Progetto di Formazione PANDORA ID-23
Milano, 25 settembre 2023

TERAPIA ANTIVIRALE: NUOVE STRATEGIE TERAPEUTICHE TRA PRESENTE E FUTURO

TERAPIA ANTIRETROVIRALE ORALE: THE NEVER ENDING STORY

Diego Ripamonti
Malattie Infettive - Bergamo

dichiarazione sul conflitto d'interessi

Il sottoscritto **RIPAMONTI DIEGO**
in qualità di relatore

ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
Janssen, Merck, Gilead, ViiV Healthcare

HIV pharmacology history

- **Plasma HIV RNA**
- HAART regimens
- Higher genetic barrier
- Lower toxicity
- Better tolerability
- Coformulations

Mile stones in HIV therapy

Treat «just those who need it»

⇩

Treat All (2016)


➢ Protease inhbitor (PI) → HAART


➢ ritonavir-boosted PI


➢ NNRTI: efavirenz


➢ Coformulations (STR)


➢ Integrase inhibitors


➢ 2DR


➢ Oral LA?

enfuvirtide: sc injections (bid)

CCR5 inhibitor: maraviroc

The New England
Journal of Medicine

VOLUME 337 SEPTEMBER 11, 1997 NUMBER 11

A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

SCOTT M. HAMMER, M.D., KATHLEEN E. SQUIRES, M.D., MICHAEL D. HUGHES, PH.D., JANET M. GRIMES, M.S.,

- ✓ Adults previously treated with zidovudine with CD4 < 200 cells.
- ✓ **(AZT** tid+ **3TC** bid) + IDV tid or placebo
- ✓ Primary end-point: AIDS or death

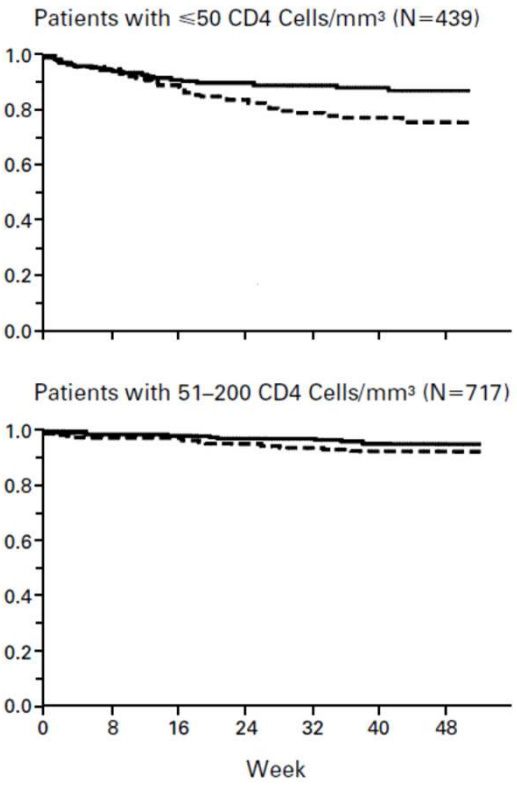


Figure 1. Kaplan–Meier Estimates of the Proportion of Patients Who Did Not Reach the Primary Study End Point of AIDS or Death.

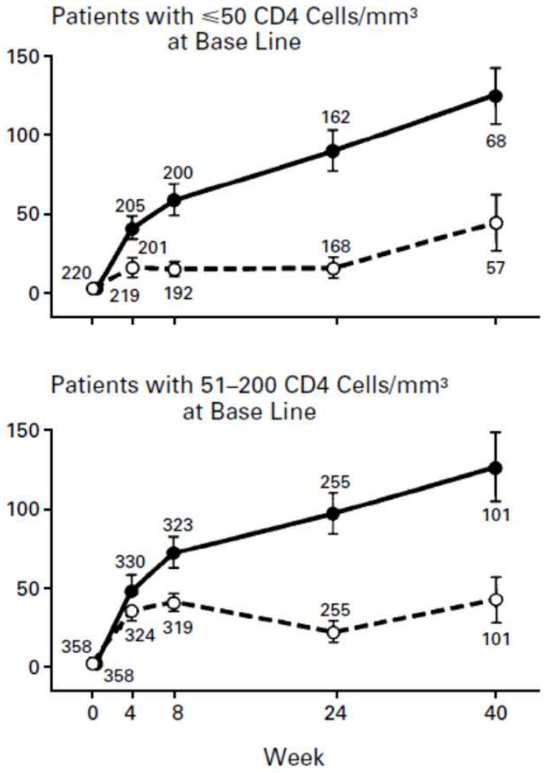


Figure 2. Mean Changes from Base Line in the CD4 Cell Count. The number of patients who could be evaluated at each time point is shown. Bars indicate 95 percent confidence intervals.

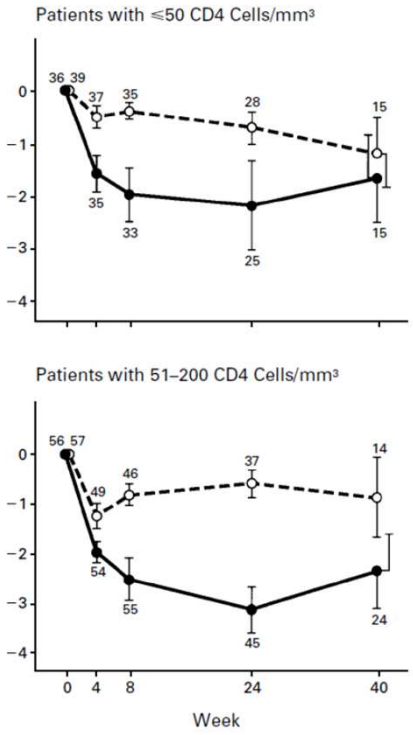


Figure 3. Mean Change from Base Line in the Plasma HIV-1 RNA Concentration.

For this analysis, 190 patients were randomly selected and their HIV-1 RNA concentrations were studied. The number of patients who could be evaluated at each time point is shown. Bars indicate 95 percent confidence intervals.

The New England
Journal of Medicine

VOLUME 338 MARCH 26, 1998 NUMBER 13

DECLINING MORBIDITY AND MORTALITY AMONG PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

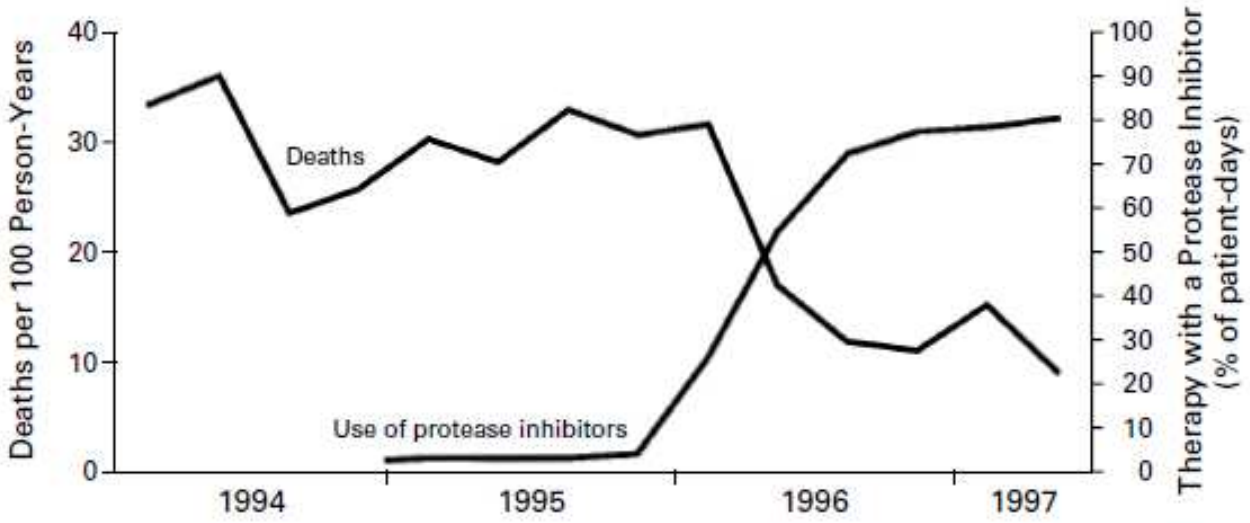


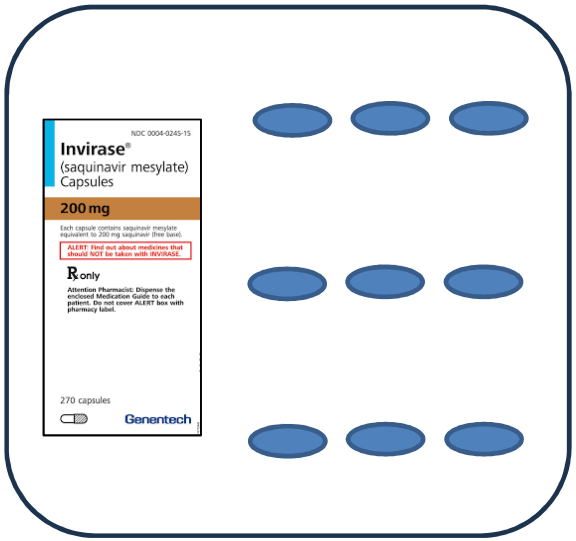
Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Palella FJ, Jr., Delaney KM, Moorman AC, et al. NEJM1998;338(13):853–860.

