Nuovi target: stato dell'arte

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S.R. conflitti di interesse

BMS, Gilead, Janssen, MSD, ViiV

Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial

JD Baxter,[1] D Dunn,[2] E White,[2] S Sharma,[3] AM Geretti,[4] MJ Kozal,[5] MA Johnson,[6] S Jacoby,[7] JM Llibre[8] and J Lundgren[9] for the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group

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Objectives

HIV-1 transmitted drug resistance (TDR) in treatment-naïve individuals is a well-described phenomenon. Baseline genotypic resistance testing is considered standard of care in most developed areas of the world. The aim of this analysis was to characterize HIV-1 TDR and the use of resistance testing in START trial participants.

Methods

In the Strategic Timing of AntiRetroviral Treatment (START) trial, baseline genotypic resistance testing results were collected at study entry and analysed centrally to determine the prevalence of TDR in the study population. Resistance was based on a modified 2009 World Health Organization definition to reflect newer resistance mutations.

Results

Baseline resistance testing was available in 1946 study participants. Higher rates of testing occurred in Europe (86.7%), the USA (81.3%) and Australia (89.9%) as compared with Asia (22.2%), South America (1.8%) and Africa (0.1%). The overall prevalence of TDR was 10.1%, more commonly to nonnucleoside reverse transcriptase inhibitors (4.5%) and nucleoside reverse transcriptase inhibitors (4%) compared with protease inhibitors (2.8%). The most frequent TDR mutations observed were M41L, D67N/G/E, T215F/Y/I/S/C/D/E/V/N, 219Q/E/N/R, K103N/S, and G190A/S/E in reverse transcriptase, and M46I/L and L90M in protease. By country, the prevalence of TDR was highest in Australia (17.5%), France (16.7%), the USA (12.6%) and Spain (12.6%). No participant characteristics were identified as predictors of the presence of TDR.

Conclusions

START participants enrolled in resource-rich areas of the world were more likely to have baseline resistance testing. In Europe, the USA and Australia, TDR prevalence rates varied by country.

Keywords: antiretroviral therapy, drug resistance, HIV

Accepted 21 November 2014

Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: a nationally representative 2015 WHO survey

*Santiago Ávila-Ríos, Claudia García-Morales, Margarita Matías-Florentino, Karla A Romero-Mora, Daniela Tapia-Trejo, Verónica S Quiroz-Morales, Helena Reyes-Gopar, Hezhao Ji, Paul Sandstrom, Jesús Casillas-Rodríguez, Juan Sierra-Madero, Eddie A León-Juárez, Marisol Valenzuela-Lara, Carlos Magis-Rodríguez, Patricia Uribe-Zuñiga, Gustavo Reyes-Terán, for the HIVDR MexNet Group**

Summary

Background WHO has developed a global HIV-drug resistance surveillance strategy, including assessment of pretreatment HIV-drug resistance. We aimed to do a nationally representative survey of pretreatment HIV-drug resistance in Mexico using WHO-recommended methods.

Methods Among 161 Ministry of Health antiretroviral therapy (ART) clinics in Mexico, the largest, including 90% of ART initiators within the Ministry of Health (66 in total), were eligible for the survey. We used a probability-proportional-to-size design method to sample 25 clinics throughout the country. Consecutive ART-naive patients with HIV about to initiate treatment were invited to participate in the survey; individuals with previous exposure to ART were excluded. We assessed pretreatment HIV-drug resistance by Sanger sequencing and next-generation sequencing of viruses from plasma specimens from eligible participants with Stanford University HIV Drug Resistance Database methods. We obtained follow-up data for a median of 9·4 months (range 6–12) after enrolment. We investigated possible relations between demographic variables and pretreatment drug resistance with univariate and multivariate logistic regression.

Findings Between Feb 3 and July 30, 2015, we screened 288 patients in 25 clinics, from whom 264 provided successfully sequenced viruses with no evidence of current exposure to antiretroviral drugs. With the Sanger method, of these 264 participants, 41 (15·5%, 95% CI 11·4–20·5) had pretreatment resistance to any antiretroviral drug and 28 (10·6%, 7·2–15·0) had pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs). At least low-level pretreatment resistance (Stanford penalty score ≥15) was noted in 13 (4 · 9%) of participants to efavirenz and in 23 (8·7%) to the combination tenofovir plus emtricitabine plus efavirenz. With next-generation sequencing, of 264 participants, 38 (14·4%, 95% CI 10·4–19·2) had pretreatment resistance to any antiretroviral drug and 26 (9·8%, 6·5–14·1) had pretreatment resistance to NNRTIs. After median follow-up of 8 months (IQR 6·5–9·4, range 5–11) after ART initiation, 97 (72%) of 135 NNRTI initiators achieved viral suppression (<50 copies per mL) compared with ten (40%) of 25 individuals who started with protease inhibitor-based regimens (p=0·0045). After multivariate regression considering pretreatment resistance and initial ART regimen as composite variables, people starting NNRTIs with pretreatment drug resistance achieved significantly lower viral suppression (odds ratio 0·24, 95% CI 0·07–0·74; p=0·014) than patients without NNRTI resistance.

Interpretation High levels of pretreatment drug resistance were noted in Mexico, and NNRTI pretreatment drug resistance significantly reduced the effectiveness of first-line ART regimens based on these drugs. Baseline HIV-drug resistance testing for initial ART follow-up and decision making should be considered.

Lancet HIV 2016; 3: e579–91

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See Comment page e553

*Members listed at the end of the report

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Journal of Antimicrobial Chemotherapy

HIV-1 drug resistance mutations emerging on darunavir therapy in PI-naive and -experienced patients in the UK

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Background: Darunavir is considered to have a high genetic barrier to resistance. Most darunavir-associated drug resistance mutations (DRMs) have been identified through correlation of baseline genotype with virological response in clinical trials. However, there is little information on DRMs that are directly selected by darunavir in clinical settings.

Objectives: We examined darunavir DRMs emerging in clinical practice in the UK.

Patients and methods: Baseline and post-exposure protease genotypes were compared for individuals in the UK Collaborative HIV Cohort Study who had received darunavir; analyses were stratified for PI history. A selection analysis was used to compare the evolution of subtype B proteases in darunavir recipients and matched PI-naive controls.

Results: Of 6918 people who had received darunavir, 386 had resistance tests pre- and post-exposure. Overall, 2.8% (11/386) of these participants developed emergent darunavir DRMs. The prevalence of baseline DRMs was 1.0% (2/198) among PI-naive participants and 13.8% (26/188) among PI-experienced participants. Emergent DRMs developed in 2.0% of the PI-naive group (4 mutations) and 3.7% of the PI-experienced group (12 mutations). Codon 77 was positively selected in the PI-naive darunavir cases, but not in the control group.

Conclusions: Our findings suggest that although emergent darunavir resistance is rare, it may be more common among PI-experienced patients than those who are PI-naive. Further investigation is required to explore whether codon 77 is a novel site involved in darunavir susceptibility.

Table 1. Subject characteristics and summary of sequencing results

All subjects, *n* (%)	278 (100)
Male, *n* (%)	231 (83.0)
Continent of origin, *n* (%)	
western Europe	180 (64.7)
eastern Europe	48 (17.3)
sub-Saharan Africa	20 (7.2)
Latin America	16 (5.8)
others	14 (5.0)
CDC class, *n* (%)	
A	230 (82.7)
B	21 (7.5)
C	22 (8.0)
unknown	5 (1.8)
CD4+ T count (cells/μL), median	411
Route of transmission, *n* (%)	
MSM/bisexual	180 (64.8)
heterosexual	61 (21.9)
IVDU	5 (1.8)
other	32 (11.5)
Viral subtype, *n* (%)	
B	186 (67.0)
C	15 (5.4)
A	11 (4.0)
F	12 (4.3)
G	6 (2.1)
D	1 (0.3)
unknown	47 (16.9)
Summary of Sanger sequencing, *n* (%)	
IAS-USA integrase mutations	5 (1.8) [74M (2), 97A (2) and 138A]
HIVdb score ≥10	11 (4.0)
Summary of 454 sequencing (*n*=56 subjects), *n* (%)	
IAS-USA integrase mutations	0
HIVdb score ≥10	8 (14.3)

J Antimicrob Chemother 201
doi:10.1093/jac/dkv202 Adv

Journal of Antimicrobial Chemotherapy

Primary resist

hibitors in Europe

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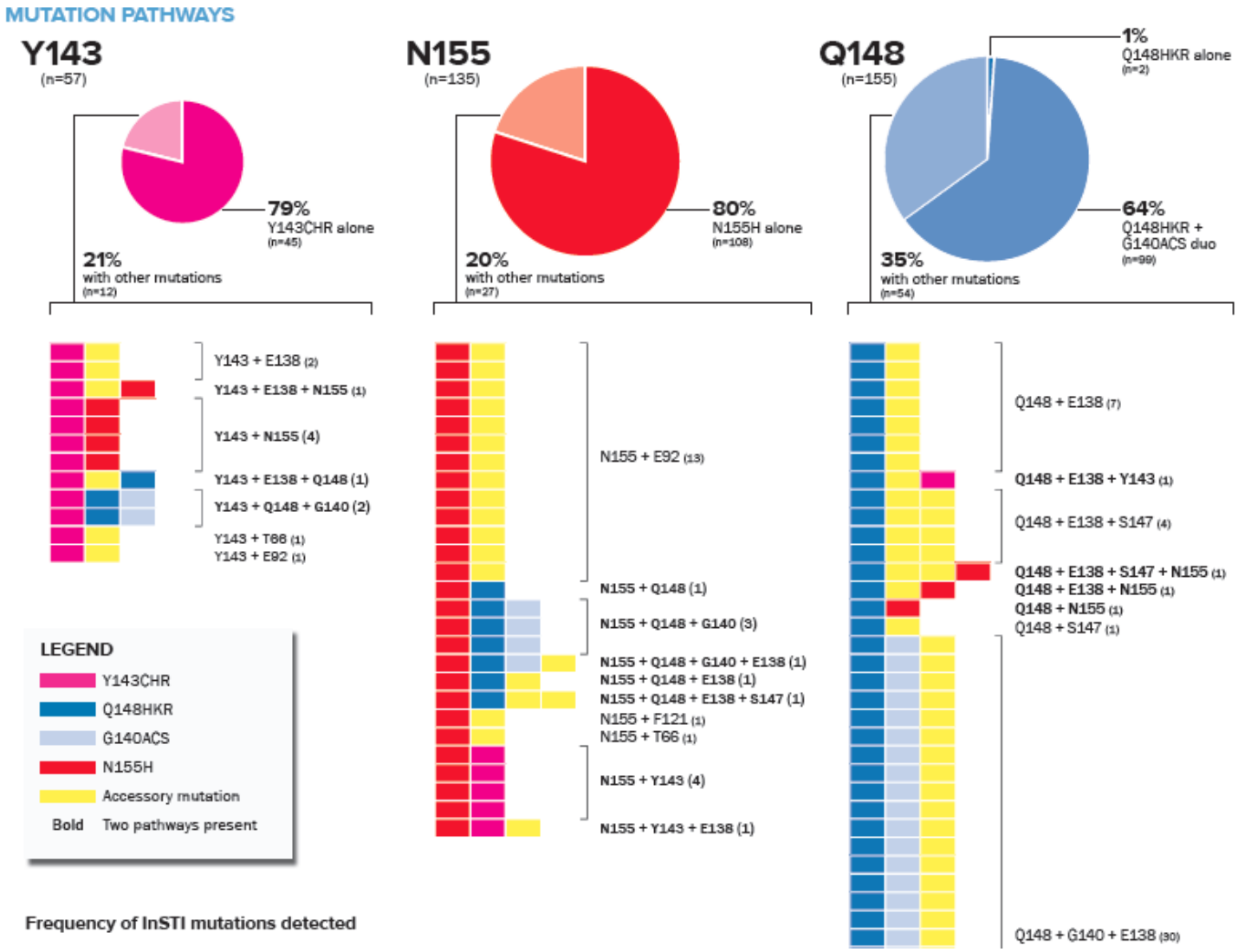
D. Struck[4], I. Alexiev[7], A. M
C. Nielsen[13], D. Otelea[14],
K. Van Laethem[20], S. Z

ofstra[2,4], J. R. Santos[5], F. Garcia[6],
ogyi[10], K. Liitsola[11], M. Linka[12],
Staneková[18], M. Stanojevic[19],
s[1,3,4] and A. M. J. Wensing[2]

One out of five US patients tested (N=1,764) during the first 3 years of InSTI GRT availability harbored at least one "major" InSTI resistance mutation



1905 sequences analyzed from InSTI GRT, representing 1764 patients in 39 states; 1168 (66%) had paired *pol* sequences. The number of tests increased over time, from 73 in 2009 to 1097 in 2011

Hurt CB, Sebastian J, Hicks CB, Eron JJ. Clin Infect Dis. 2014

French National Survey of Resistance to Integrase Inhibitors Shows High Differences of Resistance Selection Rate in Case of Virological Failure in a Context of Routine Hospital Care (ANRS AC11 Virology Network)

Anne-Genevieve Marcelin,[1] Maxime Grude,[2] Charlotte Charpentier,[3] Pantxika Bellcave,[4] Audrey Rodallec,[5] Coralie Pallier,[6] Stephanie Raymond,[7] Audrey Mirand,[8] Laurence Bocket,[9] Laurence Morand-Joubert,[10] Constance Delaugerre,[11] Brigitte Montes,[12] Helene Jeulin,[13] Thomas Mourez,[14] Samira Fafi-Kremer,[15] Corrine Amiel,[16] Catherine Roussel,[17] Julia Dina,[18] Marie-Anne Trabaud,[19] Helene Le Guillou-Guillemette,[20] Sophie Valet,[21] Anne Signori-Schmuck,[22] Anne Maillard,[23] Anne Krivine,[24] Philippe Flandre,[2] Diane Descamps,[3] Vincent Calvez[1]

