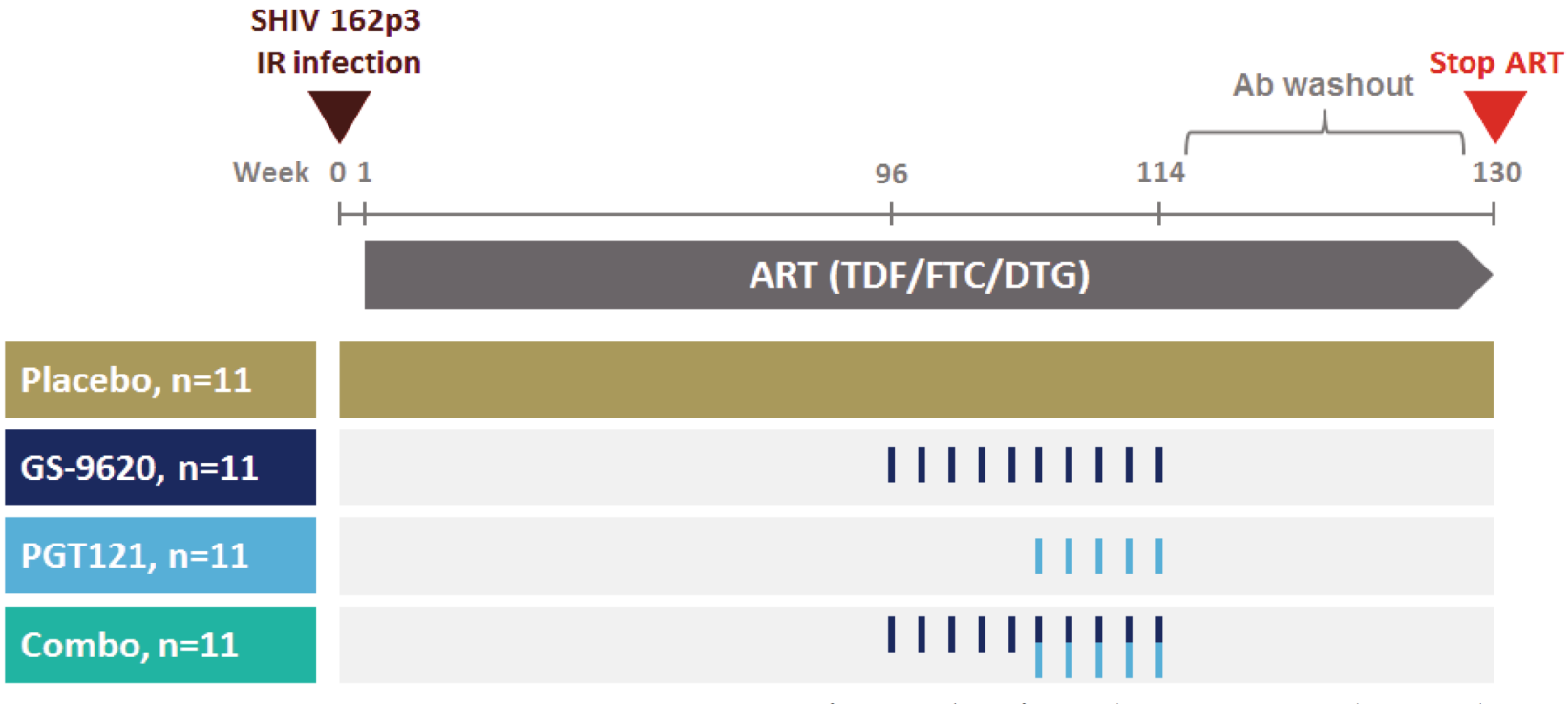
Rose R, Nolan D, Maidji E, Stoddart C, Singer E, Lamers S, McGrath MS. AIDS Res Hum Retro 2018; 34:3-8.