Protease inhibitor Era: HAART as a triple regimen.

ritonavir

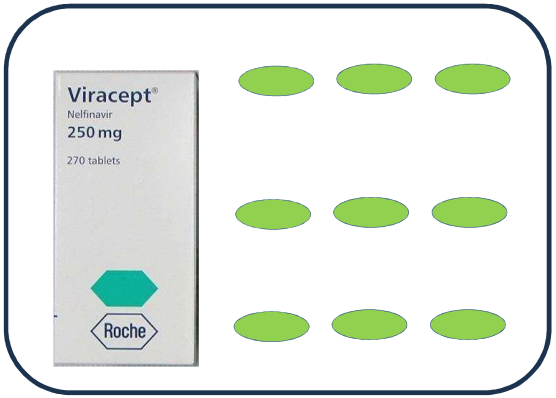
saquinavir



with fat food
bioavailability: 4%
GI intolerance

indinavir

empty stomach
drink 2 l/day



2NRTIs + 3rd drug = HAART

LOPINAVIR–RITONAVIR VERSUS NELFINAVIR FOR THE INITIAL TREATMENT OF HIV INFECTION

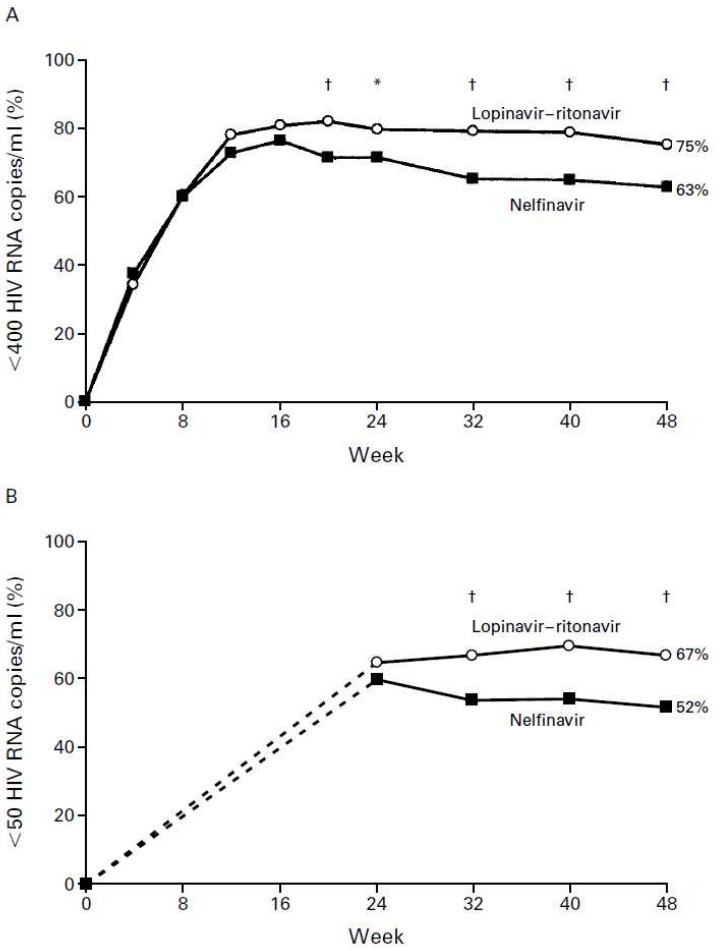
SHARON WALMSLEY, M.D., BARRY BERNSTEIN, M.D., MARTIN KING, PH.D., JOSÉ ARRIBAS, M.D., GILDON BEALL, M.D., PETER RUANE, M.D., MARGARET JOHNSON, M.D., DAVID JOHNSON, M.D., RICHARD LALONDE, M.D., ANTHONY JAPOUR, M.D., SCOTT BRUN, M.D., AND EUGENE SUN, M.D., FOR THE M98-863 STUDY TEAM*

TABLE 1. SUMMARY OF BASE-LINE CHARACTERISTICS.*

CHARACTERISTIC	LOPINAVIR–RITONAVIR PLUS LAMIVUDINE AND STAVUDINE (N=326)	NELFINAVIR PLUS LAMIVUDINE AND STAVUDINE (N=327)
Sex — no. (%)		
Male	260 (80)	264 (81)
Female	66 (20)	63 (19)
Race or ethnic group — no. (%)		
Non-Hispanic white	184 (56)	190 (58)
Non-Hispanic black	81 (25)	83 (25)
Hispanic	48 (15)	37 (11)
Asian or Pacific Islander	8 (2)	12 (4)
Native American or Alaskan Native	3 (1)	3 (1)
Mixed race	2 (1)	2 (1)
Age — yr		
Mean	38.4±9.7	37.3±8.9
Range	19–84	20–68
Weight — kg		
Mean	73.4±14.4	74.4±14.8
Range	38.5–136.1	42.5–149.0
HIV RNA — $\log_{10}$ copies/ml		
Mean	4.89±0.75	4.92±0.74
Median	5.01	4.98
Range	2.60–6.82	2.79–6.84
CD4+ cell count — cells/mm³		
Mean	260±214	258±196
Median	232	232
Range	2–944	3–949

*Plus–minus values are means ±SD.

Boosted PI and genetic barrier: the LOPINAVIR story



N Engl J Med, Vol. 346, No. 26 · June 27, 2002

The New England
Journal of Medicine

VOLUME 341 DECEMBER 16, 1999 NUMBER 25

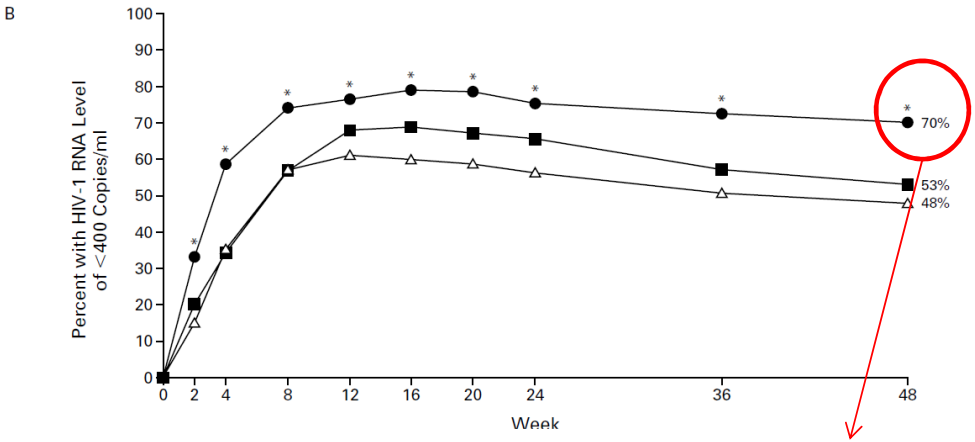
EFAVIRENZ PLUS ZIDOVUDINE AND LAMIVUDINE, EFAVIRENZ PLUS INDINAVIR, AND INDINAVIR PLUS ZIDOVUDINE AND LAMIVUDINE IN THE TREATMENT OF HIV-1 INFECTION IN ADULTS

SCHLOMO STASZEWSKI, M.D., JAVIER MORALES-RAMIREZ, M.D., KAREN T. TASHIMA, M.D., ANITA RACHLIS, M.D.,

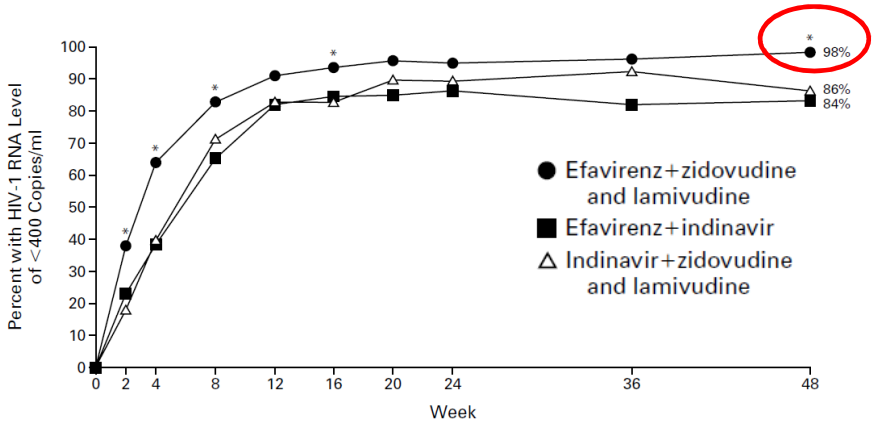
Once a day NNRTI: the EFAVIRENZ story

EFV	AZT bid	3TC bid
IDV	AZT bid	3TC bid
EFV	IDV tid	

Proportion HIV-1 RNA < 400 c/ml at week 48, ITT analysis



Proportion HIV-1 RNA < 400 c/ml at week 48, OT analysis

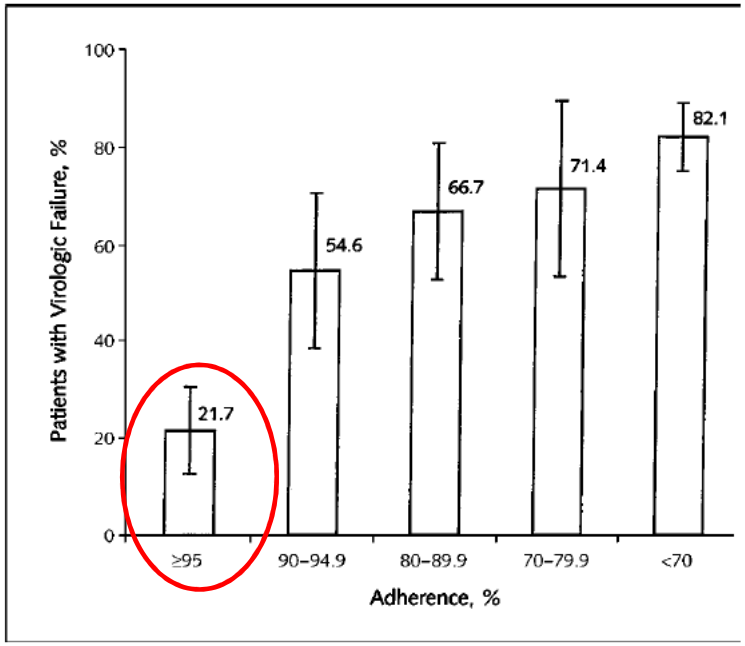


HIV RNA < 50 c/ml: 64%

Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection

David L. Paterson, MB, BS, FRACP; Susan Swindells, MD; Jeffrey Mohr, MSW; Michelle Brester, RN; Emanuel N. Vergis, MD; Cheryl Squier, RN; Marilyn M. Wagener, MPH; and Nina Singh, MD

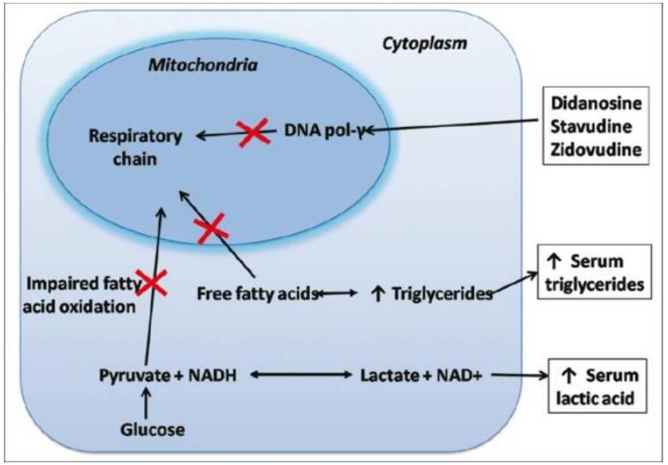
Figure 1. Adherence to antiretroviral therapy and virologic failure.