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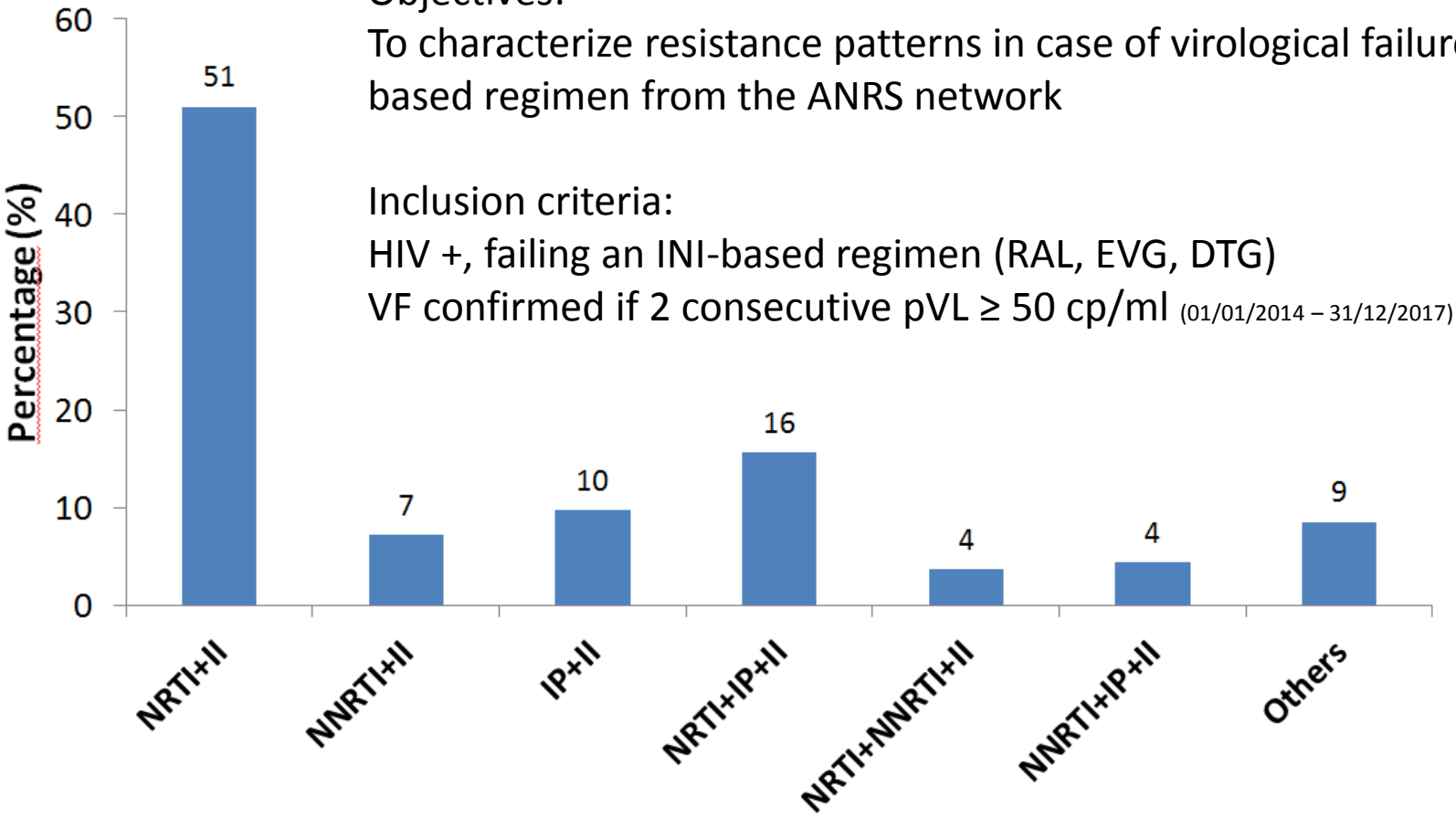
Marcelin et al. HIV Glasgow 2016; Glasgow, UK. Slides O332.

ARV Treatment Associated to INI (n=439)

Objectives:
To characterize resistance patterns in case of virological failure to INI-based regimen from the ANRS network

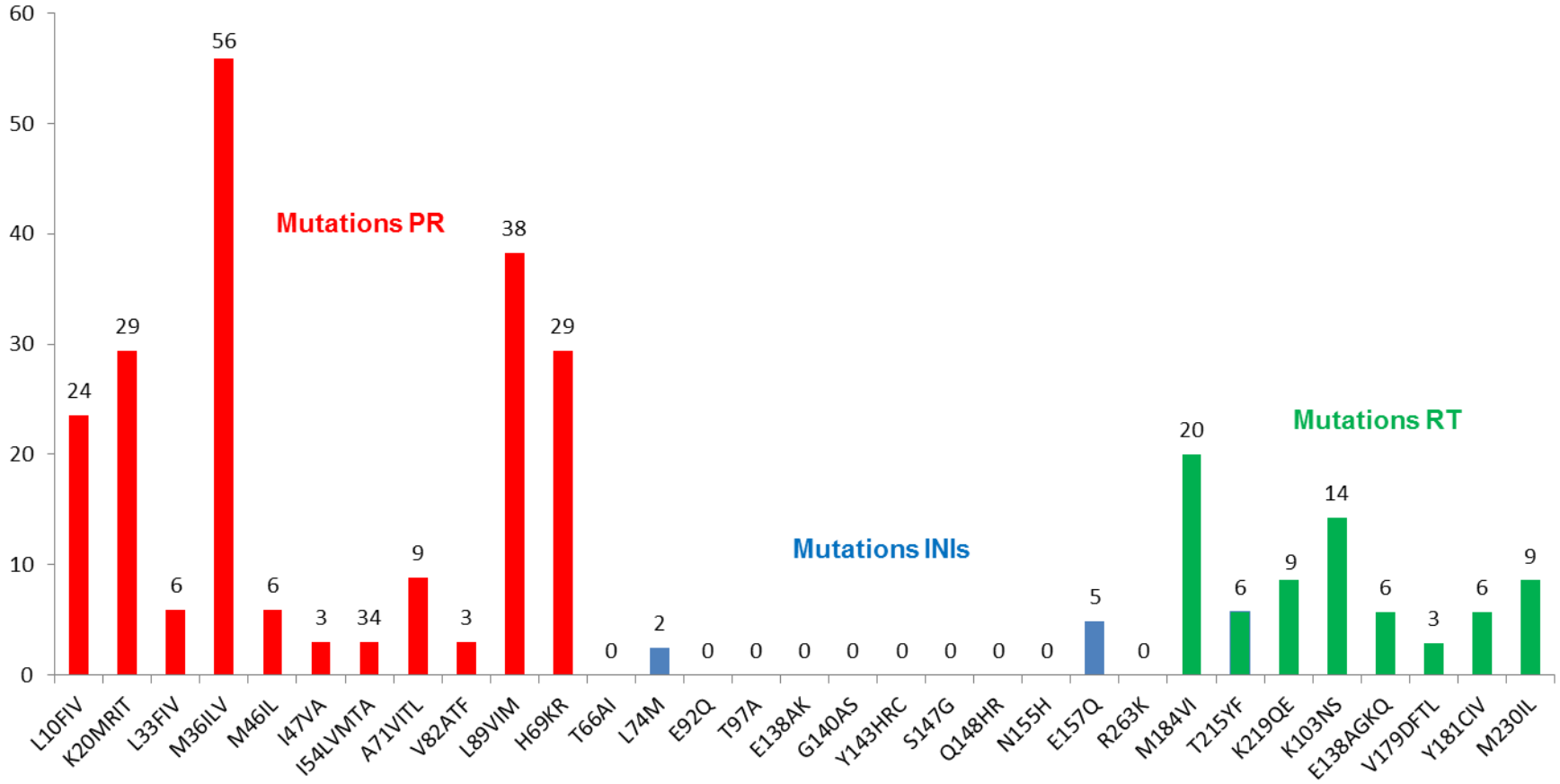
Inclusion criteria:
HIV +, failing an INI-based regimen (RAL, EVG, DTG)
VF confirmed if 2 consecutive pVL ≥ 50 cp/ml (01/01/2014 – 31/12/2017)



Adapted from Marcelin et al. HIV Glasgow 2016; Glasgow, UK. Slides O332.

Patients Treated by DTG as First INI (n=41; cont)

Resistance mutations



Marcelin et al. HIV Glasgow 2016; Glasgow, UK. Slides O332.

Patients Treated by DTG as First INI (n=41; cont)

Resistance to INI	DTG_BID	DTG_QD	RAL	EVG
Resistance (%)	0	0	0	2* (5%)
Possible resistance (%)	2* (5%)	2* (5%)	NA	NA
Susceptible (%)	39 (95%)	39 (95%)	41 (100%)	39 (95%)

*2 patients with only one E157Q mutation.

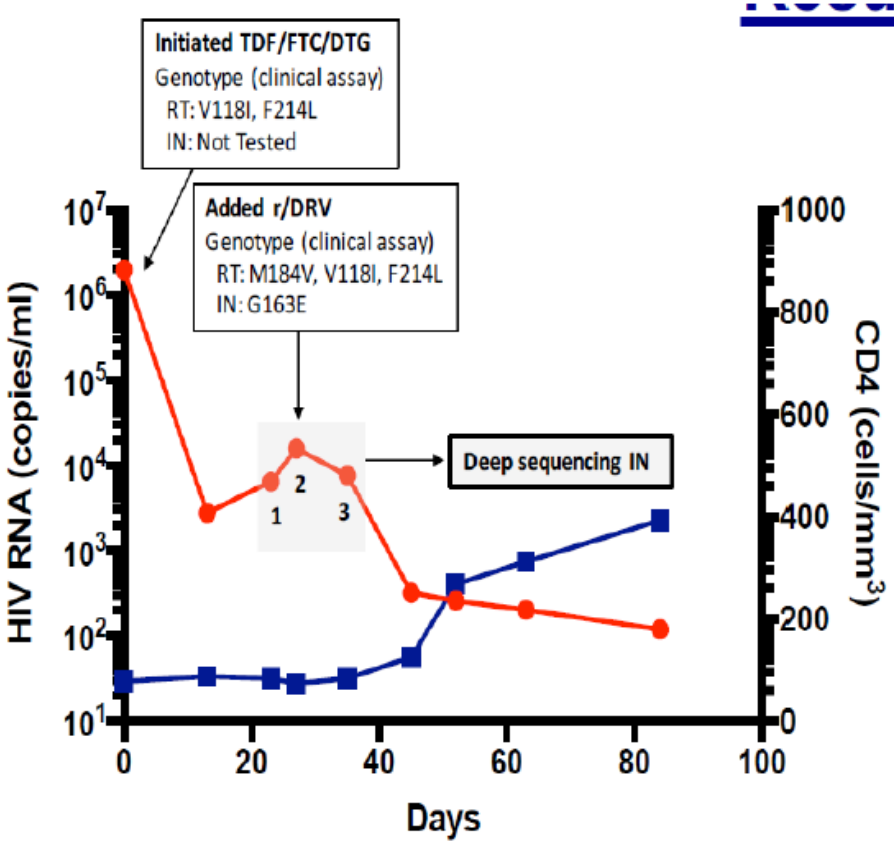
Marcelin et al. HIV Glasgow 2016; Glasgow, UK. Slides O332.

500LB

Emergence of Integrase Resistance Mutations During Initial Therapy with TDF/FTC/DTG

Jennifer A. Fulcher[1], Yushen Du[2], Ren Sun[2], Raphael J. Landovitz[1,3]

[1]Division of Infectious Diseases, Department of Medicine, [2]Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA [3]UCLA Center for Clinical AIDS Research and Education (CARE), Los Angeles, CA