PGT121 + vesatolimod (GS-9620) in SHIV-Infected Monkeys

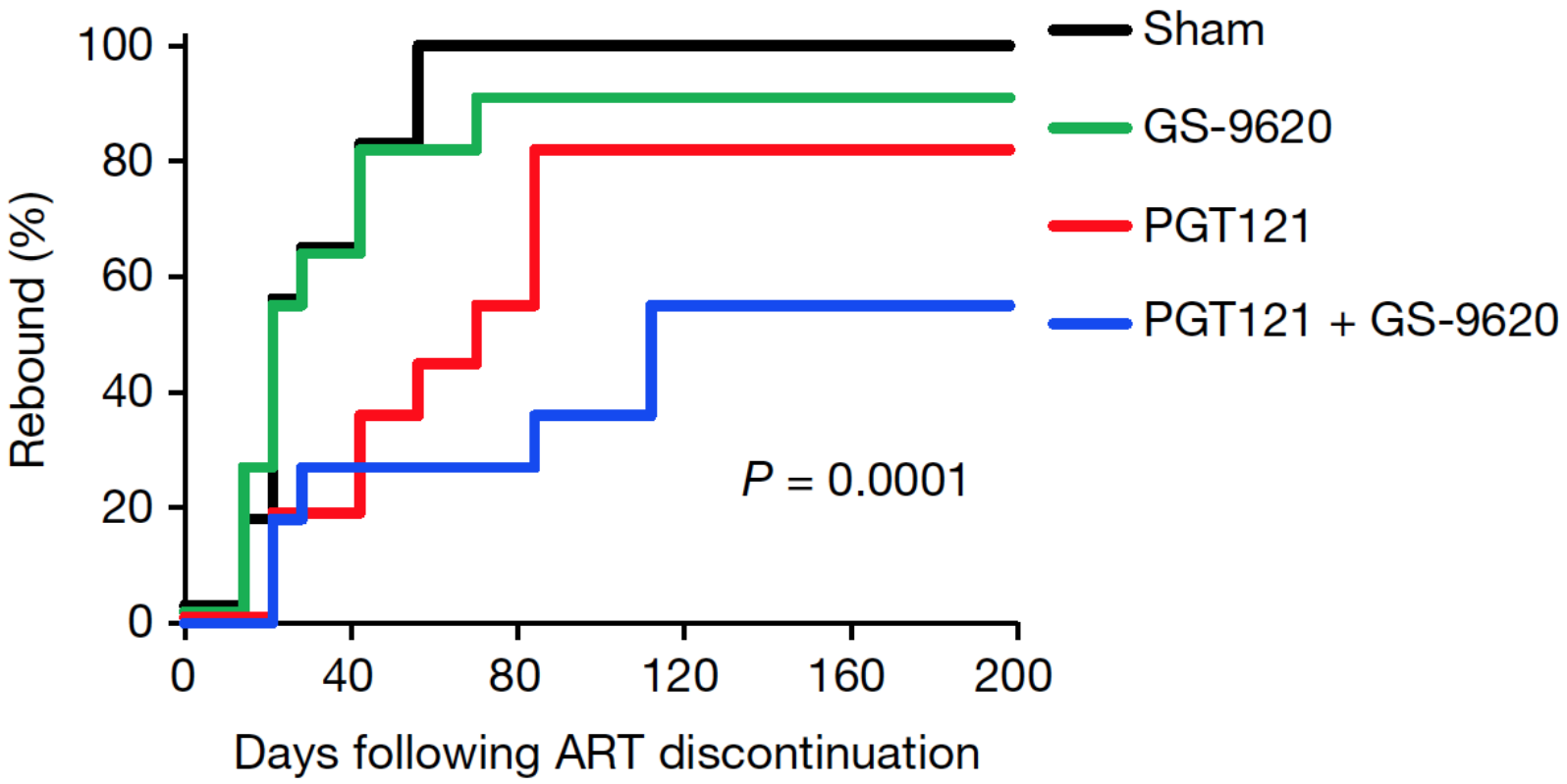
- The bNAb PGT121 and vesatolimod (a TLR7 agonist; innate immune stimulant) alone and in combination were given during ART (DTG/FTC/TDF) in acutely treated monkeys.
- Time to viral rebound was evaluated after ATI.