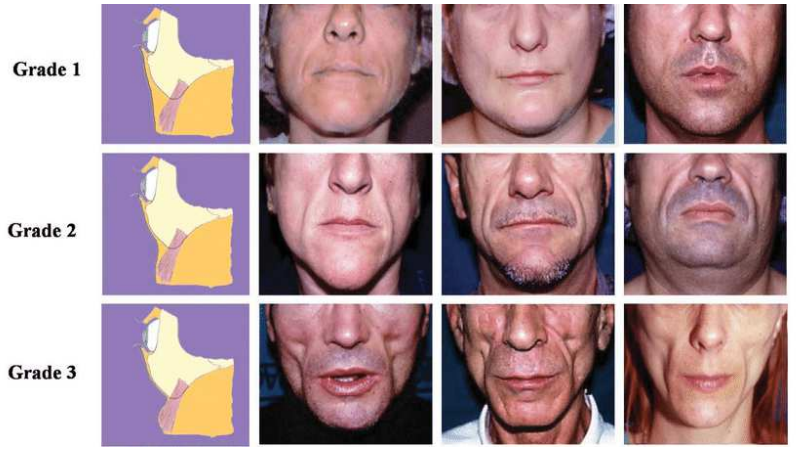


The degree of adherence was significantly associated with risk for virologic failure ($P < 0.001$). Adherence of 95% or greater was associated with the lowest incidence of virologic failure.

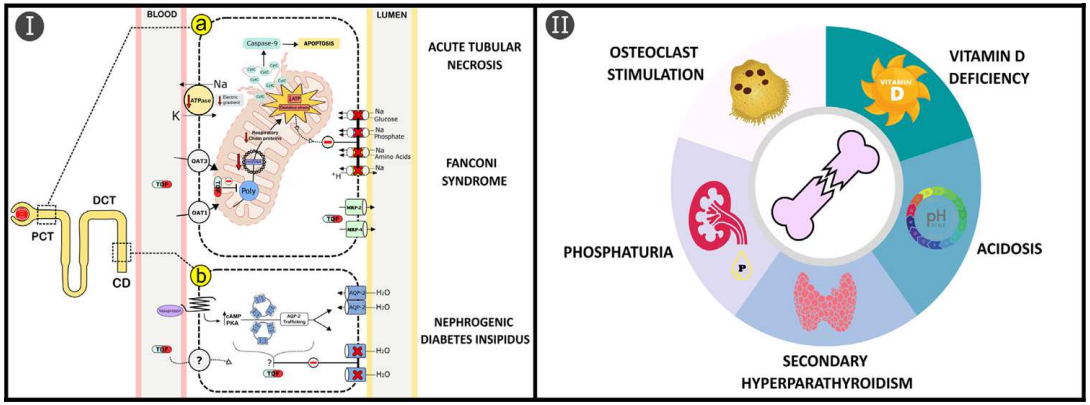
Was prescribed the following protease inhibitors at baseline, *n*	
Indinavir	23
Nelfinavir	33
Ritonavir	3
Saquinavir‡	3
Ritonavir and saquinavir‡	17
Amprenavir	2

Ann Intern Med. 2000;133:21-30.





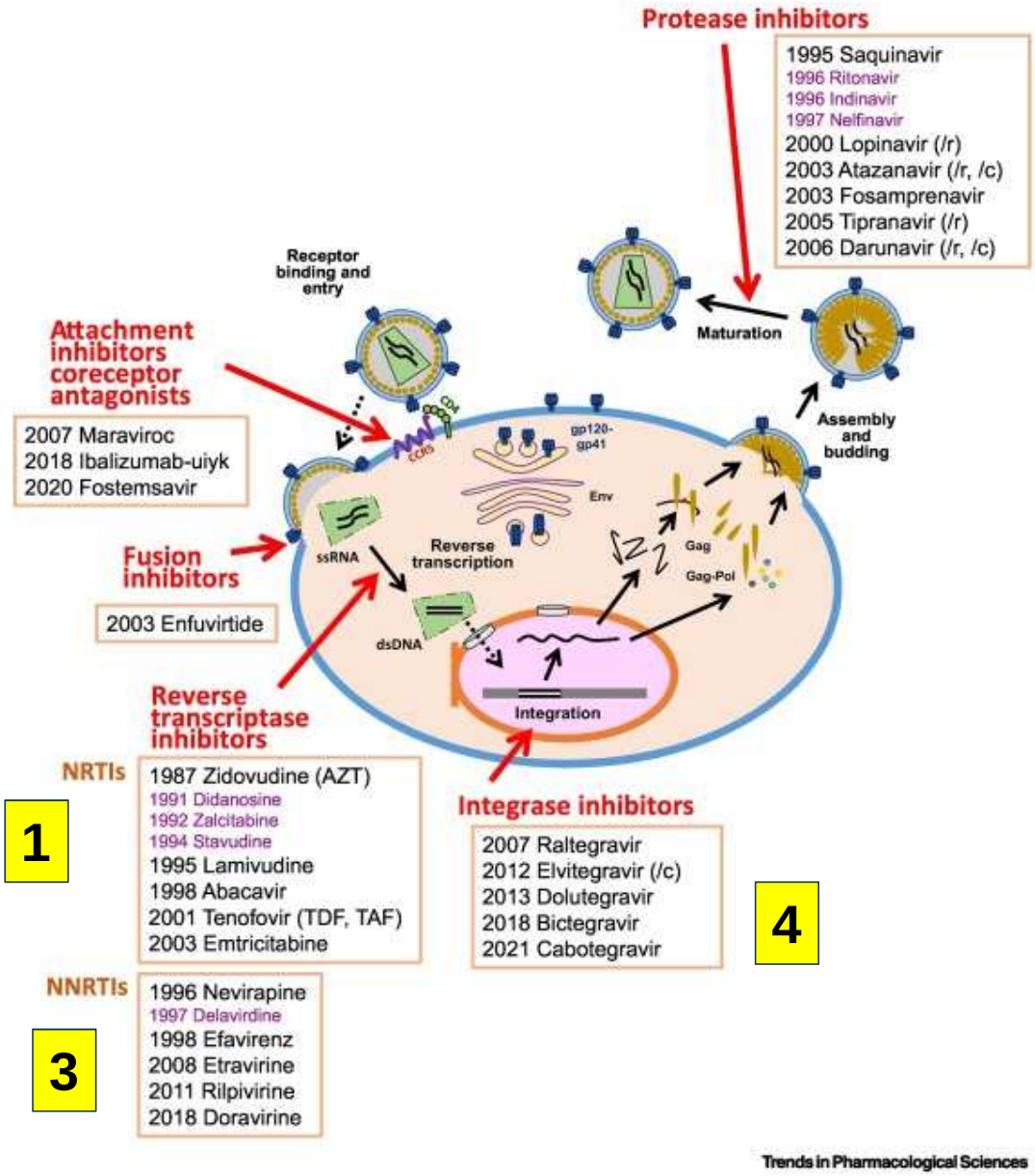
HIV Med. 2008 October ; 9(9): 731–737. d



Impact of long-term treatment with neurotoxic dideoxynucleoside antiretrovirals: implications for clinical care in resource-limited settings

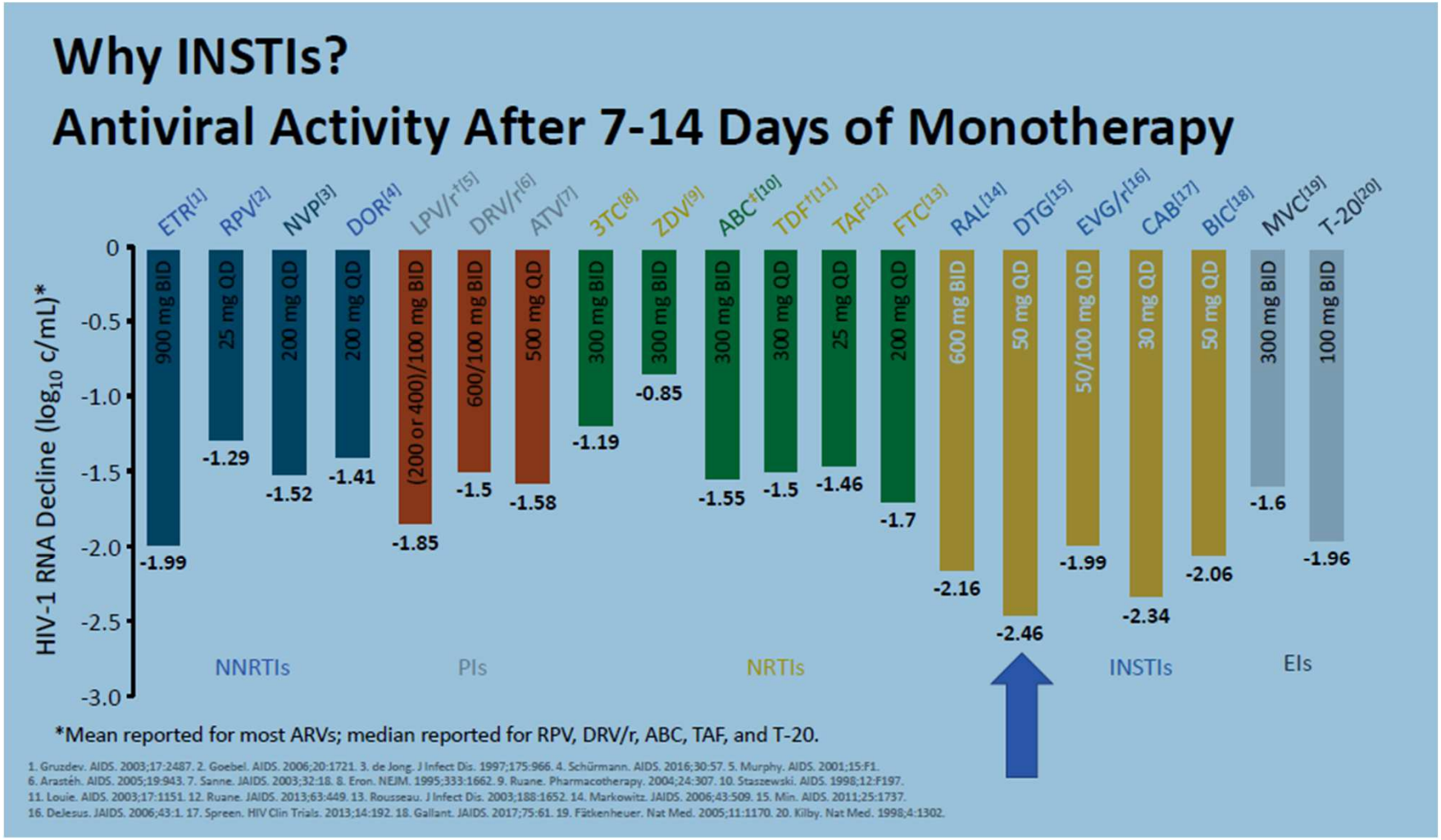
CF Hung, SA Gibson, SL Letendre, JT Lonergan, JA Marquie-Beck, F Vaida, and **RJ Ellis**
University of California, San Diego, CA, USA