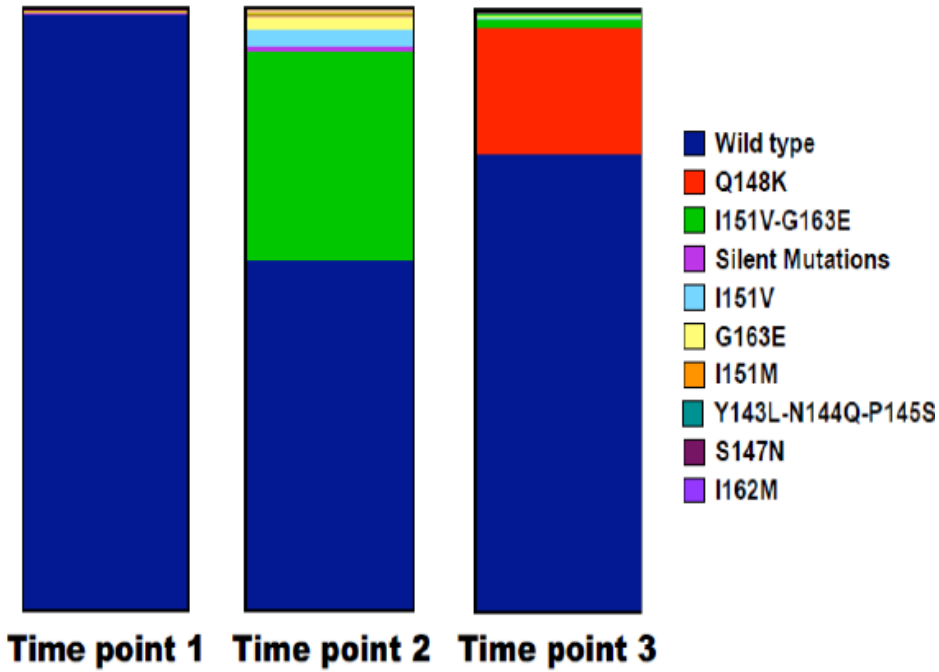
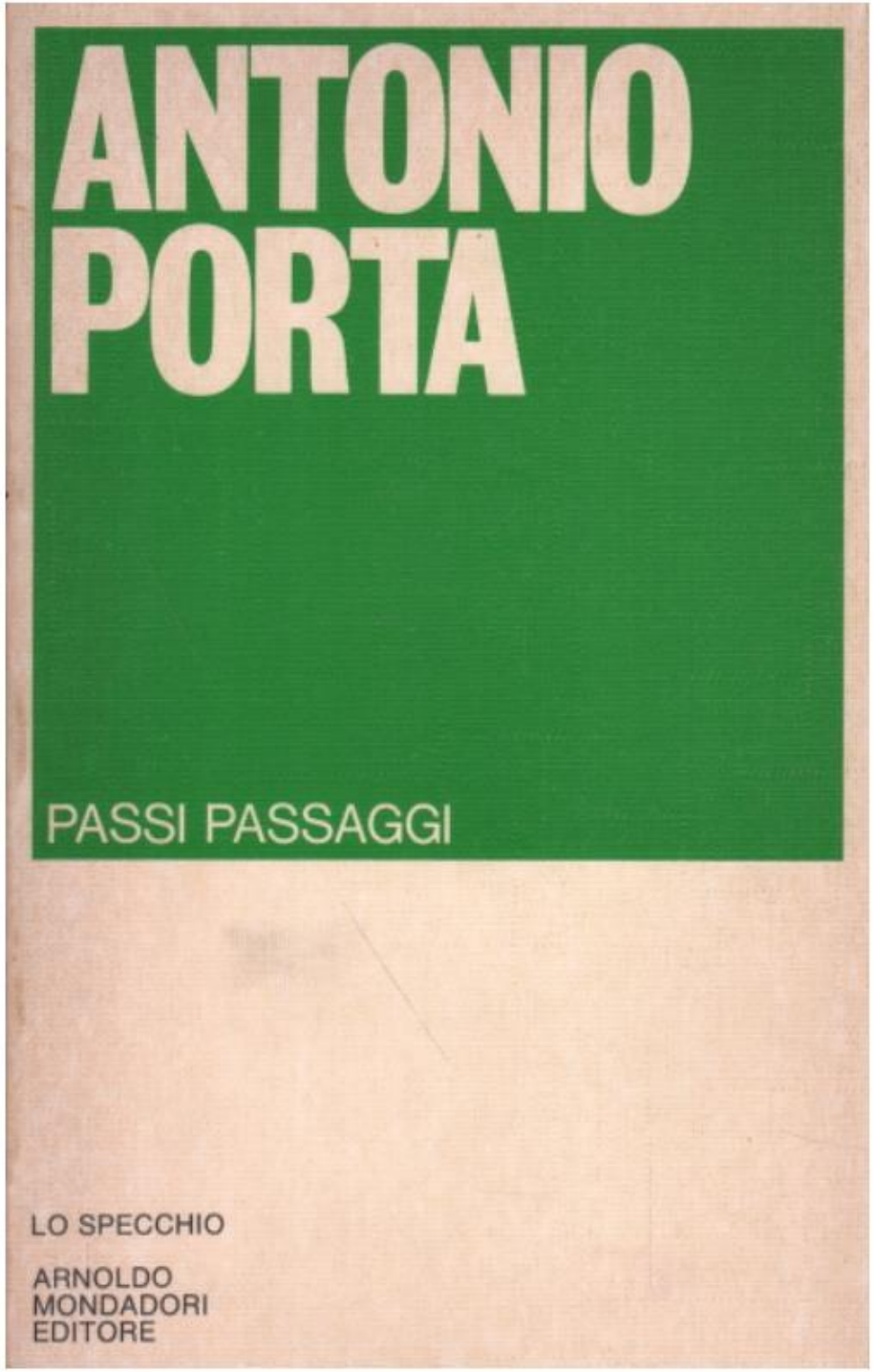


Figure 2. Paired end deep sequencing of IN amino acid region 142-165. Deep sequencing analysis was


ANTONIO
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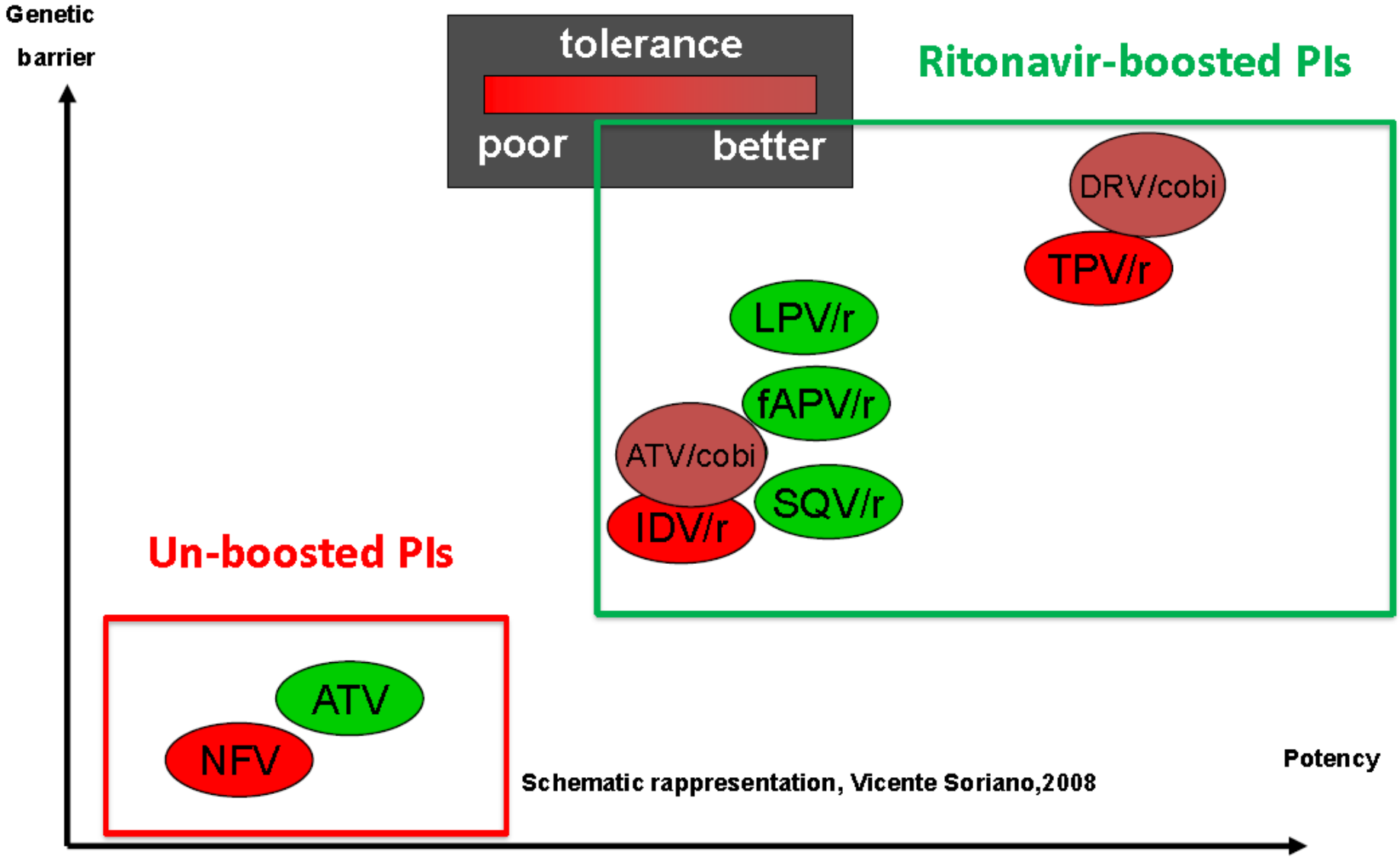
(1976-1979)

PI Potency & Resistance genetic barrier



Schematic rappresentation, Vicente Soriano,2008

Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251

Chasity D. Andrews[a], Leslie St. Bernard[a], Amanda Yee Poon[a], Hiroshi Mohri[a], Natanya Gettie[a], William R. Spreen[b], Agegnehu Gettie[a], Kasi Russell-Lodrigue[c], James Blanchard[c], Zhi Hong[d], David D. Ho[a] and Martin Markowitz[a]

Objective: We evaluated the effectiveness of cabotegravir (CAB; GSK1265744 or GSK744) long acting as preexposure prophylaxis (PrEP) against intravenous simian immunodeficiency virus (SIV) challenge in a model that mimics blood transfusions based on the per-act probability of infection.

Design: CAB long acting is an integrase strand transfer inhibitor formulated as a 200 mg/ml injectable nanoparticle suspension that is an effective PrEP agent against rectal and vaginal simian/human immunodeficiency virus transmission in macaques.

Methods: Three groups of rhesus macaques ($n = 8$ per group) were injected intramuscularly with CAB long acting and challenged intravenously with 17 animal infectious dose 50% SIVmac251 on week 2. Group 1 was injected with 50 mg/kg on week 0 and 4 to evaluate the protective efficacy of the CAB long-acting dose used in macaque studies mimicking sexual transmission. Group 2 was injected with 50 mg/kg on week 0 to evaluate the necessity of the second injection of CAB long acting for protection against intravenous challenge. Group 3 was injected with 25 mg/kg on week 0 and 50 mg/kg on week 4 to correlate CAB plasma concentrations at the time of challenge with protection. Five additional macaques remained untreated as controls.

Results: CAB long acting was highly protective with 21 of the 24 CAB long-acting-treated macaques remaining aviremic, resulting in 88% protection. The plasma CAB concentration at the time of virus challenge appeared to be more important for protection than sustaining therapeutic plasma concentrations with the second CAB long acting injection.

Conclusion: These results support the clinical investigation of CAB long acting as PrEP in people who inject drugs.

AIDS 2017, **31**:461–467

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Trial record **7 of 8** for: cabotegravir

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Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex With Men

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2017 by National Institute of Allergy and Infectious Diseases (NIAID)

Sponsor:
National Institute of Allergy and Infectious Diseases (NIAID)

Collaborators:
ViiV Healthcare
Gilead Sciences

Information provided by (Responsible Party):
National Institute of Allergy and Infectious Diseases (NIAID)

ClinicalTrials.gov Identifier:
NCT02720094

First received: March 21, 2016
Last updated: February 20, 2017
Last verified: February 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

4000 PTS – June 2020

Evaluation of Resistance to Cabotegravir Long-Acting (CAB LA) in SIVmac251-Infected Macaques

Chasity D. Andrews[1], Hiroshi Mohri[1], Leslie St. Bernard[1], Amanda Poon[1], William Spreen[2], Agegnehu Gettie[1], Kasi Russell-Lodrigue[3], Zhi Hong[4], David D. Ho[1], and Martin Markowitz[1]

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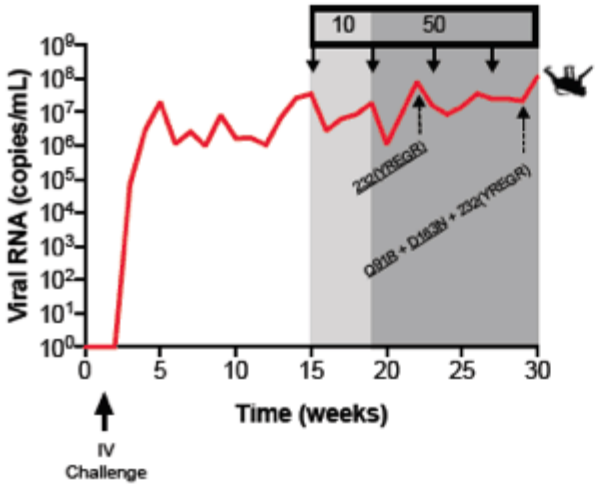
[4]GlaxoSmithKline, Research Triangle Park, NC, USA

Objective

Evaluate the *in vivo* selection of CAB resistance in SIVmac251-infected rhesus macaques

A novel five amino acid (5AA) duplication identified in FN62 results in broad high-level resistance to all InSTIs



Susceptibility of Q91R + D163N + 5AA duplication-containing clone

InSTI	IC_{50} (nM)	Fold change*
CAB	113	38
DTG	126	33
EVG	151	47
RAL	452	41

**relative to SIVmac239*

HIV Research for Prevention (HIVR4P 2016), October 17-19, 2016, Chicago. Abstract OA03.04.

RESISTANCE EMERGENCE IN MACAQUES ADMINISTERED CABOTEGRAVIR LA DURING ACUTE INFECTION

Gerardo Garcia-Lerma

Summary of integrase mutations identified in macaques compared with known resistance associated mutations

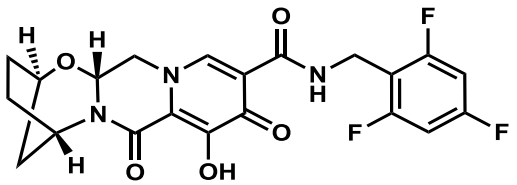
						E92Q/M														
Known Major Primary Resistance Mutations				T66IAK				**E92Q**			E138KA G140SA Y143RCH S147G Q148HRK				N155H					
Known Major Accessory Mutations	H51Y				L74MI			**T97A**				V151ILA S153YF			E157Q **G163RK**					
	I31L R34K G47A			I73V		Q91R		T97A/I	G106S V110I H112L L113I A122V Q124K H137R						H156GR D163N	V172L 5AA D278G A289T				
Number of macaques expressing mutation																	1	2	3	

Bictegravir (GS-9883)

- INSTI
- Two phase III trials of FDC containing GS-9883/F/TAF compared with dolutegravir-based regimens
- No booster required
- STR with TAF/FTC

ASM, Boston June 2016: Poster 413; 415; 416; 417.