Borducchi E, et al., Barouch D. Nature 2018; 563:360-79.

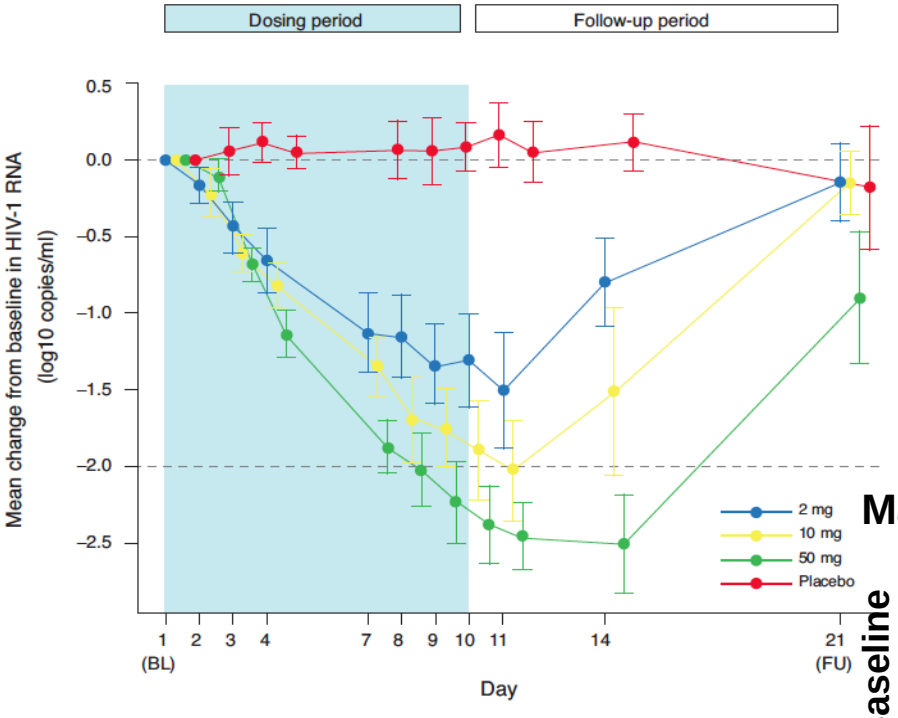
PGT121 + vesatolimod (GS-9620)

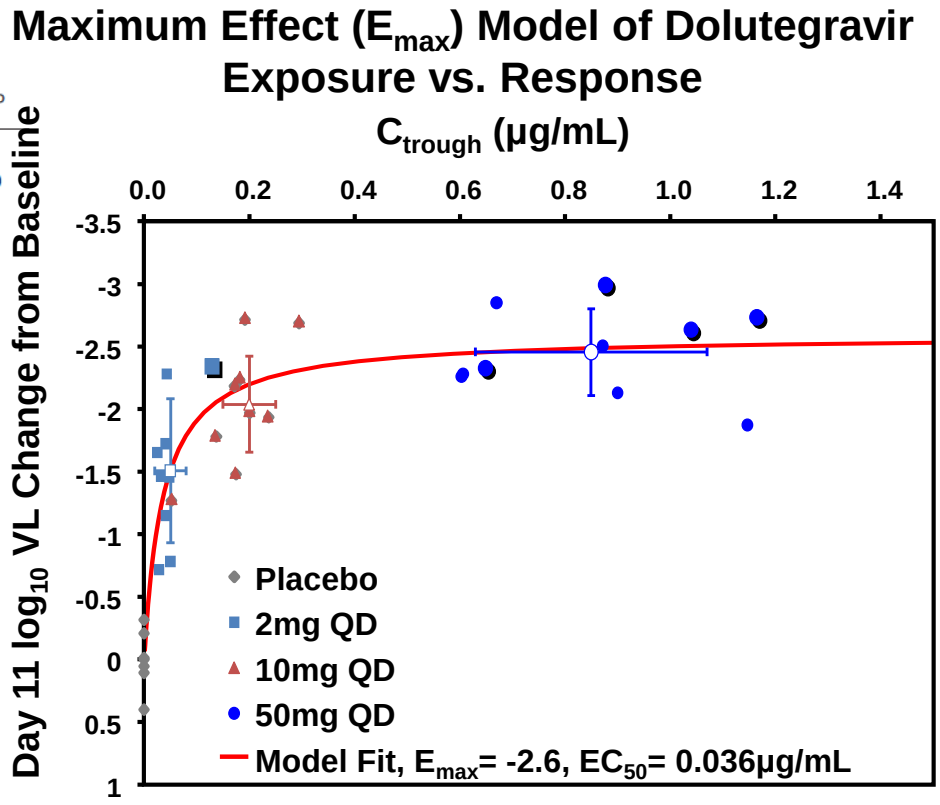
- 5 of 11 monkeys showed no rebound for > 6 months
- bNAb plus an innate immune stimulant may represent a strategy to target the viral reservoir; the mechanism includes cell activation and binding/elimination of virally-infected cells.