Treatment fatigue



Multiple HIV targets

Antiviral decay by study drugs



1. Gruzdev. AIDS. 2003;17:2487. 2. Goebel. AIDS. 2006;20:1721. 3. de Jong. J Infect Dis. 1997;175:966. 4. Schürmann. AIDS. 2016;30:57. 5. Murphy. AIDS. 2001;15:F1. 6. Arasteh. AIDS. 2005;19:943. 7. Sanne. JAIDS. 2003;32:18. 8. Eron. NEJM. 1995;333:1662. 9. Ruane. Pharmacotherapy. 2004;24:307. 10. Staszewski. AIDS. 1998;12:F197. 11. Louie. AIDS. 2003;17:1151. 12. Ruane. JAIDS. 2013;63:449. 13. Rousseau. J Infect Dis. 2003;188:1652. 14. Markowitz. JAIDS. 2006;43:509. 15. Min. AIDS. 2011;25:1737. 16. DeJesus. JAIDS. 2006;43:1. 17. Spreen. HIV Clin Trials. 2013;14:192. 18. Gallant. JAIDS. 2017;75:61. 19. Fätkenheuer. Nat Med. 2005;11:1170. 20. Kilby. Nat Med. 1998;4:1302.

The AIDS Education and Training Center (AETC) National Coordinating Resource Center (NCRC)

HIV Medication Chart

Combination Antiretrovirals

Single-Tablet Regimens

- **Atripla**† (EFV/TDF/FTC)
- **Biktarvy** (BIC/TAF/FTC)
- **Complera** (RPV/TDF/FTC)
- **Delstrigo** (DOR/TDF/3TC)
- **Dovato** (DTG/3TC)
- **Genvoya** (EVG/COBI/TAF/FTC)
- **Juluca** (DTG/RPV)
- **Odefsey** (RPV/TAF/FTC)
- **Stribild** (EVG/COBI/TDF/FTC)
- **Symtuza** (DRV/COBI/TAF/FTC)
- **Triumeq** (DTG/ABC/3TC)

Long-Acting Injectable Regimens

- **Cabenuva** (CAB/RPV)

Regimens Used in Combination with Other HIV Medications

- **Combivir**† (ZDV/3TC)
- **Descovy** (TAF/FTC)
- **Epzicom**† (ABC/3TC)
- **Truvada**† (TDF/FTC)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

- **Emtriva***† (emtricitabine, FTC)
- **Epivir***† (lamivudine, 3TC)
- **Viread***† (tenofovir DF, TDF)
- **Ziagen***† (abacavir, ABC)
- **Vemlidy** (tenofovir alafenamide, TAF) FDA approved for HBV only

Protease Inhibitors (PI)

- **Evotaz** (ATV/COBI)
- **Kaletra*** (lopinavir/ritonavir, LPV/RTV)
- **Prezcobix** (DRV/COBI)
- **Prezista*** (darunavir, DRV)
- **Reyataz***† (atazanavir, ATV)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- **Edurant** (rilpivirine, RPV)
- **Intelence**† (etravirine, ETR)
- **Pifeltro** (doravirine, DOR)
- **Sustiva**† (efavirenz, EFV)
- **Viramune***† (nevirapine, NVP)

Entry Inhibitors

- **Rukobia** (fostemsavir, FTR) gp120 Attachment Inhibitor
- **Selzentry*** (maraviroc, MVC) CCR5 Antagonist
- **Trogarzo** (ibalizumab, IBA) Post-Attachment Inhibitor

Boosting Agents

- **Norvir***† (ritonavir, RTV)
- **Tybost** (cobicistat, COBI)

Integrase Inhibitors (INSTI)

- **Isentress***▲ (raltegravir, RAL)
- **Isentress HD** (raltegravir, RAL)
- **Tivicay*** (dolutegravir, DTG)
- **Vocabria** (cabotegravir, CAB)

All pills shown in relative size/scale. *Medication brand names appear in bold. Generic names and commonly used abbreviations appear in parentheses.*

*Also available in liquid or powder form. †Generic formulation available. ▲Chewable form available.

8/22

Infrequently Used

Protease Inhibitors (PI)

- **Aptivus*** (tipranavir, TPV)
- **Lexiva*** (fosamprenavir, FPV)
- **Viracept*** (nelfinavir, NFV)

Combination Antiretrovirals

- **Trizivir**† (ABC/3TC/ZDV)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

- **Retrovir***† (zidovudine, ZDV)

Entry Inhibitors

- **Fuzeon** (enfuvirtide, T-20) Fusion Inhibitor

Generic Formulations

- **Cimduo** (TDF/3TC)
- **Symfi** (EFV/TDF/3TC)
- **Symfi Lo** (EFV/TDF/3TC)

Discontinued Medications or Formulations

- **Agenerase** (amprenavir, APV)
- **Crixivan** (indinavir, IDV)
- **Fortovase** (saquinavir, SQV)
- **Hivid** (zalcitabine, ddC)
- **Invirase** (saquinavir, SQV)
- **Kaletra** (lopinavir/ritonavir, LPV/RTV) Soft Gel Capsule
- **Rescriptor** (delavirdine, DLV)
- **Temixys** (TDF/3TC)
- **Videx** (didanosine, ddI)
- **Videx EC** (didanosine, ddI)
- **Vitekta** (elvitegravir, EVG)
- **Zerit** (stavudine, d4T)

Helpful Hints:

- Refill prescriptions before you run out. Call for refills when you have at least 3 or 4 days left.
- Use cues as a reminder to take your pills (after a meal or favorite TV show, or before bedtime).
- Use reminder aids such as phone alarms and pillboxes. Ask your pharmacist about these.
- Plan ahead (vacations, travel, count out weekly doses).
- Do not stop taking your medications until you have spoken with your health care provider or pharmacist.
- If you have a severe reaction or in case of emergency, contact your health care provider IMMEDIATELY.

Contact Information: Provider_____

Clinic Phone_____ Pharmacy_____ Phone_____

Colorado AIDS Education & Training Center
University of Colorado, Anschutz Medical Campus
303-724-0646 • www.caetc.org
Developed by Lisa Lawrence, MSW and Steven Johnson, MD
Reviewer: Jasjit Gill, PharmD, University of Colorado

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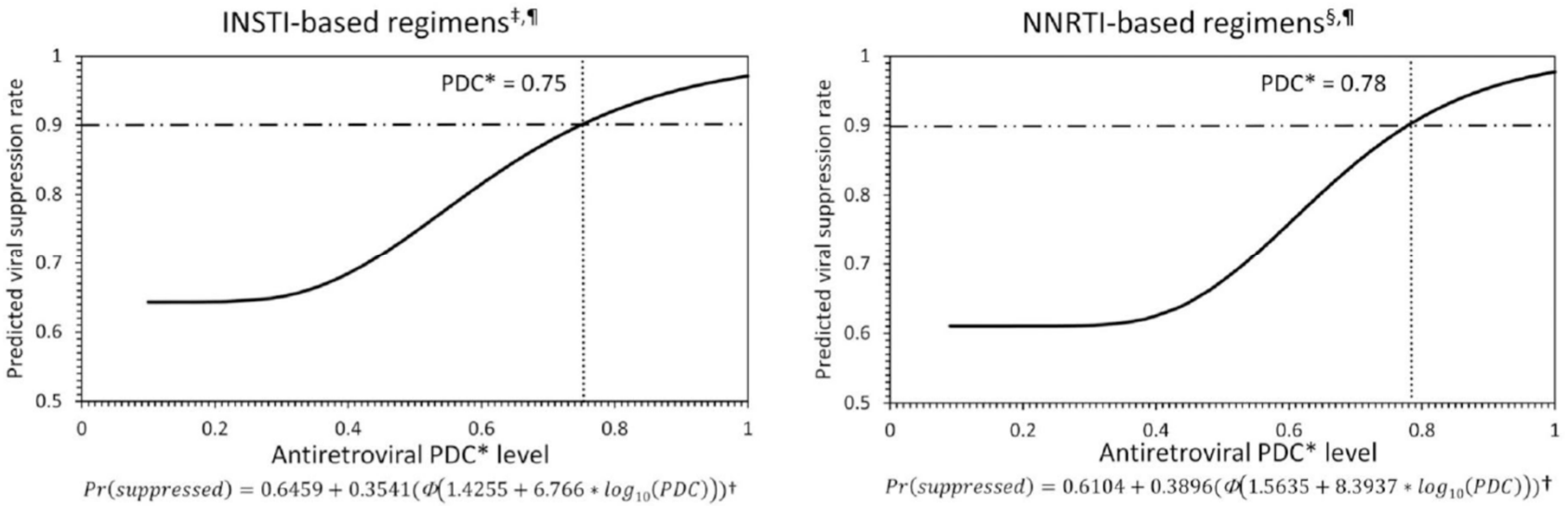
https://aidsetc.org/sites/default/files/media/document/2022-11/HIV%20Medication%20Chart_August%202022.pdf

How much adherence is needed with Modern HAART

Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-World Data

Kathy K. Byrd, MD, MPH[a], John G. Hou, PhD[b], Ron Hazen, MPH[b], Heather Kirkham, PhD, MPH[b], Sumihiro Suzuki, PhD[c], Patrick G. Clay, PharmD[d], Tim Bush, MS[a], Nasima M. Camp, MPH[e], Paul J. Weidle, PharmD, MPH[a], Ambrose Delpino, PharmD[f] for the Patient-Centered HIV Care Model Team



integrase inhibitor- and NNRTI-based regimens achieved **90%** viral suppression with adherence levels of **75% and 78%,** respectively.