Bictegravir



- Metal-chelating core
- 2,4,6-trifluorophenyl ring
- [3.2.1] oxaza bridging bicyclic side chain

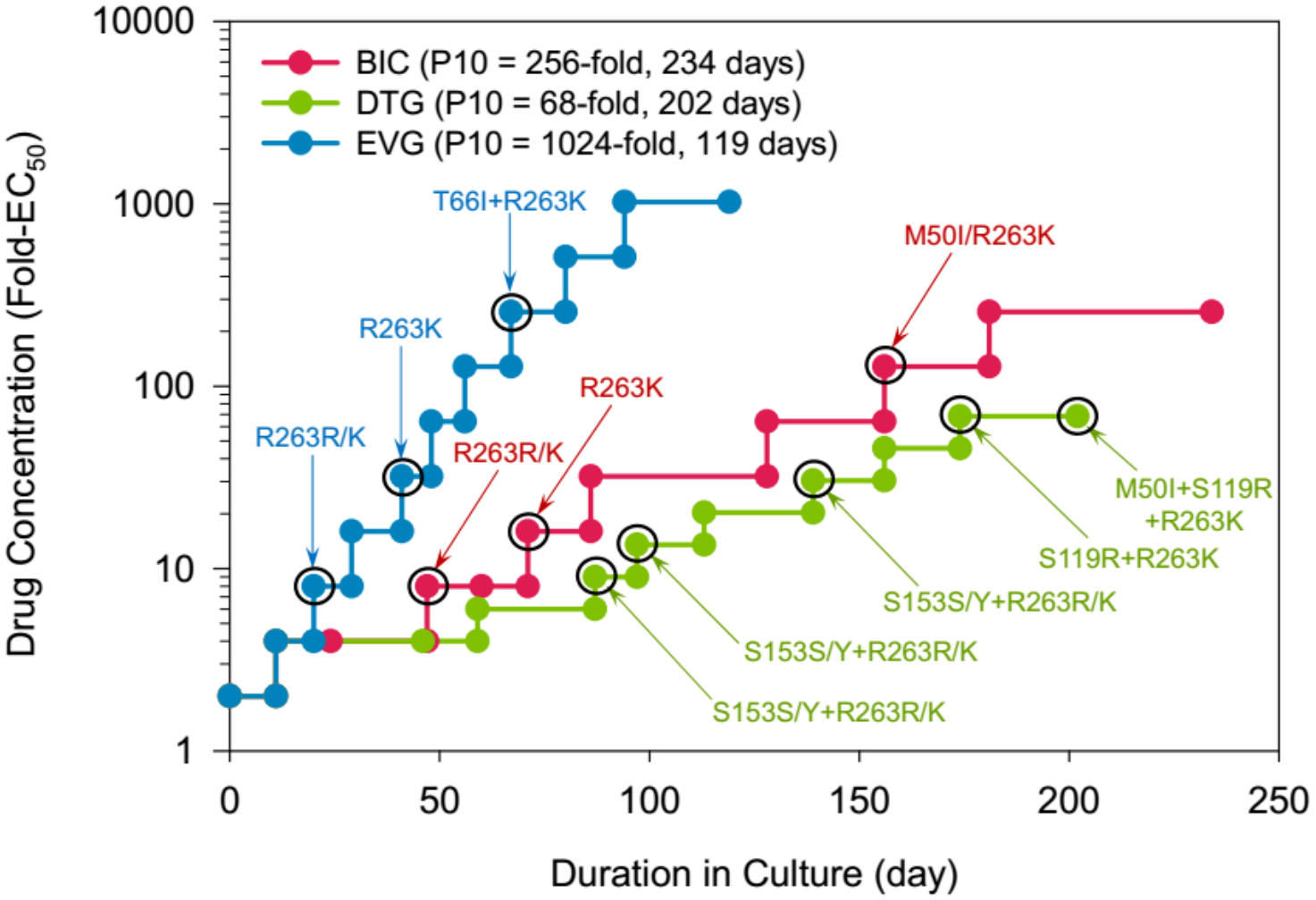
	RAL	EVG	DTG	BIC
Human Plasma Half-Life	9 hours	8.7 hours	14 hours	18 hours
G140S/Q148H Mean Fold Change vs WT	>143	>150	7.6	3.4
WT IN-DNA Dissociation Half-life, hours	5.2	1.5	16	38
G140S/Q148H IN-DNA Dissociation Half-life, hours	--	--	0.65	2.5
OCT-2 IC_{50}	--	--	0.13 µM	0.49 µM

- BIC is a novel, potent INSTI with a high barrier to resistance and a favorable PK profile (longest plasma $T_{1/2}$ with dose-proportional PK, and fewer DDIs)
- Active against HIV-1 and HIV-2
- BIC demonstrates
  - Preserved antiviral activity against multiple integrase mutants including G140/Q148
  - Minimal impact on estimated creatinine clearance

DDIs, drug-drug interactions; IC, inhibitory concentration; IN, integrase; OCT-2, organic cation transporter-2; PK, pharmacokinetic; $T_{1/2}$, half-life; WT, wild type.

1. Gallant J, et al. ASM 2016. Boston, MA. Poster #415. 2. Isentress US Prescrbing Information. Merck & Co. February 2015 3. Lazerwith SE, et al. ASM 2016. Boston, MA. Poster #414. 4. Tivicay US Prescribing Information, ViiV Healthcare. June 2016. 5. Tsiang M, et al., AAC 2016;60:7086-7097 6. Vitekta US Prescribing Information, Gilead Sciences. June 2015. 7. White K, et al. CROI 2017. Seattle, WA. Poster 0893. 8. Zhang H, et al. CROI 2017. Seattle, WA. Oral 0860.

In vitro resistance selection by EVG, DTG, BIC



Tsiang, AAC 2016, Sept 19

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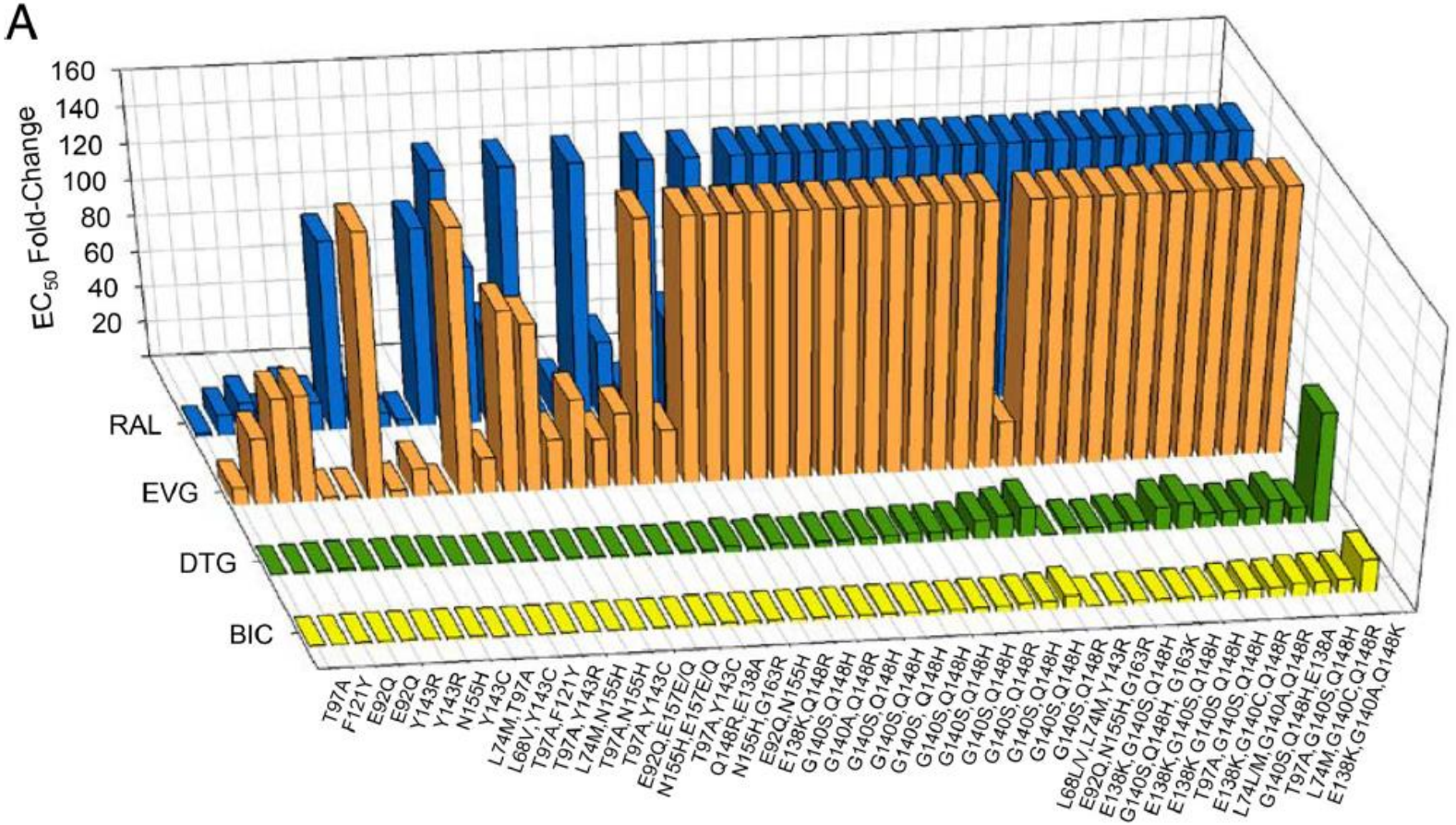

B

Compound	% of Isolates[a] (Fold-Change vs. WT)				Fold-Change vs. WT			
	(≤2.5)	(2.5 to <5)	(5 to <10)	(≥10)	Mean	Median	Range	p-value
BIC	70	15	13	2	2.8	2	0.50 - 19	1
DTG	49	17	17	17	5.8	3.4	0.54 - 63	0.042
EVG	6	2	0	92	>106	>150	1.9 - >150	<0.001
RAL	2	4	4	89	>100	>143	1.8 - >143	<0.001

Tsiang, AAC 2016, Sept 19

Tempo di dissociazione di BIC nel virus WT

Table 3. Dissociation Half-lives of INSTIs from WT HIV-1 Integrase-DNA Complexes

INSTI	Dissociation of INSTI from Wild-type IN-DNA Complexes*			
	By Exponential Decay		By Equilibrium Binding Model	
	Apparent $t_{1/2}$ (hr) [**]	p-value vs BIC	$t_{1/2}$ (hr)	p-value vs BIC
BIC	135 ± 20 [na]	--	38 ± 19	--
DTG	79 ± 13 [71]	< 0.0001	16 ± 9	0.017
RAL	14 ± 3 [8.8]	< 0.0001	5.2 ± 0.6	0.003
EVG	3.6 ± 0.7 [2.7]	< 0.0001	1.5 ± 0.2	0.0006

*Average ± standard deviation from 5 to 7 experiments
**Published $t_{1/2}$ values from Hightower et al., Antimicrobial Agents and Chemotherapy. (2011) 55(10):4552-4559.

Kirsten White et al. CROI 2017 Feb 14-16 Seattle, WA

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Tempo di dissociazione di BIC nel virus mutato

Table 4. Dissociation Half-lives of INSTIs from WT and G140S/Q148H HIV-1 Integrase-DNA Complexes by the Equilibrium Binding Model

INSTI	Dissociation $t_{1/2}$ of INSTI from IN-DNA Complexes			
	Wild-Type IN		G140S/Q148H Mutant IN	
	$t_{1/2}$ (hr)*	p-value vs BIC	$t_{1/2}$ (hr)*	p-value vs BIC
BIC	38 ± 19	--	2.5 ± 0.07**	--
DTG	16 ± 9	0.017	0.65 ± 0.2***	0.0076
RAL	5.2 ± 0.6	0.003	ND	ND
EVG	1.5 ± 0.2	0.0006	ND	ND

*Average ± standard deviation from 2 to 7 experiments
**BIC $t_{1/2}$ with G140S/Q148H mutant IN-DNA complexes was statistically longer than the EVG dissociation $t_{1/2}$ with wild-type IN-DNA complexes.
***DTG $t_{1/2}$ with G140S/Q148H mutant IN-DNA complexes was statistically shorter than the EVG dissociation $t_{1/2}$ with wild-type IN-DNA complexes.