Borducchi E, et al., Barouch D. Nature 2018; 563:360-79.

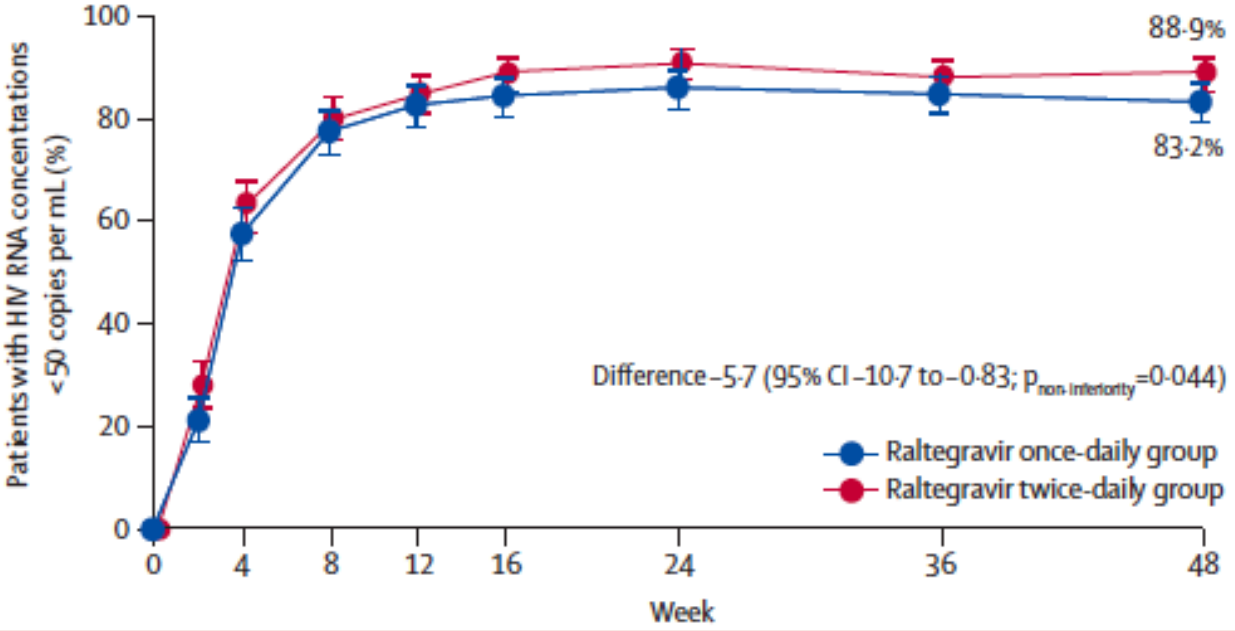
PK/PD of Dolutegravir





Min S, et al. AIDS 2011;25:1737-45.