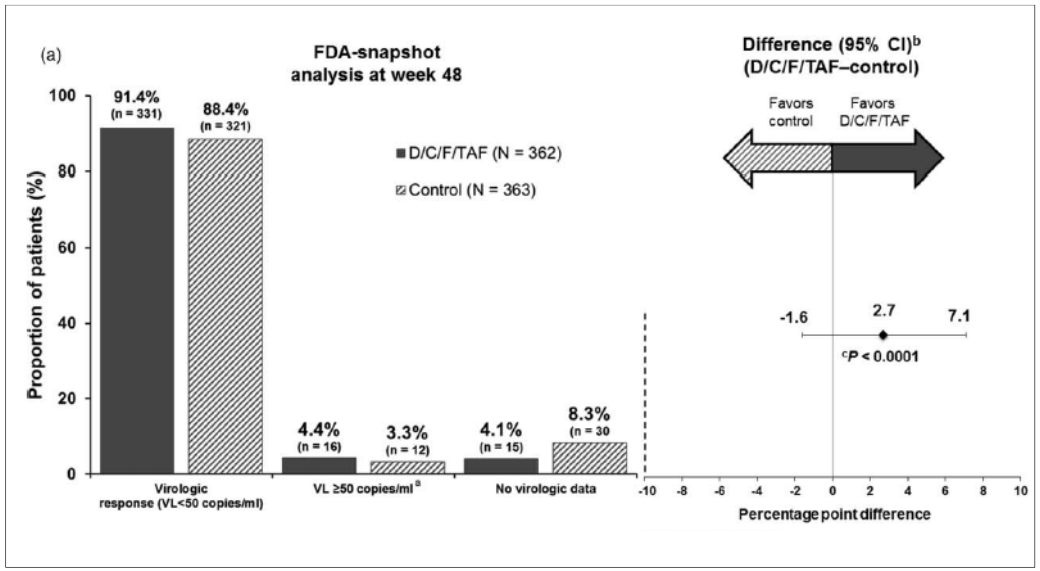
J Acquir Immune Defic Syndr. 2019; 82(3): 245–251.

PI-based STR

1125 paziente in STR, a 48 weeks:
PI-emergent mutations: 0

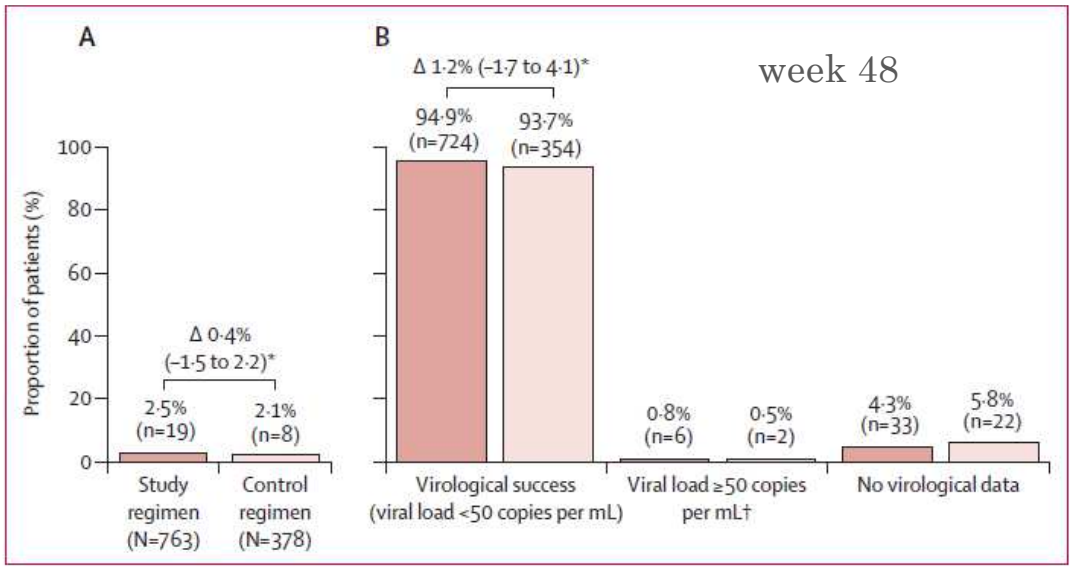
Lathouwers et al. AIDS Res Hum Retroviruses. 2020

AMBER: naive
DRV/c/FTC/TAF versus DRV/c + FTC/TDF



Eron JJ et al. AIDS 2018

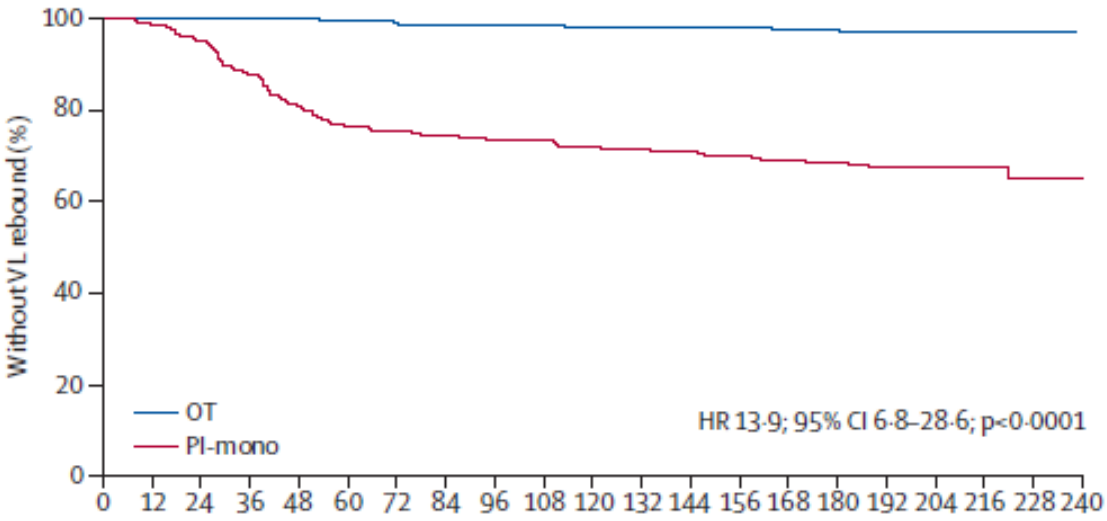
EMERALD: experienced
switch to DRV/c /FTC/TAF (STR)



Orkin C et al. Lancet HIV 2018

Genetic barrier of boosted-PI

PIVOT trial PI monotherapy in HIV infection



Number at risk

OT	291	289	287	283	280	279	276	247	133	64	10
PI-mono	296	281	240	220	216	210	208	183	100	53	9

No PI mutation at failure

Paton N et al. Lancet HIV 2015

Integrase -based

Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials

Paul E. Sax,[a,*] José R. Arribas,[b] Chloe Orkin,[c] Adriano Lazzarin,[d] Anton Pozniak,[e] Edwin DeJesus,[f] Franco Maggiolo,[g] Hans-Jürgen Stellbrink,[h] Yazdan Yazdanpanah,[i] Rima Acosta,[j] Hailin Huang,[j] Jason T. Hindman,[j] Hal Martin,[j] Jared M. Baeten,[j] and David Wohl,[k] on behalf of the GS-US-380-1489 and GS-US-380-1490 study investigators

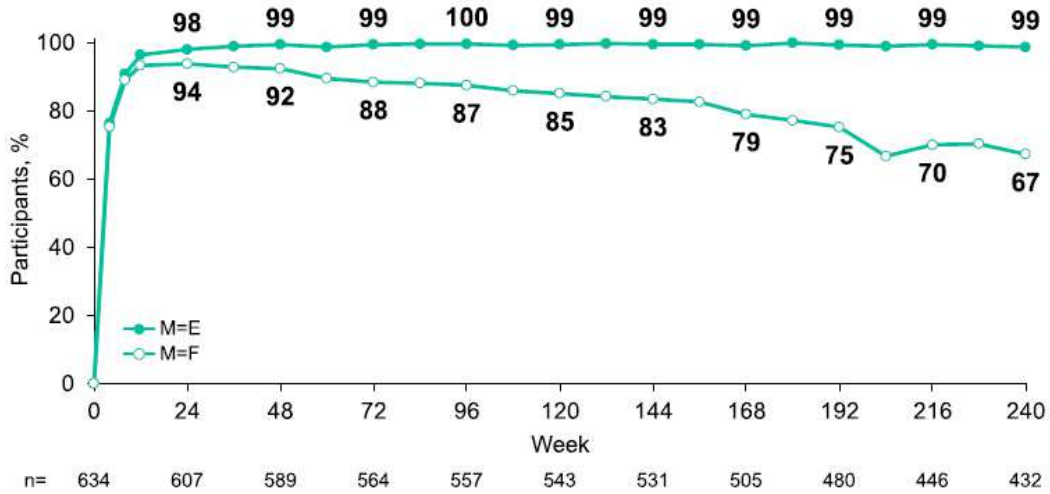
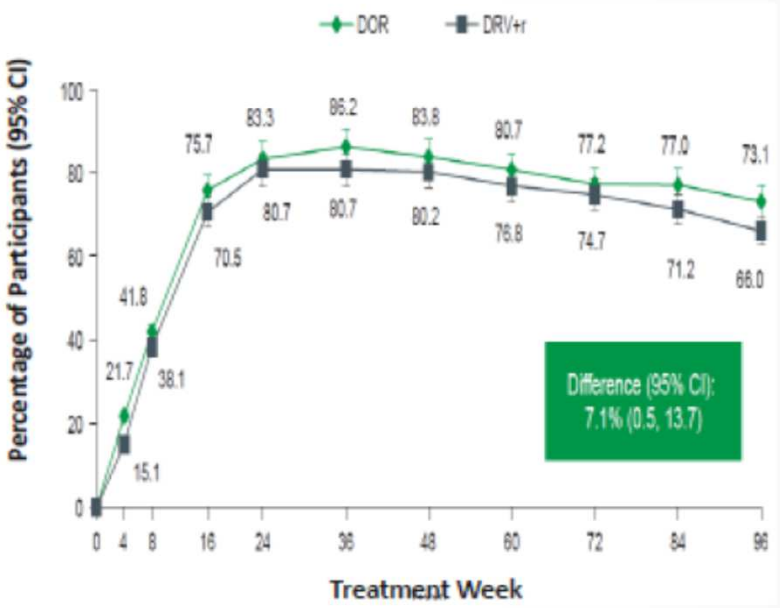
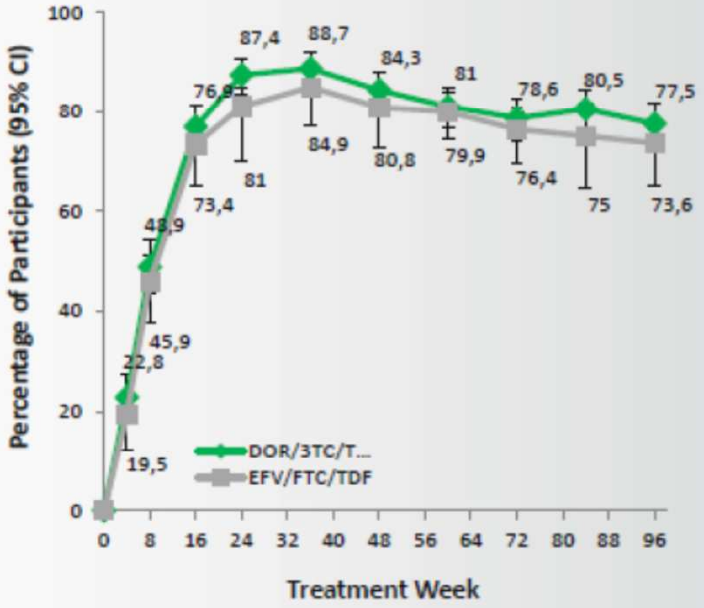