- Bictegravir has the longest measured dissociation half-life compared to DTG, RAL, and EVG
  - Significantly longer from wild-type HIV-1 IN-DNA complexes
  - Significantly longer from G140S/Q148H HIV-1-DNA complexes

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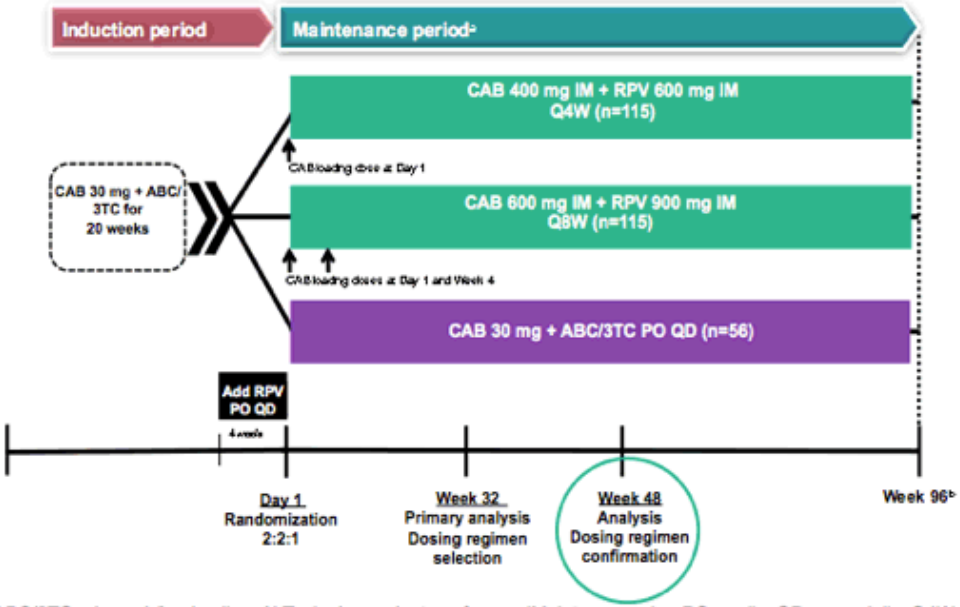
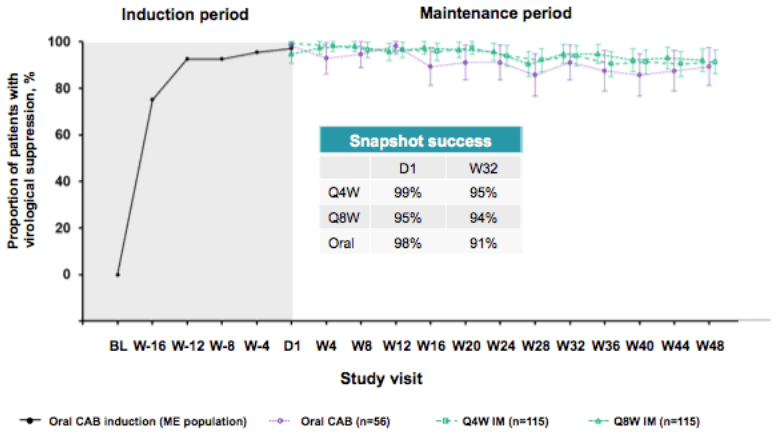
LATTE-2 Study Design

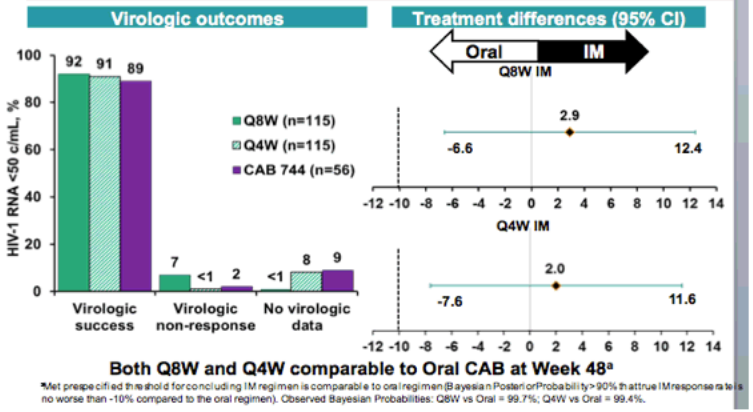


ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

LATTE-2 Week 48 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



HIV-1 RNA <50 c/mL at Week 48 ITT-ME (Snapshot)

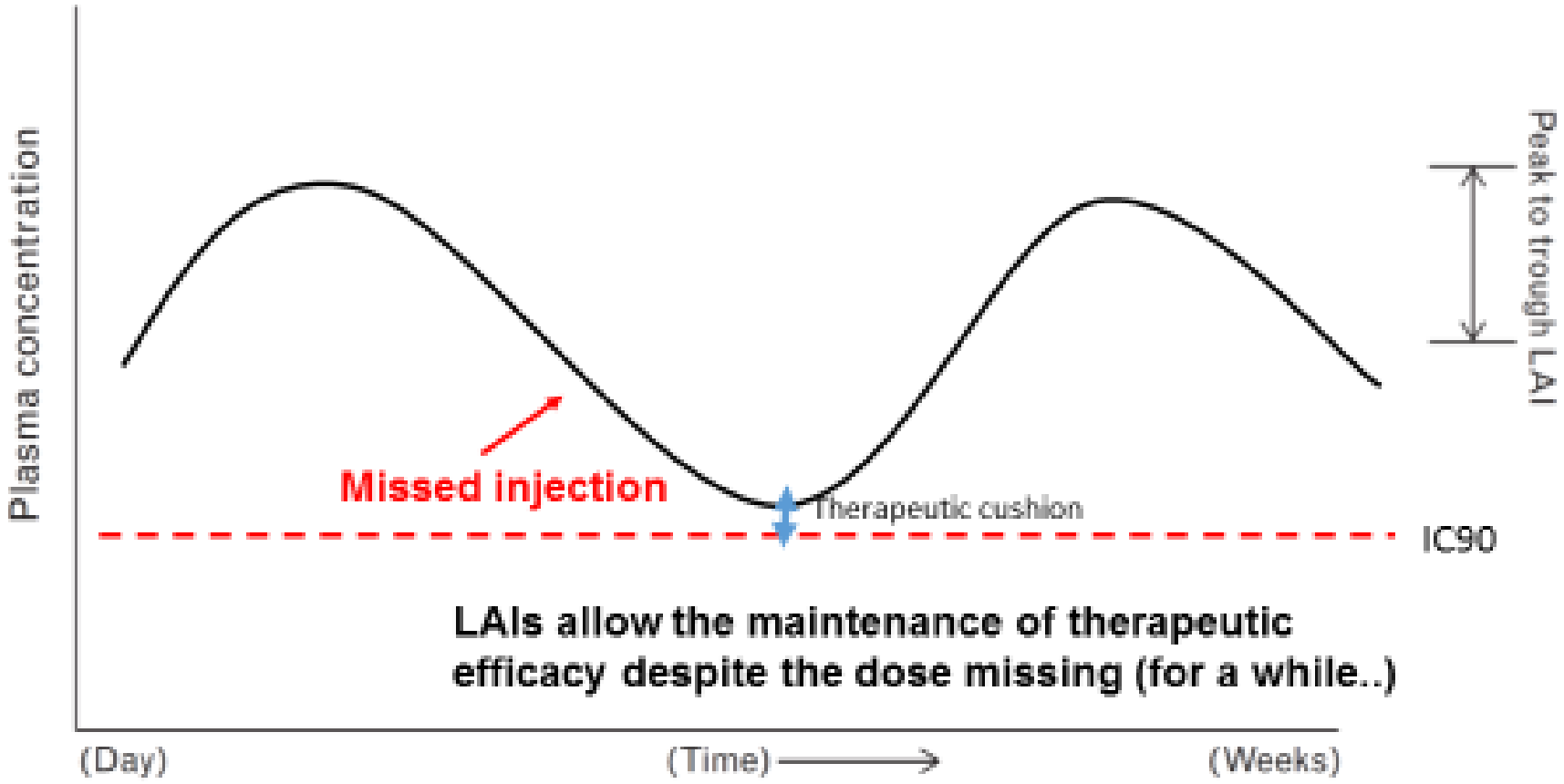


Both Q8W and Q4W comparable to Oral CAB at Week 48[a]

[a]Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Injectable long-acting: phase 3 studies now planned using 4-weekly injections

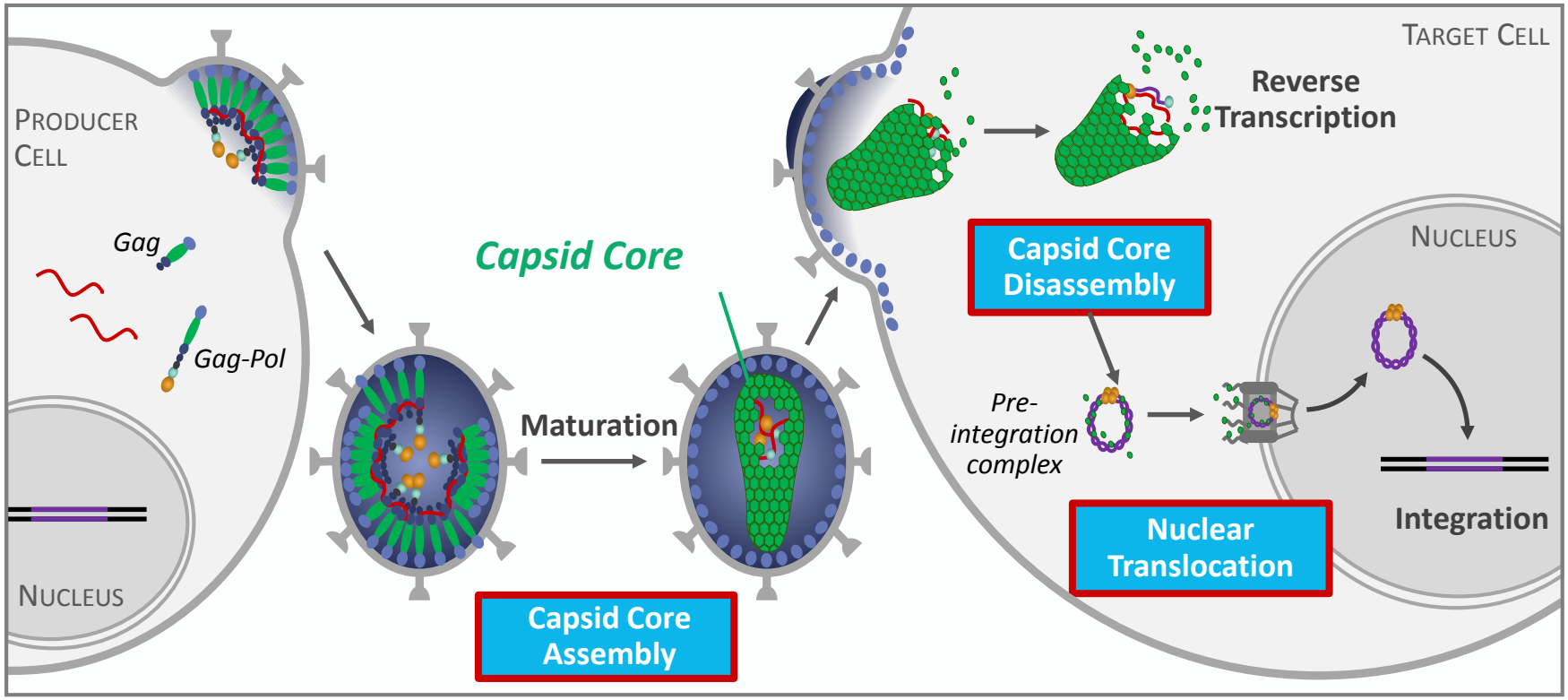
Margolis IAS 2016 #THAB0206LB



Hickey MB et al. Curr Opin Infect Dis. 2015

HIV Capsid Acts at Multiple Stages in the Viral Life Cycle

- GS-CA1 inhibits HIV capsid function, resulting in aberrant core assembly/disassembly via multiple steps in HIV replication cycle