Raltegravir Once vs. Twice Daily



	Raltegravir once-daily group		Raltegravir twice-daily group		Geometric mean ratio (once daily:twice daily; 90% CI)
	Patients	Least-squares mean* (% CV)	Patients	Least-squares mean* (% CV)	
From intensive pharmacokinetic profiles					
AUC† (μM·h)	22	30·87 (70)	20	13·14 (99)	1·17 (0·80–1·72)
C_{max} (μM)	22	13·46 (69)	20	3·38 (135)	3·98 (2·58–6·16)
C_{trough} (nM)‡	22	40 (111)	20	257 (167)	0·15 (0·09–0·26)

Eron JJ, et al. Lancet Infect Dis 2011;11:907-15

Emergence of Nevirapine Resistance

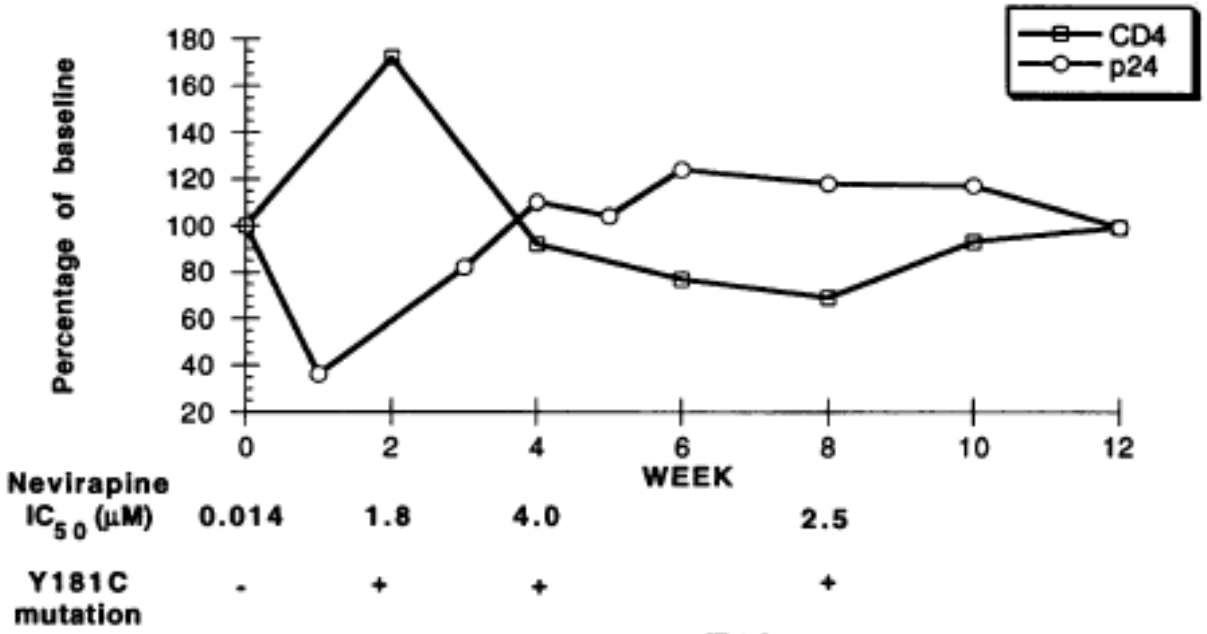


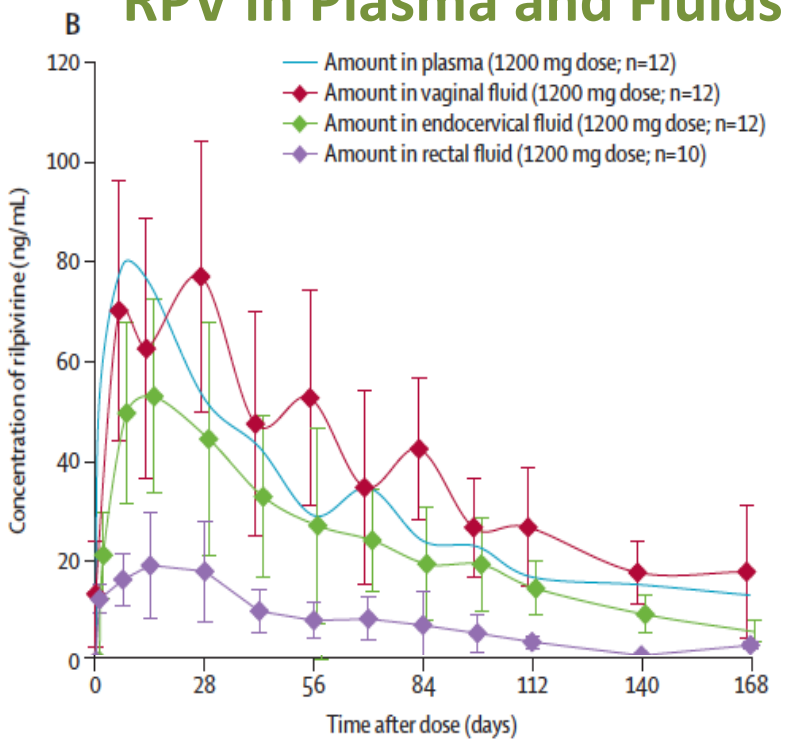
TABLE 1. Emergence of isolates of HIV with reduced susceptibility and resistance mutations with nevirapine therapy[a]

Wk of therapy	Cumulative proportion with:		
	Reduced susceptibility	Known resistance mutation[b]	Either
1	3/3		3/3
2	12/14	6/8	12/15
4	23/26	18/21	24/26
8	32/32	30/30	33/33
≥12	38/38	38/38	38/38