Fig. 2: **Virologic outcomes through 240 weeks (missing = excluded and missing = failure).** Percent of participants with plasma HIV-1 RNA <50 copies/mL; n = participants with non-missing HIV-RNA value.

NNRTI –based: doravirine

DOR Ph3 Trials Efficacy at 96 Weeks:
DRIVE-FORWARD (DOR vs DRV) and DRIVE-AHEAD (DOR vs EFV)

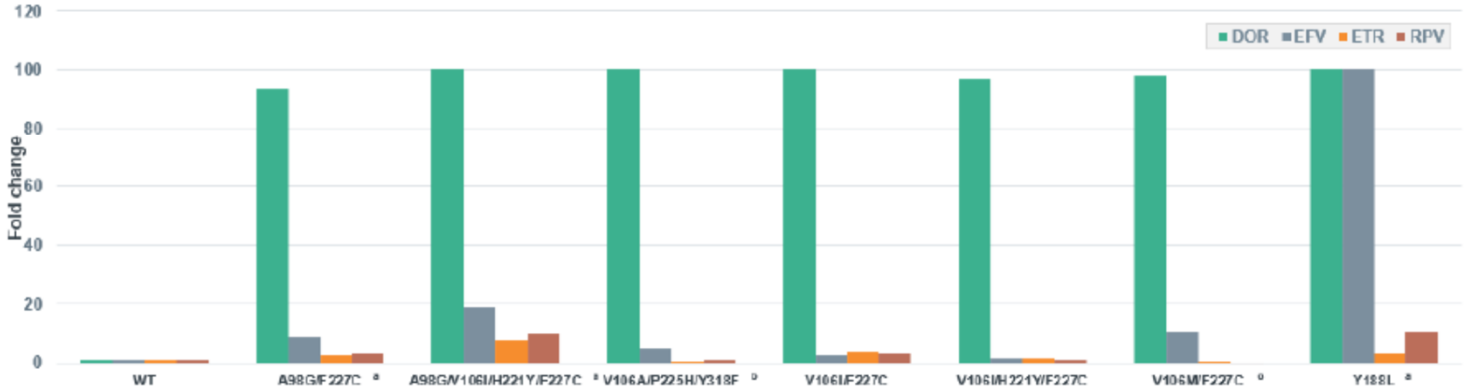




DOR shows greater efficacy than DRV at Week 96

DOR/3TC/TDF is non-inferior to EFV/FTC/TDF at Week 96

Susceptibility of DOR-Resistant Clinical Isolates to NNRTIs



		A98G/F227C[a]	A98G/V106I/H221Y/F227C[a]	V106A/P225H/Y318F[b]	V106I/F227C	V106I/H221Y/F227C[b]	V106M/F227C[c]	Y188L[a]
DOR	1.0	>93	>110	>210	>105	>96	>98	>181
EFV	1.0	9.0 (R)	19 (R)	4.8 (R)	2.5 (S)	1.7 (S)	11.0 (R)	>120 (R)
ETR	1.0	2.8 (S)	7.9 (PS)	0.7 (S)	4.0 (PS)	1.5 (S)	0.6 (S)	3.4 (PS)
RPV	1.0	3.8 (R)	10 (R)	1.0 (S)	3.4 (R)	1.2 (S)	0.4 (S)	11 (R)

Performed by Monogram Biosciences

[a] With NRTI mutation M184V; [b] with NRTI K65R mutation; [c] with NRTI M184V/K65R mutation

S=susceptible; PS=partial susceptible; R=resistant.

Fold-change cut-off: EFV=3; RPV= 2; ETR=2.9-10

Lai, MT, XU, M, Ngo, W, et al. Characterization of Doravirine-Selected Resistance Patterns from Participants in Treatment-Naïve Phase 3 Clinical Trials. Presented at the 22nd International AIDS Conference; Amsterdam, Netherlands; 23-27 July 2018.

2-drug regimens era in HIV therapy

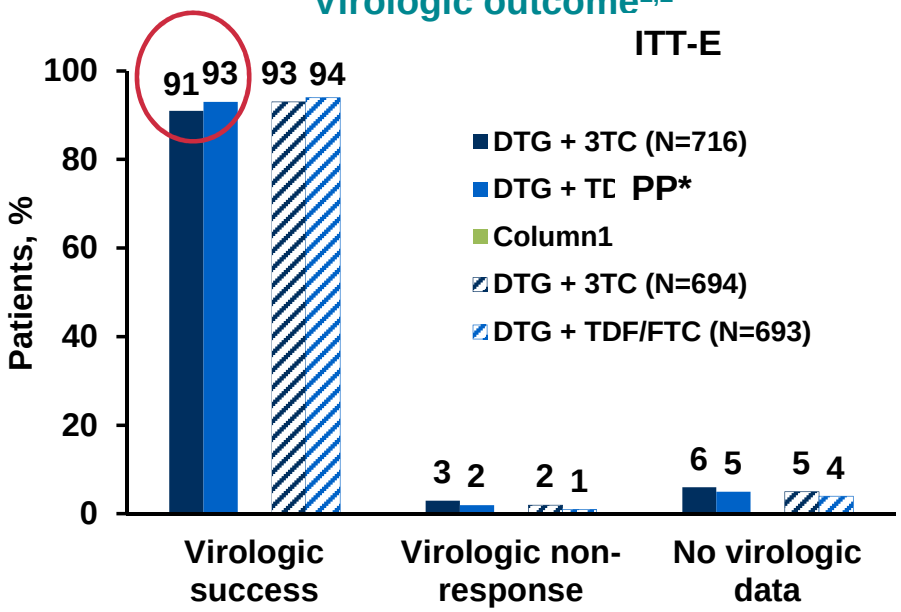
Experimental dual regimen	Study	Design	Baseline regimen	Number of pts	Follow-up weeks	Emergent resistance
LOP/r + 3TC [1]	OLE	switch	bPI	**1051**	48	1
ATV/r + 3TC [2]	SALT				96	1
ATV/r + 3TC [3]	ATLAS-M				96	---
DRV/r + 3TC [4]	DUAL				48	1
DTG + RPV [5]	SWORD 1-2	switch	any	1024	149	6
DTG + 3TC [6]	GEMINI 1-2	naive	-	1433	144	0
DTG + 3TC [7]	TANGO	switch	any, TAF-based	741	144	0
DTG + 3TC [8]	SALSA	switch	any	503	48	0
DTG + DRV-r [9]	DUALIS	switch	DRV-r based	263	48	0
DRV-r + RPV [10]	PROBE2	switch	any	160	24	0
CAB + RPV (LA)	ATLAS[11]	switch	any	618	48	3
	FLAIR[12]	switch	ABC/3TC/DTG	629	48	3
	ATLAS-2M[13]	switch	ATLAS[11]	1045	48	8

1. Arribas JR et al. Lancet ID 2015; 2. Perez-Molina JA et al. Lancet ID 2015; 3. Di Giambenedetto S et al. JAC 2017; 4. Pulido F. et al. CID 2017;65:2112-211;
5. Llibre JM et al. Lancet 2018;391:839-849; 6. Cahn P et al. IAS 2019; slides WEAB0404LB7. 7. van Wyk et al. IAS 2019; slides WEAB0403LB. 8. Llibre et al. IAS 2021; Virtual. Slides OALB0303 9. Spinner CD et al. Open Forum Infect Dis 2020; 10. Maggiolo F. et al. J Antimicrob Chemother. 2020;75:1332-1337. 11. Swindells S et al. N Engl J Med. 2020; 12. Orkin C, et al. N Engl J Med. 2020;382:1124-1135. 13 Overton ET, et al. Lancet. 2021;396:1994-2005