Tse W, et al. CROI 2017. Seattle, WA. Oral #38

HIV Capsid Acts at Multiple Stages in the Viral Life Cycle

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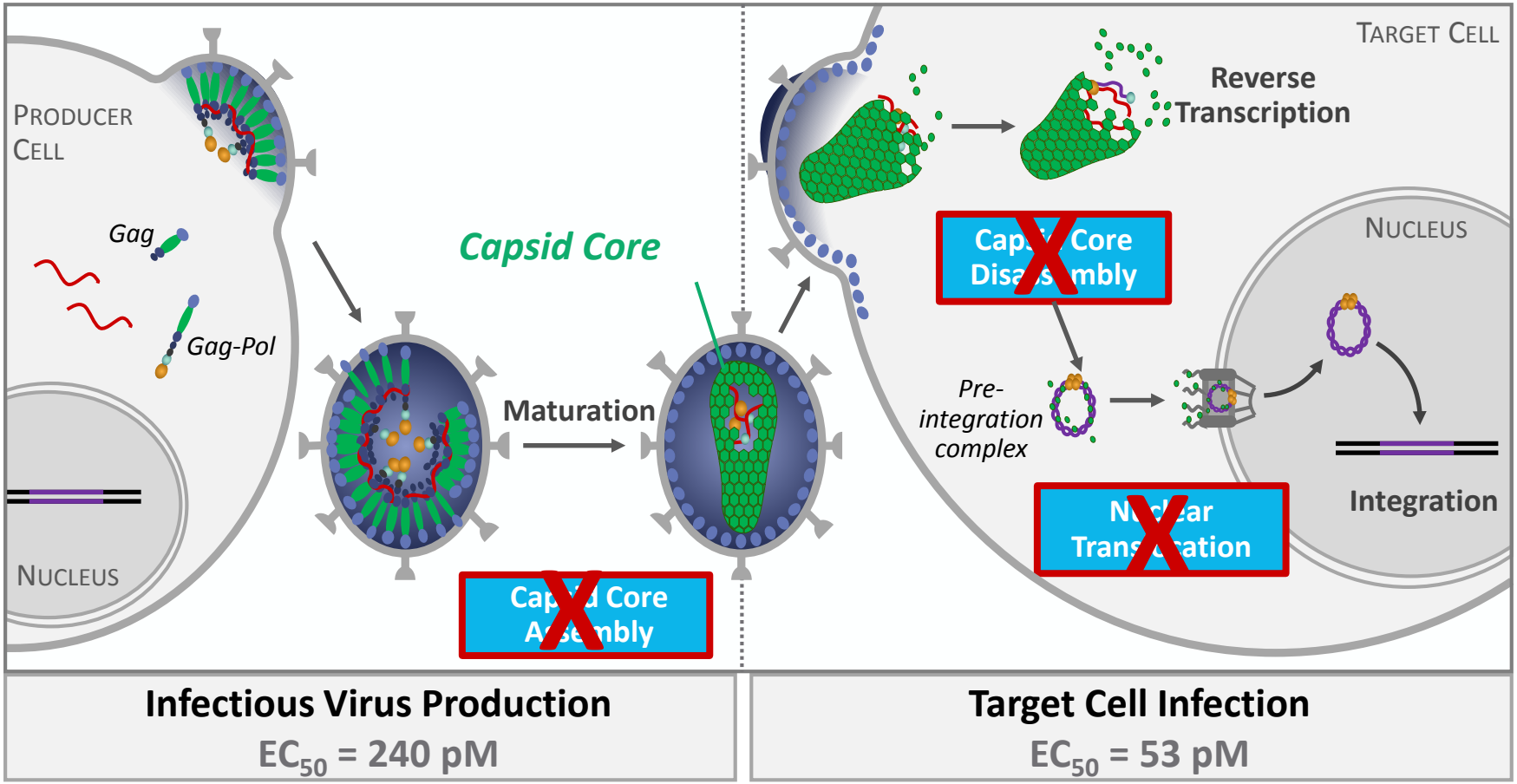
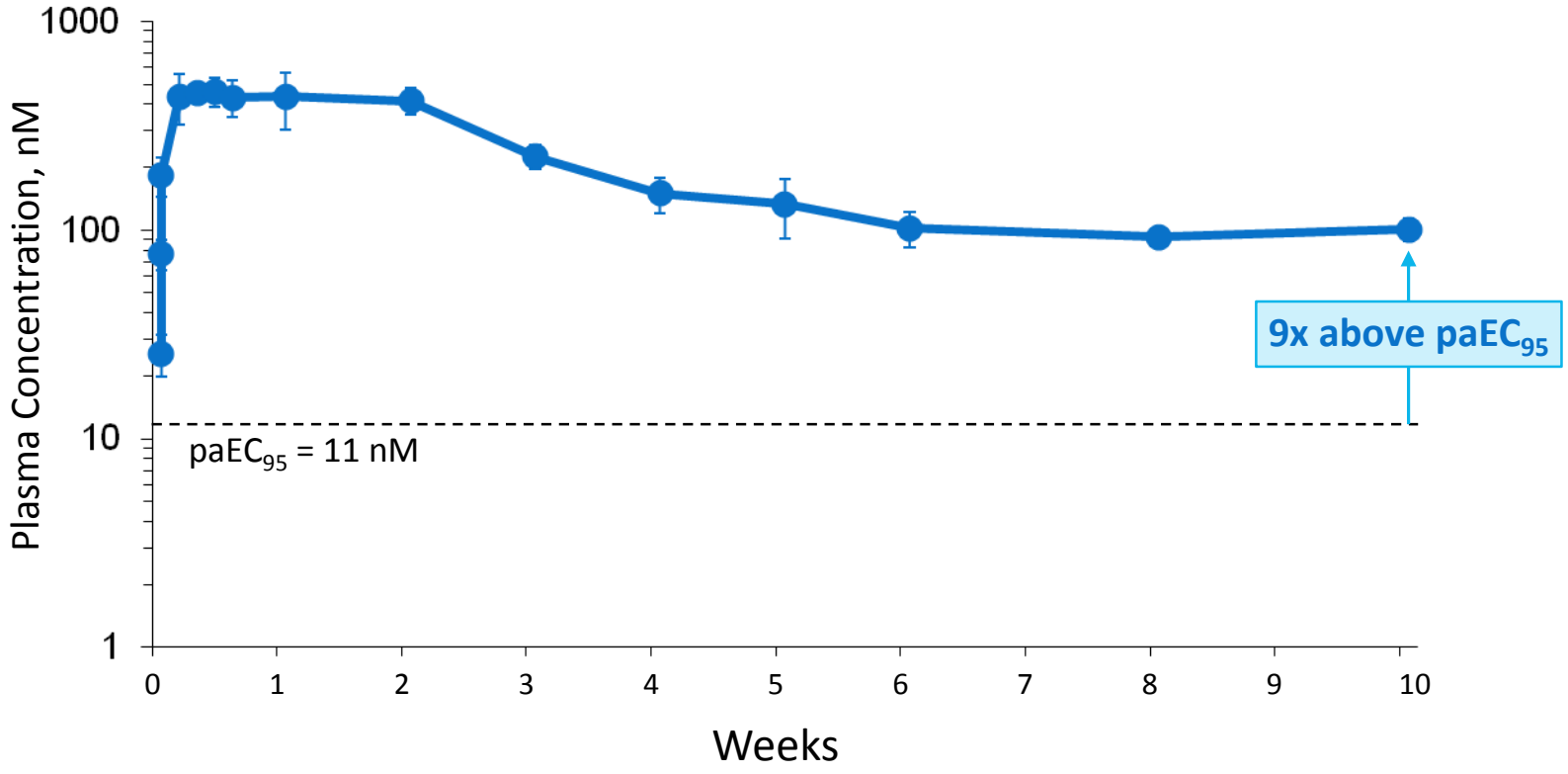


- For a full single round of replication the EC_{50} is 85 pM

Tse W, et al. CROI 2017. Seattle, WA. Oral #38.

GS-CA1 Pharmacokinetics in Rats Extended Release Formulation

- Single subcutaneous injection maintains plasma concentrations well above $paEC_{95}$ for >10 weeks in rats

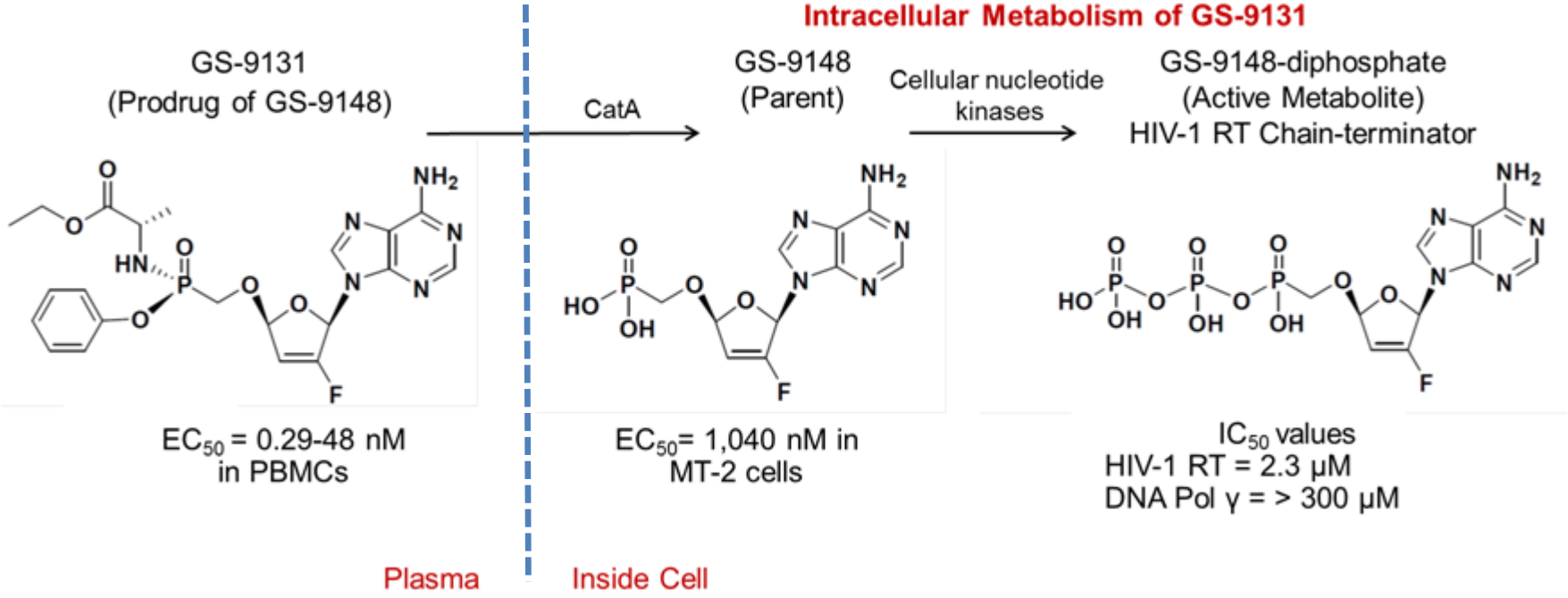


- Potential for a monthly dosing interval or longer in humans

paEC95, plasma-binding-adjusted effective concentration required to inhibit replication by 95%

Tse W, et al. CROI 2017. Seattle, WA. Oral #38.

GS-9131: A Novel NtRTI with a Broad Resistance Profile



- GS-9131 is a prodrug of the novel NtRTI GS-9148 that is phosphorylated and inhibits HIV-1 reverse transcription by chain termination[1]
- GS-9131 has low potential for mitochondrial toxicity and renal accumulation[2]
- GS-9131 has broad in vitro activity against HIV-1 and HIV-2[1]

1. Cihlar T, et al. AAC 2008;52(2):655-665
2. Cihlar T, et al. AAC 2009;53(1):150-156

White K, et al. CROI 2017. Seattle, WA. Poster #436

Susceptibility of HIV-1 with NRTI Resistance to GS-9131

NRTI Mutation	Susceptibility of HIV-1 to ARVs (Fold-change vs WT)							
	GS-9131	GS-9148	TFV	FTC	ABC	ddI	ZDV	d4T
K65R	0.56	0.66	1.98	8.22	2.46	1.87	0.23	1.22
M184V	0.31	0.43	0.47	>110	2.82	1.29	0.19	0.61
L74V	0.61	0.66	0.57	1.30	1.93	1.34	0.22	0.86
L74I	0.67	0.75	0.82	0.92	1.13	0.90	0.40	0.74
K65R+M184V	0.40	0.42	1.20	>110	7.72	3.16	0.17	0.85
K70E+M184V	0.28	0.31	0.58	>110	6.19	1.52	0.10	0.60
L74V+M184V	0.40	0.38	0.35	>110	6.41	2.35	0.12	0.73
4-TAM (4Y)	0.68	0.69	1.69	3.60	2.15	1.05	9.85	1.51
4-TAM (4F)	0.73	0.83	1.36	3.88	1.57	0.96	9.60	1.38
4-TAM (4Y)+M184V	0.41	0.45	0.85	>110	4.66	1.35	1.91	1.35
6 TAMs	1.50	1.65	4.2	5.70	4.70	1.86	379	3.20
6TAMs+M184V	0.75	0.85	2.07	>110	9.60	1.96	32	2.54
T69-insertion+4TAMs	1.11	1.39	5.70	7.68	5.59	3.1	>664	3.57
Q151M	0.97	0.89	0.78	1.40	3.59	3.99	1.97	3.20
Q151M Complex	3.79	3.79	1.53	4.67	6.96	8.22	46	10
Q151M Complex+M184V	0.88	0.96	1.24	>110	>35	13	88	7.06

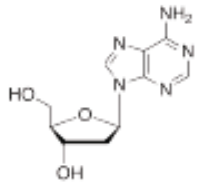
Color coding uses Monogram PhenoSenseGT cut-offs, with GS-9131 and its prodrug GS-9148 arbitrarily set at 2.5-fold.

GS-9131 exhibited potent activity against HIV-1 with most patterns of NRTI resistance

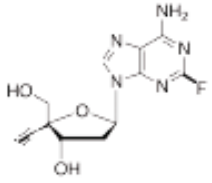
White K, et al. CROI 2017. Seattle, WA. Poster #436

MK-8591 Concentrations at Sites of HIV Transmission and Replication

EFdA is a novel, 4′-modified nucleoside analog inhibitor



dA
(2′-deoxyadenosine)



EFdA (MK-8591)
(4′-ethynyl-2-fluoro-2′-deoxyadenosine)
PubChem CID: 6483431

- The levels of MK-8591-TP achieved in both rectal and vaginal tissue are comparable to the levels of tenofovir diphosphate observed in rectal tissue from human subjects treated with tenofovir disoproxil fumarate
- Given the significantly greater potency of MK-8591 (IC_{50} = 0.2 nM) compared with TDF (IC_{50} = 73 nM), these data suggest utility of MK-8591 for prophylaxis in both men and women
- As lymphoid tissues are sites of active HIV replication and persistence, the observation that MK-8591 is enriched in lymphoid tissues in rats suggests the potential to address the ongoing replication of HIV in lymph nodes

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440

Antiviral Activity of EFdA Against NRTI-Sensitive and -Resistant Strains of HIV-2

Vincent H. Wu[1], Robert A. Smith[1], Sara Masoum[1], Dana N. Raugi[1], Selly Ba[2], Moussa Seydi[2], Jay Grobler[3], and Geoffrey S. Gottlieb[1,4]
for the University of Washington-Dakar HIV-2 Study Group

[1]Department of Medicine, Division of Allergy and Infectious Diseases and [4]Department of Global Health, University of Washington, Seattle, Washington, USA
[2]Clinique des Maladies Infectieuses Ibrahima DIOP Mar, Centre Hospitalier Universitaire de Fann, Universite Cheikh Anta Diop de Dakar, Dakar, Senegal
[3]Merck & Co., Inc., West Point, Pennsylvania, USA

correspondence: smithra@uw.edu

EFdA is a nucleoside reverse transcriptase translocation inhibitor (NRTTI). It is highly active against HIV-1 in culture, with EC50 values in the low nanomolar to picomolar range and negligible cytotoxicity

As observed for HIV-1, K65R mutants of HIV-2_{ROD9} are hypersusceptible to EFdA. K65R+Q151M mutants of HIV-2 are also hypersusceptible to the drug.