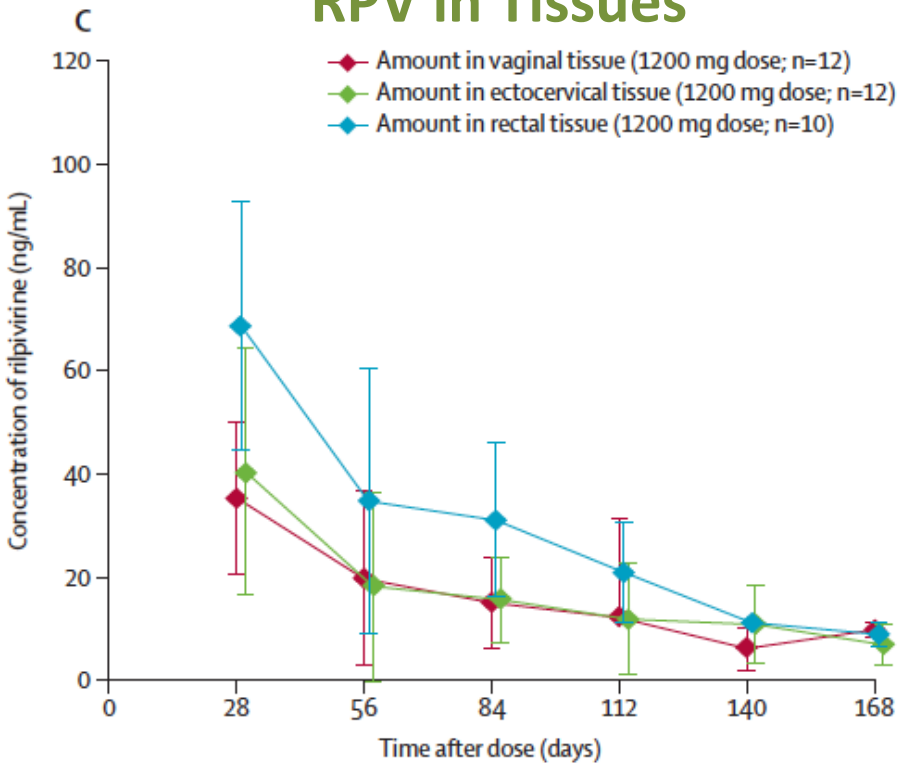
Richman D, J Virol 1994;68:1660-6

Compartmental differences in RPV levels following a single IM dose of RPV-LA

RPV in Plasma and Fluids