GEMINI 1&2 trials

DTG + 3TC vs DTG + FTC/TDF

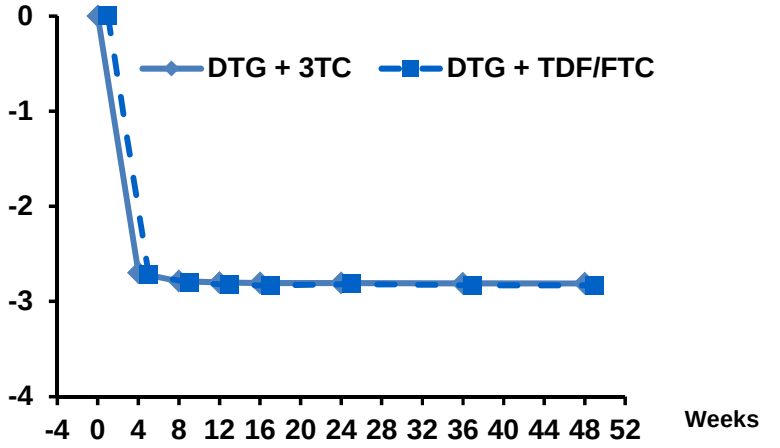
Virologic outcome[1,2]



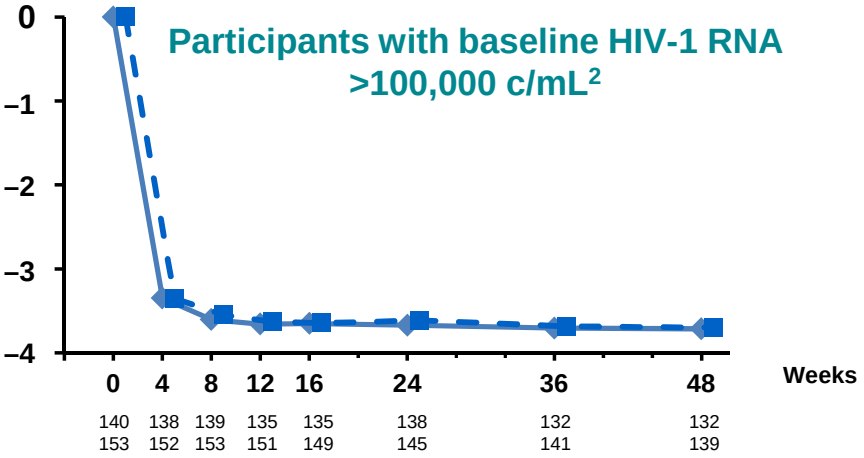
- Data pooled from both GEMINI-1 and -2 studies
*PP population consisted of subjects in the ITT-E population except those with protocol violations that could affect assessment of antiviral activity; †Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).[1] PP, per protocol

Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55
2. Cahn P, et al. IAS 2018. TUAB0106LB

Viral Load Decline by study arm



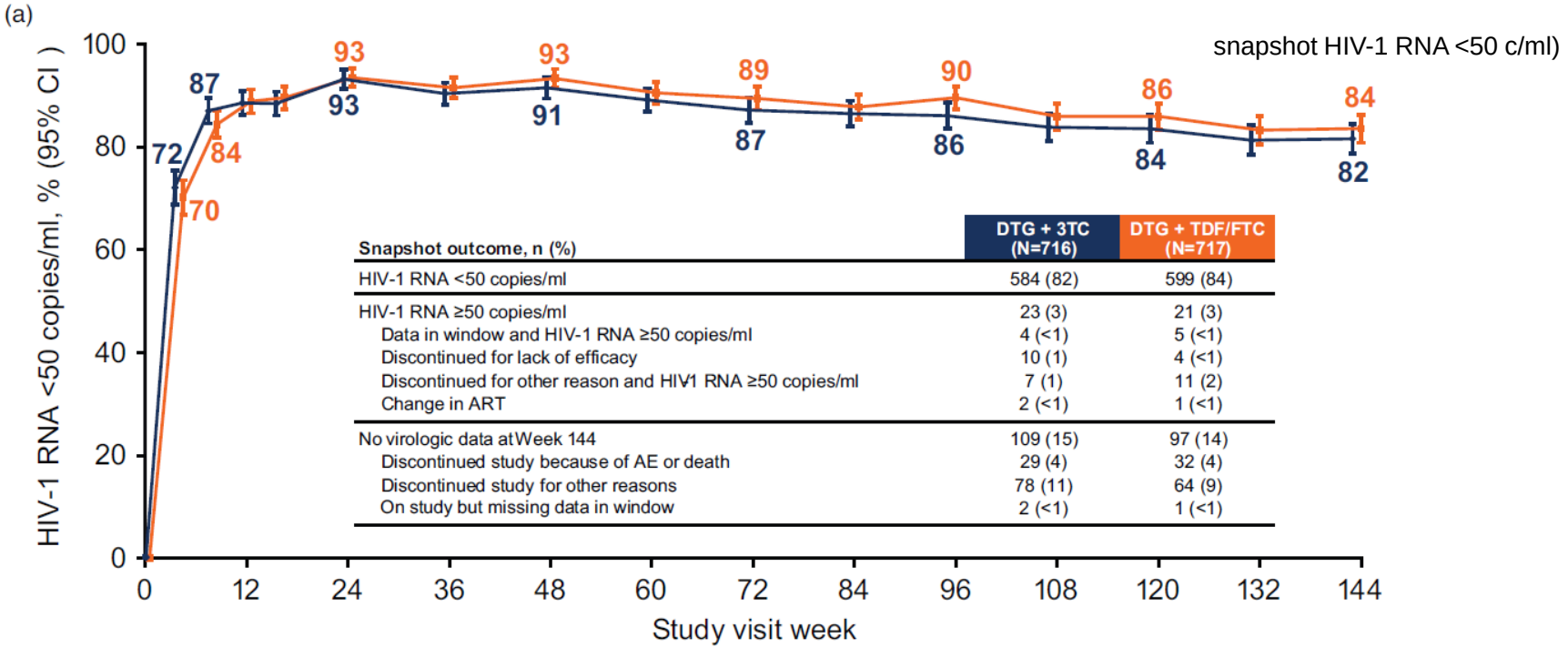
DTG + 3TC, n	716	704	681	688	674	664
DTG + TDF/FTC, n	717	699	688	688	681	675



Adapted from: 1. Cahn P, et al. Lancet 2019;393:143–55 plus supplementary appendix
2. Eron J, et al. HIV DART and Emerging Viruses 2018. Oral Presentation 7

Dolutegravir + lamivudine
in naive patients: 144-week results

No emergence
of resistance



Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 copies/ml	584 (82)	599 (84)
HIV-1 RNA ≥50 copies/ml	23 (3)	21 (3)
Data in window and HIV-1 RNA ≥50 copies/ml	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV1 RNA ≥50 copies/ml	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data at Week 144	109 (15)	97 (14)
Discontinued study because of AE or death	29 (4)	32 (4)
Discontinued study for other reasons	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

One DTG + 3TC participant (with no adherence), not meeting CVW criteria, developed M184V (week 132) and R263R/K (week 144) conferring a 1.8-fold change in susceptibility to DTG.

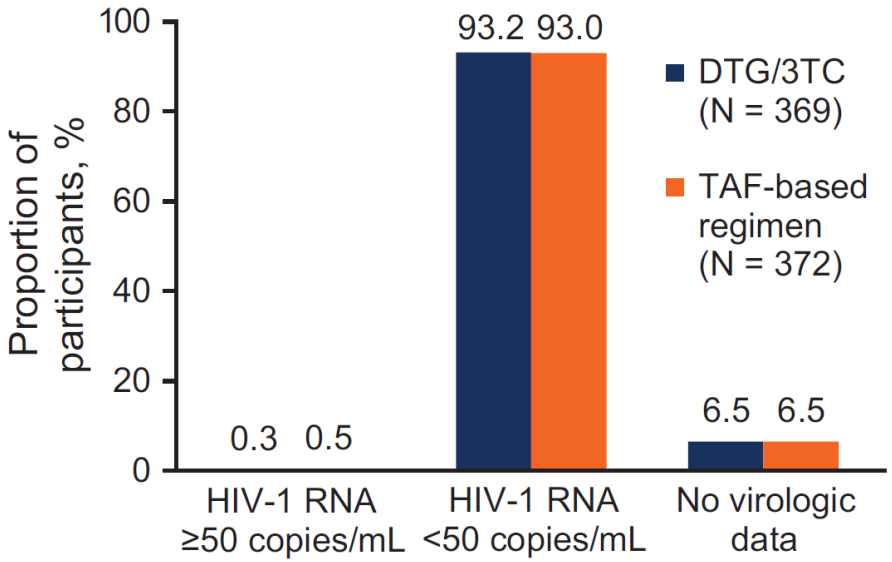
Cahn P et al. AIDS. 2022 ;36:39-48.