The M184V change in HIV-2_{ROD9} confers a 20-fold shift in the potency of EFdA, but the EC_{50} for the mutant virus is only 3-fold higher than the mean EC_{50} for HIV-1. Addition of other NRTI resistance changes in combination with M184V does not increase the level of EFdA resistance in HIV-2.

MK-8591 Concentrations at Sites of HIV Transmission and Replication

Abstract

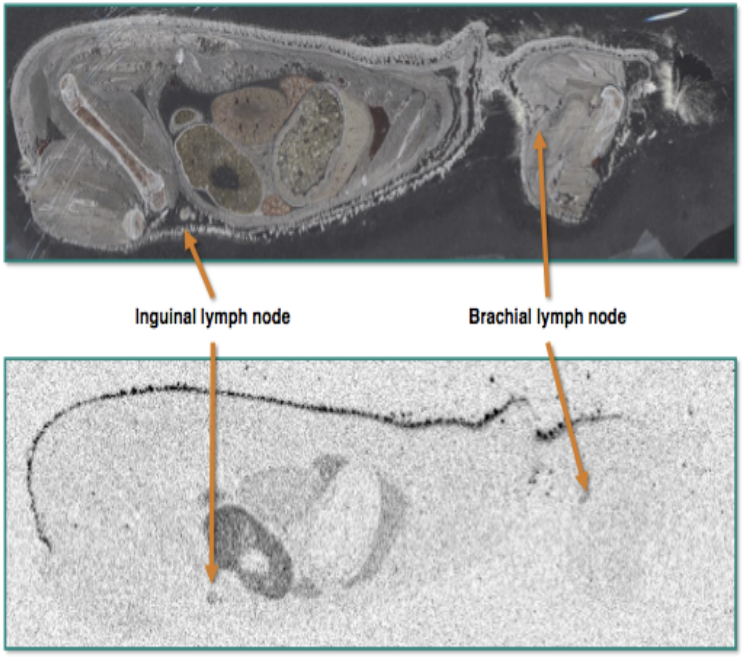
Background: MK-8591 is a long-acting nucleoside reverse transcriptase translocation inhibitor (NRTTI) that has demonstrated potent antiviral activity in HIV-1–infected subjects administered a once-weekly (QW) 10-mg dose as monotherapy in a clinical trial and in SIV-infected rhesus macaque models. MK-8591 extended-duration dosing potential was suggested by the long intracellular half-life of MK-8591-triphosphate (MK-8591-TP) in peripheral blood mononuclear cells (PBMCs) in vitro and in preclinical models. Here we describe the tissue distribution of MK-8591 and its anabolites in rats by quantitative whole-body autoradiography and in rhesus vaginal and rectal mucosa by biopsy.

Methods: Wistar Hannover rats dosed orally at 50 mpk (mg/kg) of [^{14}C]MK-8591 were sacrificed at 0.5 hours and 24 hours, cryosectioned (40 µm thick sagittal), and phosphor imaged after a 4 day exposure. Radioactivity in tissues was quantified using the blood standards along with Raytest AIDA image analysis software. For rectal and vaginal tissue distribution studies, monkeys were dosed 3.9 mpk orally on Days 1 and 8. PBMCs were isolated from blood collected at Days 1, 7, 14, and 21. Colorectal and vaginal biopsies were collected on Days 7 (predose) and 14, pooled separately, and snap-frozen with liquid nitrogen. PBMC and biopsy samples were analyzed by LC-MS/MS.

Results: In rat, MK-8591-related material distributed widely within 30 minutes of dosing and was notably enriched in lymphoid tissue (75.9 nmol-eq/g) compared with blood (lymph node:blood ratio = 2.7). In rat, MK-8591-related material remained enriched in lymphoid tissue at 24 hours (11.1 nmol-eq/g; lymph node:blood ratio = 7.1). In rhesus macaques, on Days 7 and 14, levels of MK-8591-TP in rectal tissue (36 pmol/g and 31 pmol/g) were similar to those measured in vaginal tissue (49 pmol/g and 78 pmol/g).

Conclusions: The levels of MK-8591-TP achieved in both rectal and vaginal tissue are comparable to the levels of tenofovir diphosphate observed in rectal tissue from human subjects treated with tenofovir disoproxil fumarate. Given the significantly greater potency of MK-8591 (IC_{50} = 0.2 nM) compared with TDF (IC_{50} = 73 nM), these data suggest utility of MK-8591 for prophylaxis in both men and women. In addition, as lymphoid tissues are sites of active HIV replication and persistence, the observation that MK-8591 is enriched in lymphoid tissues in rats suggests the potential to address the ongoing replication of HIV in lymph nodes.

QWBA Study [^{14}C]MK-8591 in Male Rats at 24 Hours After 50 mg/kg P.O. Single Dose



Top: Scanned optical image of 40 µm male rat whole body sagittal sections. Re

Novel HIV PI With High Resistance Barrier and Potential for Unboosted QD Oral Dosing

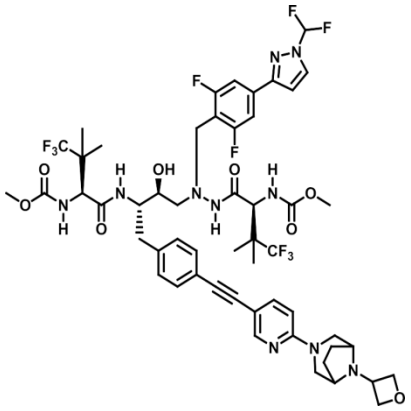
GS-PI1:

- A novel, potent HIV PI
- Has an improved resistance profile, with high activity against DRV and ATV resistance associated mutations
- Prevents viral breakthrough in vitro at inhibitory quotient of 1
- Has long PK t1/2 in rat and dog
  - 14 hours compared to 0.4 and 1 hour for DRV and ATV, respectively
- Is highly metabolically stable in human liver microsomes
- Has the potential for unboosted QD dosing

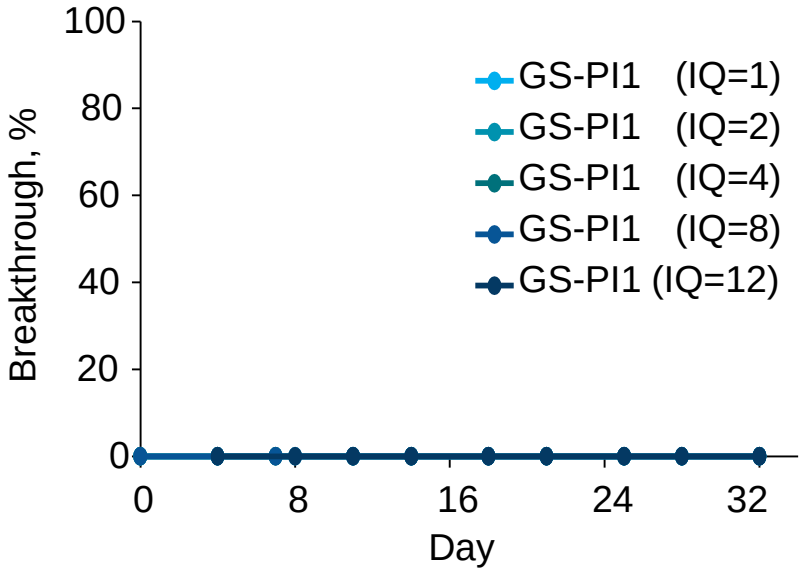
Represents a new generation of HIV PIs with potential for combination in an unboosted single-tablet regimen for HIV treatment

Link J, et al. CROI 2017. Seattle, WA. Poster #433

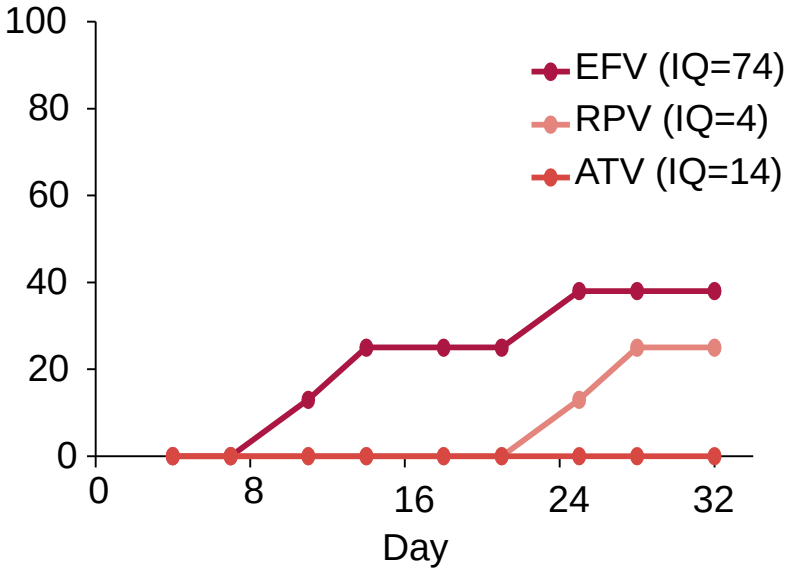
GS-PI1 Is a Novel Potent PI with a High Barrier to Resistance



	GS-PI1	DRV	ATV
EC_{50}, nM	6.8	7.2	9.7
EC_{95}, nM	11.4	19.9	25
Protein adjusted EC_{95}, nM	353	42	75



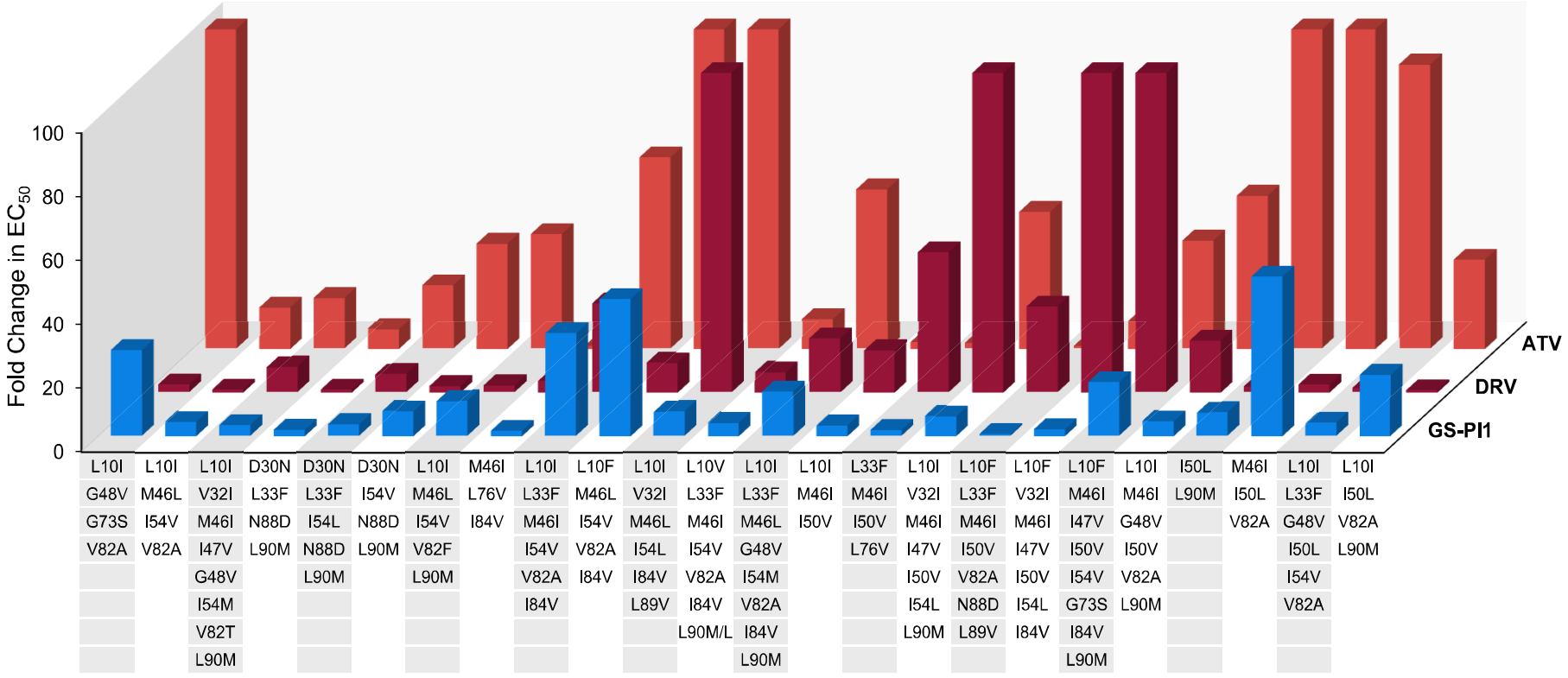
- GS-PI1 does not show breakthrough at IQ of 1 in MT2 cells over 32 days