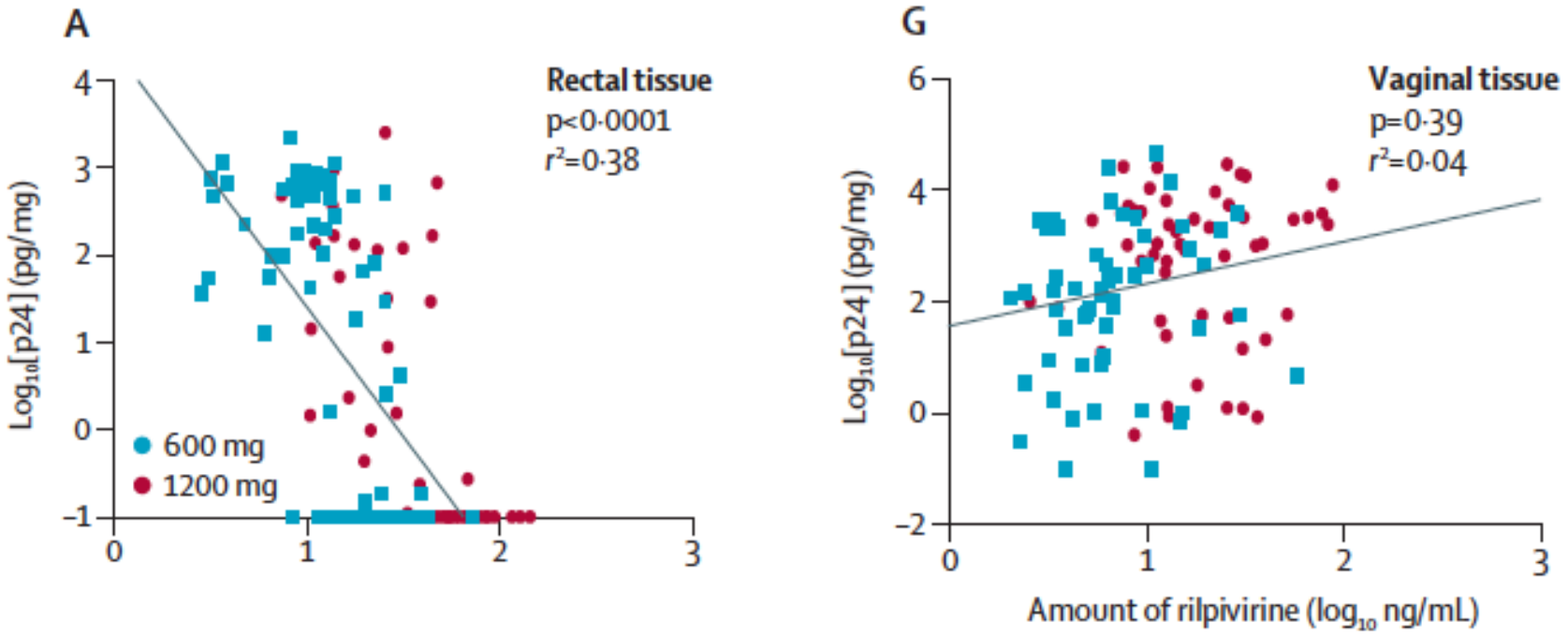


RPV in Tissues



Fluid to Plasma Ratio		Tissue to Plasma Ratio	
Vaginal	1.18-1.37	Vaginal	0.44-0.72
Endocervical	0.77	Ectocervical	0.42-0.77
Rectal	0.28-0.66	Rectal	1.10-1.22