- EFV and RPV breakthrough at their clinical IQ; ATV does not

Link J, et al. CROI 2017. Seattle, WA. Poster #433

GS-PI1: Fold Change vs Wild Type for Clinically Relevant RAMs



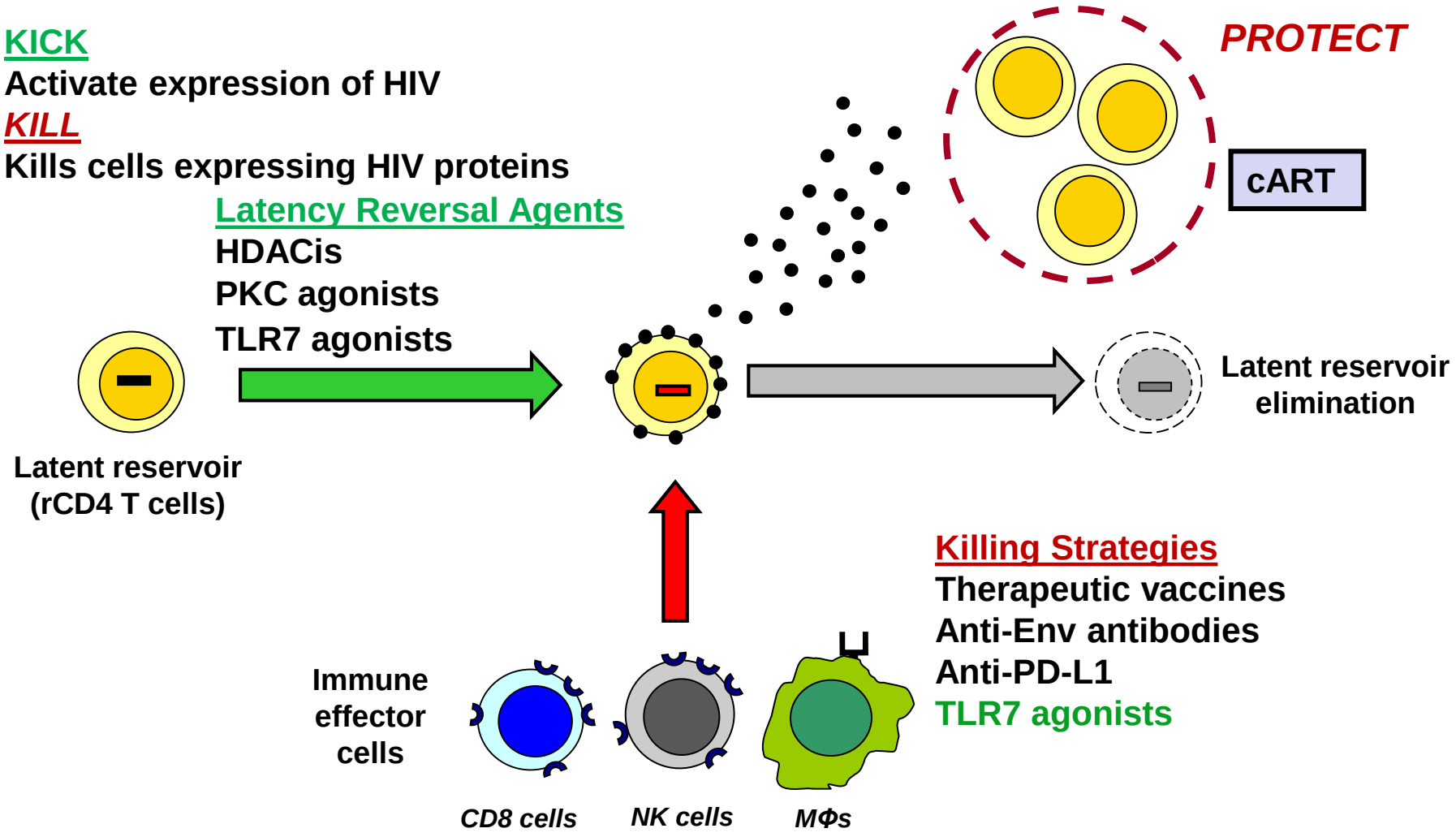
Mutant Virus

GS-PI1 has an improved resistance profile, with high activity against most DRV and ATV RAMs

Link J, et al. CROI 2017. Seattle, WA. Poster #433

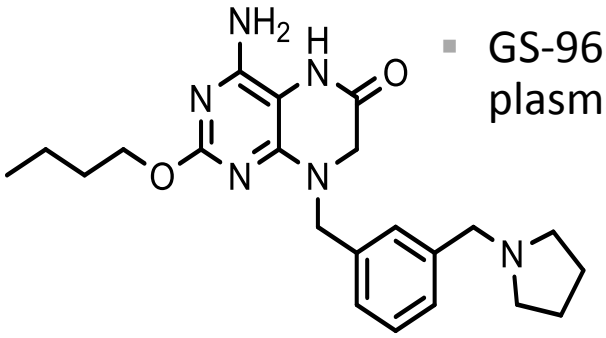
CURE

"Kick and Kill" Strategy to Eliminate Reservoirs of Latent HIV

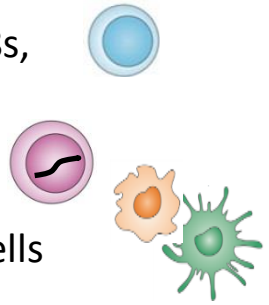


Vesatolimod (GS-9620): A Potent and Selective Toll-like Receptor 7 (TLR7) Agonist

- TLR are primarily expressed on plasmacytoid dendritic cells (DC) and B cells
- Part of the innate immune system linked to adaptive immunity
- TLR7 activation leads to increased antigen presentation, enhanced NK and CD8+ T cell activation (KILL), activation of CD4+ T cells



- GS-9620 is 30-fold selective for TLR7 over TLR8
- GS-9620 stimulates immunity to HIV through plasmacytoid DC production of type I IFNs
  - ↑ CD69 on T cells, HIV-specific polyfunctional CD8s, CD8-mediated caspase induction in targets
  - ↑ HIV production from latently infected cells
  - ↑ Antibody-mediated clearance of HIV-infected cells



- Phase 1b study ongoing in HIV infected ART-suppressed adults to assess GS-9620 safety and effects on the HIV reservoir

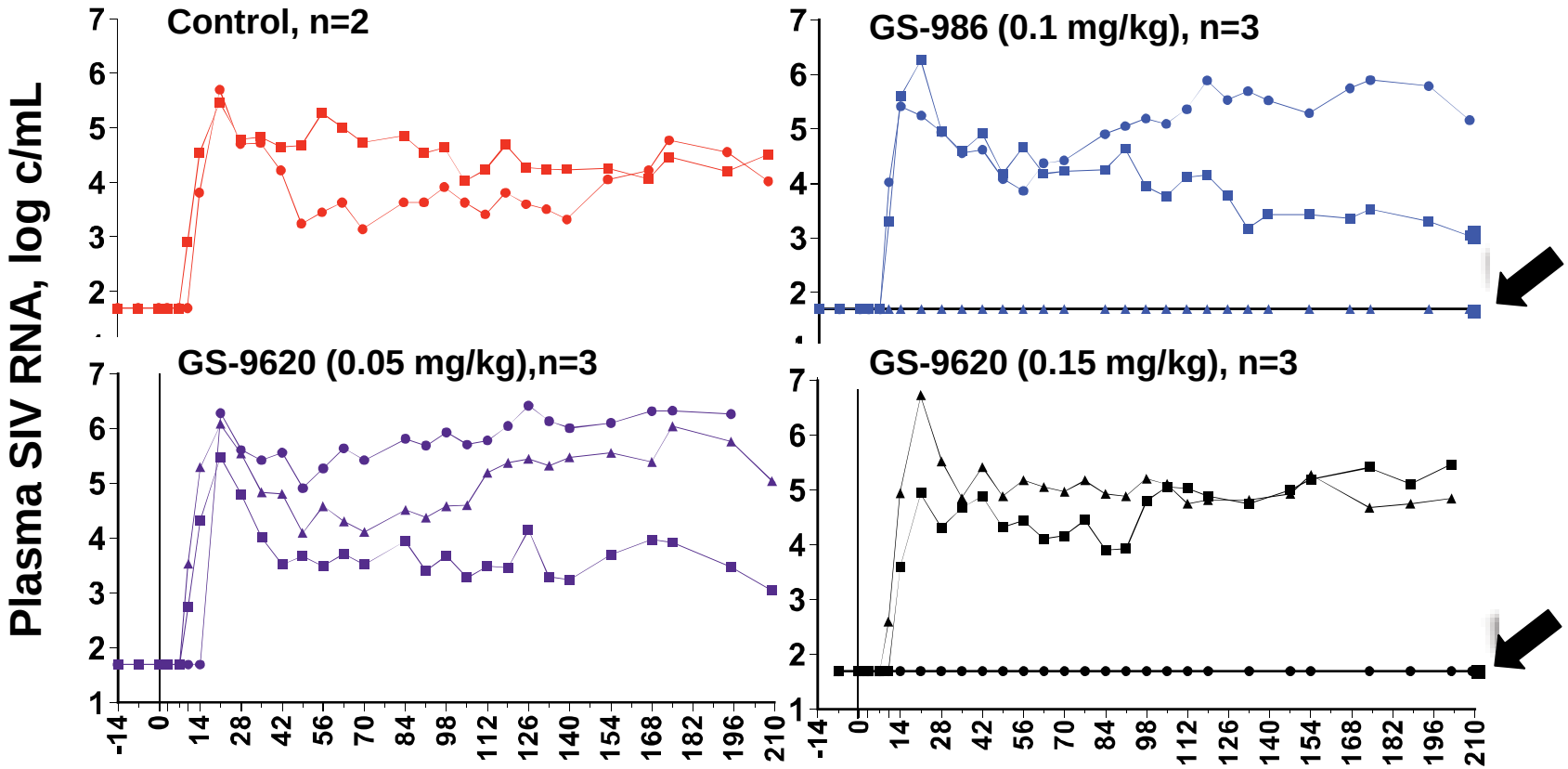
IFN, interferon; NK, natural killer

Irrinki A, et al. CROI 2017. Seattle, WA. Oral #118

Virologic Outcomes in Rhesus Macaques treated with TLR7 Agonists GS-986 and GS-9620

Evaluation of TLR7 agonists GS-986 and GS-9620 in SIV+ Rhesus macaques (N=11)

- After ART discontinuation SIV+ ART-suppressed macaques* had
  - Lower viral set-point after rebound
  - Induce durable long-term remission (2/9; ➘)



* Each line represents one macaque.

Lim SY, et al. CROI 2017. Seattle, WA. Poster #338LB

In Vivo Evidence for TLR-7 Agonist-Mediated SIV Remission

Comparison of SIV+ Rhesus macaques with viremia (n=7) and the 2 aviremic macaques after administration of TLR7 agonists GS-986 and GS-9620 and ART discontinuation

In Vitro Viral Outgrowth & Co-culture

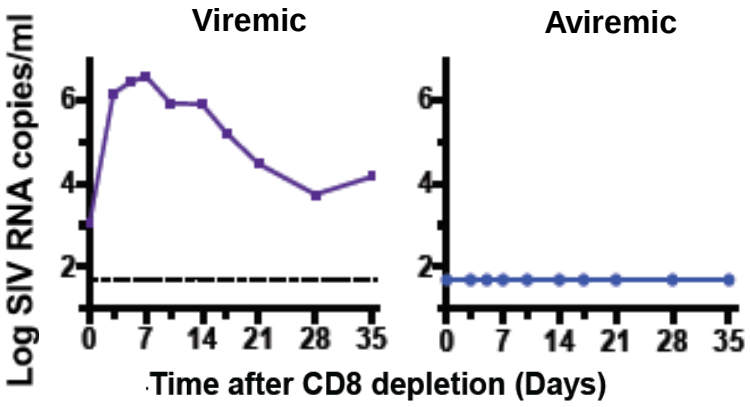
- No recovery of replication competent virus from PBMCs & no infectivity demonstrated

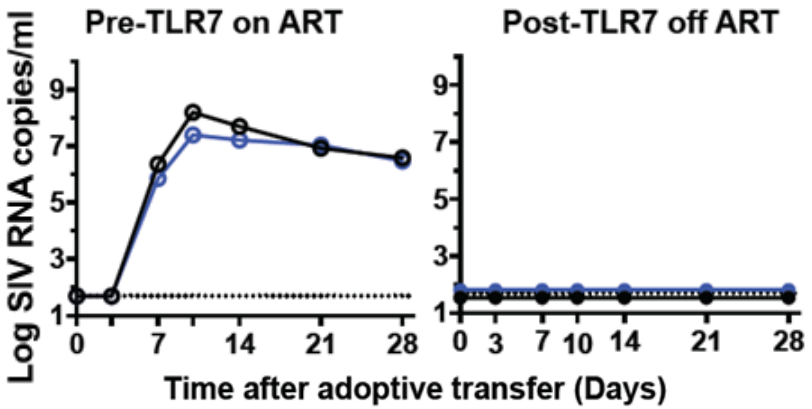
In Vivo CD8 Depletion

- Viremic macaques experienced rebound
- Both aviremic macaques did not have SIV RNA rebound

Adoptive Transfer: Infusion of Cells from Aviremic to Naïve Macaques

- Only mononuclear cells from pre-TLR-7 agonist treatment could infect naïve macaques
- Cells isolated 448 days after ART discontinuation (post-TLR-7 agonist treatment) did not induce SIV infection in naïve macaques





In vivo experiments indicate that 2 Rhesus macaques are in remission due to TLR7 agonist treatment

Lim S-Y, et al. CROI 2017. Seattle, WA. Poster #338LB

Antiretroviral Therapy: The Future

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Long Acting Injectable?

Integrase Era

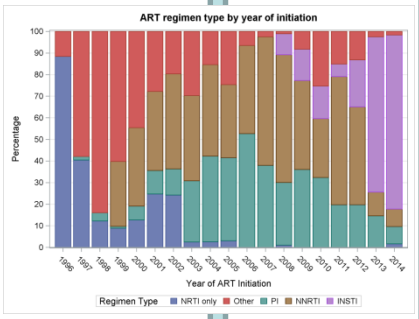
Single Tablet Regimens

Triple Drug Therapy

ZDV/3TC

ZDV monotherapy

HIV-1 discovered



1983 1987 1995 1996 2006 2012-13 2017 2020

Slide courtesy of Joe Eron, MD

MEDICI
CON L'AFRICA
CUAMM

la salute è un diritto, battersi per il suo rispetto è un dovere