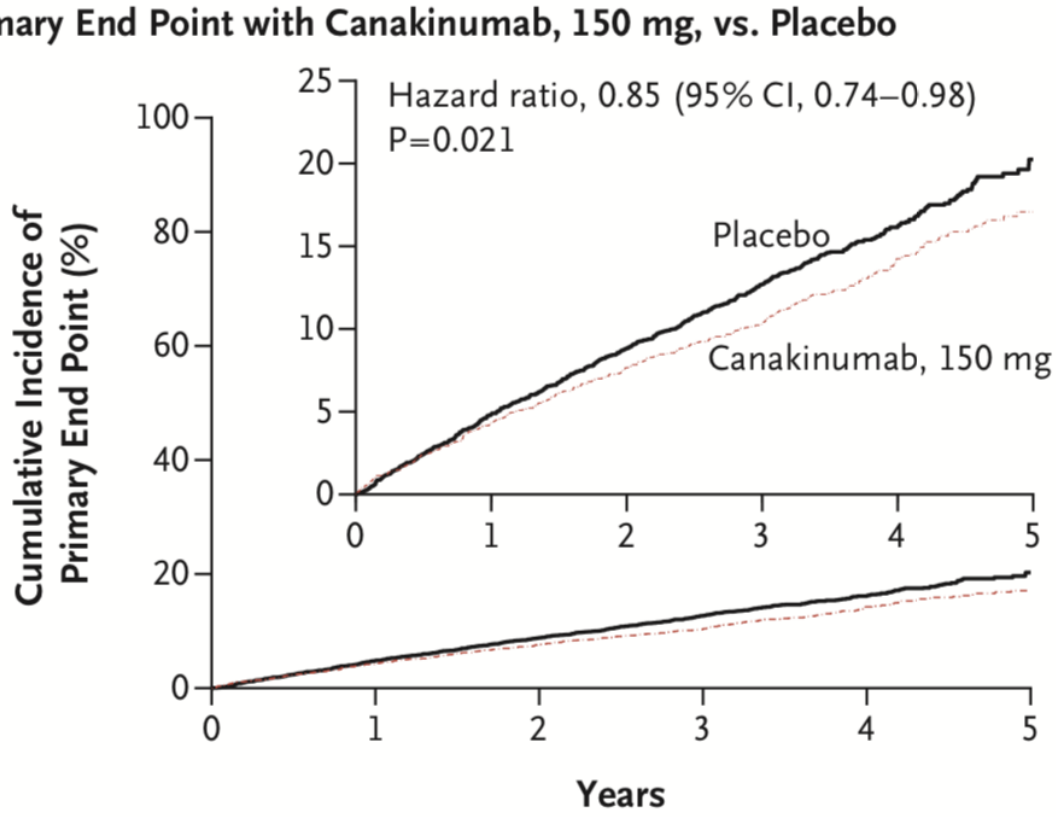
PKPD Correlations between Explant Infections and RPV Concentrations



- A significant PKPD relationship was observed for rectal tissue and fluid explant infection models; no relationships were found for cervical or vaginal models.
- Single dose RPV was associated with viral suppression in colorectal but not in cervicovaginal tissue.

McGowan I, et al. Lancet HIV 2016; online Sept 15.

Antiinflammatory therapy with canakinumab for atherosclerotic disease



Adverse Event	Placebo	Canakinumab			P value
		50 mg	150 mg	300 mg	
Fatal Infection or Sepsis	0.18	0.31	0.28	0.34	0.02

Ridker PM et al. NEJM 2017;377:1119-31.

Enhancing ARV Clinical Pharmacology Contributions to HIV Cure-Remission

- Formulation:
  - *Prodrugs, nanoformulations*
- Mechanism of action:
  - *Potent, selective agents with novel mechanisms of action and additive-to-synergistic with existing agents*
- Pharmacokinetics
  - *Improved tissue/organ distribution (C_t or $C_c = C_p$)*
- Pharmacodynamics
  - *Full suppression of viral replication in all tissues, compartments, reservoirs*
  - *Novel, highly synergistic combinations and new, precision medicine approach to combinatorial therapeutics*

It is our task, both in science and in society at large, to prove the conventional wisdom wrong and to make unpredictable dreams come true.

Freeman Dyson

Thank You