Switch to Dolutegravir + lamivudine

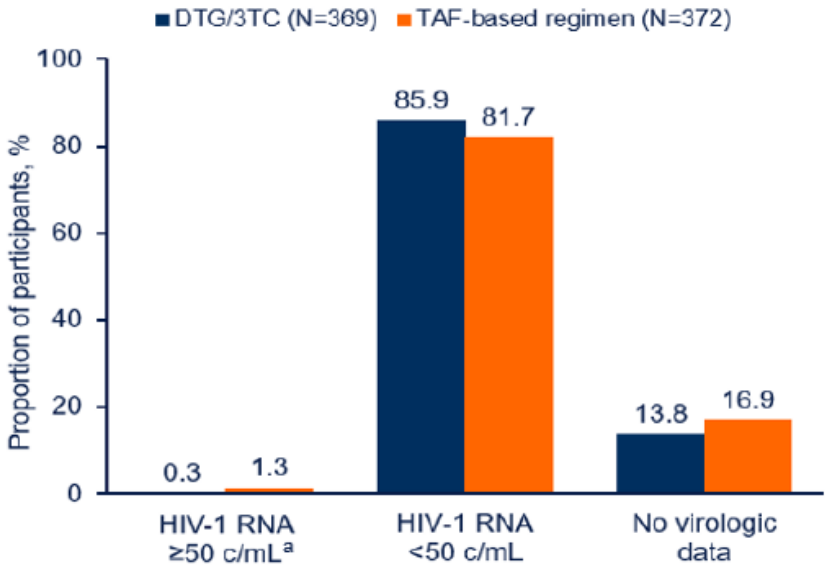
TANGO trial

No emergence of resistance

48-week data



144-week data



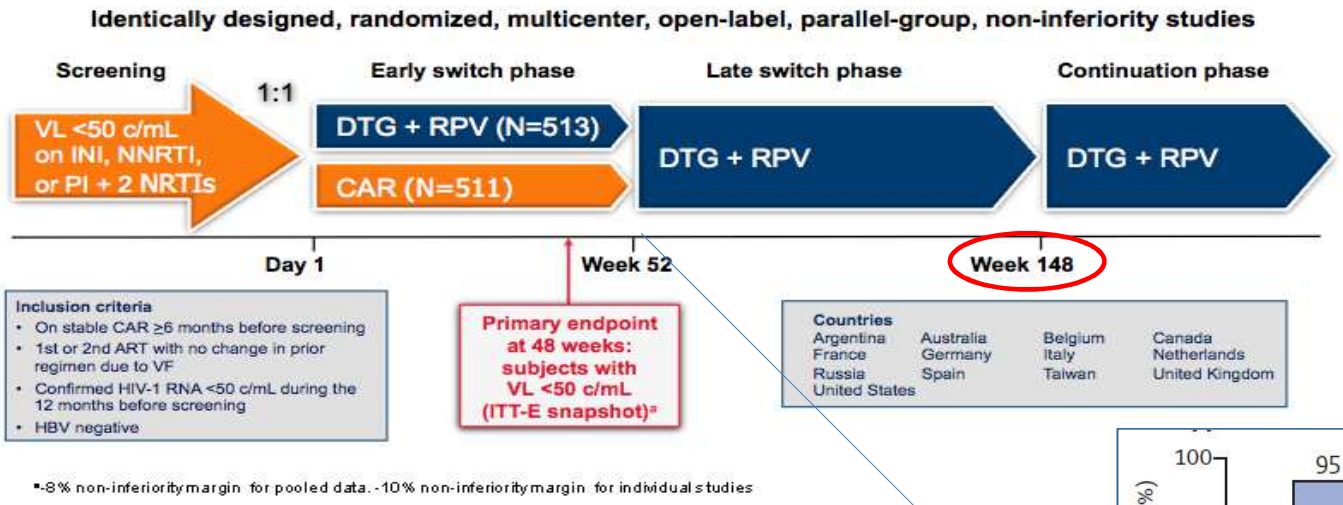
At baseline, the median **CD4+/ CD8+ cell count ratio** was 0.**95** for the DTG/3TC group and **0.96** for the TAF-based regimen group, with median changes at week 48 of **0.03** and **0.05**, respectively.

Van Wick J et al. CID 2020:71(15 October)

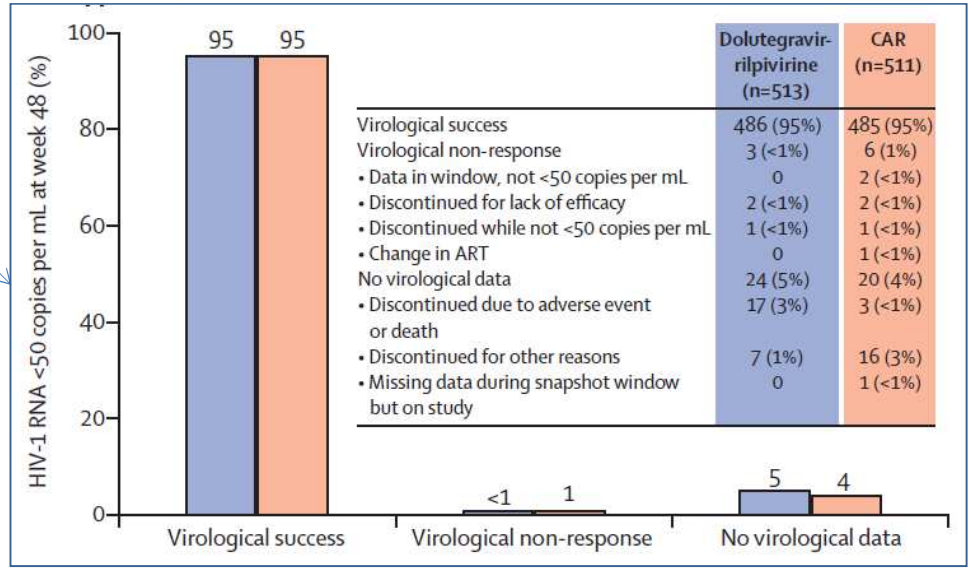
van Wyk et al. IAS 2021; Virtual. Poster PEB164.

Dolutegravir + rilpivirine (DTG + RPV)

SWORD 1&2 trials



Entry criteria:
- no prior virologic failure
- no documented resistance mutations
- no HBV infection

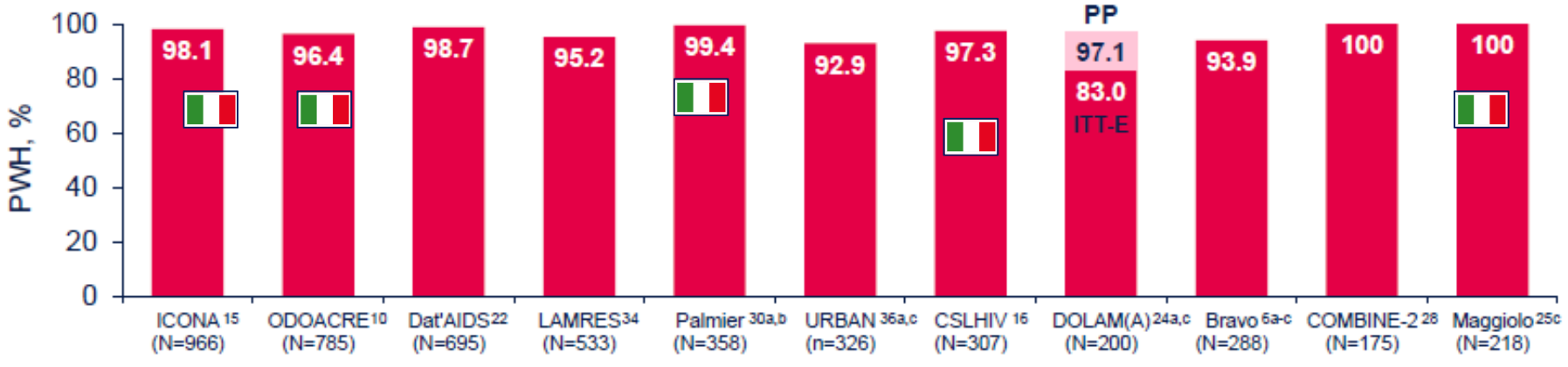


	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	0	1 (<1%)
No virological data	24 (5%)	20 (4%)
• Discontinued due to adverse event or death	17 (3%)	3 (<1%)
• Discontinued for other reasons	7 (1%)	16 (3%)
• Missing data during snapshot window but on study	0	1 (<1%)

Llibre JM, et al. Lancet. 2018;391:839-849

DTG+3TC in real world

Figure 3. Effectiveness Outcomes Reported in Studies With N >100 Virologically Suppressed, Treatment-Experienced PWH Who Received DTG + 3TC (N=4851)



Time point	1505 PYFU	2014.7 PYFU, up to Week 240	Median FU 1.2 years	2 years	Week 48	1 year	1 year	Week 48	Week 48	96 weeks	5 years
Effectiveness outcome	Remained free of VF	Estimated probability of maintaining VS	Remained free of VF	Probability of remaining free of VF	Remained free of VF	Achieved/ Maintained VS (MEX)	Estimated probability of remaining free of VF	HIV-1 RNA <50 c/mL (PP, ITT-E)	HIV-1 RNA <50 c/mL (MEX)	Remained free of VF	Remained free of VF (MEX)
Virologic failure, n (%)	0.7-1.2 × 100 PYFU	0.9 per 100 PYFU	9/695 (1.3%)	Probability of VF, 4.8%	2/358 (0.6%)	2/326 (0.6%)	3.3 per 100 PYFU	5/200 (2.5%)	0%	0%	0%

6. Bravo et al. GeSIDA 2019; Toledo, Spain. Poster P-145. 10. Ciccullo et al. J Acquir Immune Defic Syndr. 2021;88:234-237. 15. Gagliardini et al. CROI 2020; Boston, MA. Poster 486. 16. Galizzi et al. Int J Antimicrob Agents. 2020;55:105893. 22. Hocqueloux et al. EACS 2021; Virtual and London, UK. Slides OS1/2. 25. Maggiolo et al. IAS 2021; Virtual. Poster PEB179. 28. Mussini et al. EACS 2021; Virtual and London, UK. 30. Palmier et al. EACS 2021; Virtual and London, UK. Poster PE2/51. 34. Santoro et al. CROI 2021; Virtual. Poster 429. 36. Scholten et al. EACS 2021; Virtual and London, UK. Poster PE2/52

Letang E et al. BHIVA Spring Conference 2022; Abs 023

DTG+3TC in real world

Figure 5. Treatment-Emergent Resistance in Treatment-Experienced PWH Who Received DTG + 3TC (N=3527)

PWH with documented treatment-emergent resistance

0/785
ODOACRE[10]
2014.7 PYFU, up to 240

0/695
Dat'AIDS[22]
Median follow-up 1.2 years
0 emergent M184V;
no other information given

0/533
LAMRES[34]
2-year follow-up
0 INI/NRTI resistance in
4 PWH with genotypic testing

0/326
URBAN[36a,b]
1-year follow-up
0 resistance in 7 PWH
with resistance testing

1/307
CSLHIV[16]
1-year follow-up
n=1 emergent M41M/L mutation;
n=1 with resistance at VF but no BL data[c]

0/288
Bravo[6a]
48-week follow-up
No VFs reported

0/200
DOLAM(A)[24a]
48-week follow-up
n=1 with resistance at
VF but no BL data[c]

0/175
COMBINE-2[28]
96-week follow-up
No VFs reported

0/218
Maggiolo[25]
5-year follow-up
No VFs reported

BL, baseline; PYFU, person-years of follow-up; VF, virologic failure. [a]PWH viremic at baseline: URBAN, n=14; DOLAM(A), n=8; Bravo, n=16. [b]7 PWH were excluded from the URBAN analysis due to missing data. [c]PWH did not have baseline resistance tests available.

Letang E et al. BHIVA Spring Conference 2022; Abs 023

Oral HAART evolution

NNRTI-based
INSTI-based
bPI-based

Ad=Anchor drug

2NRTIs + 3rd drug

HAART

~~single drug~~

2NRTIs + Ad drug

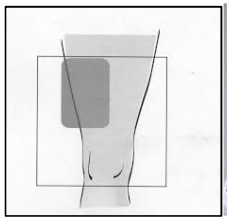
1NRTIs + Ad drug

HAART

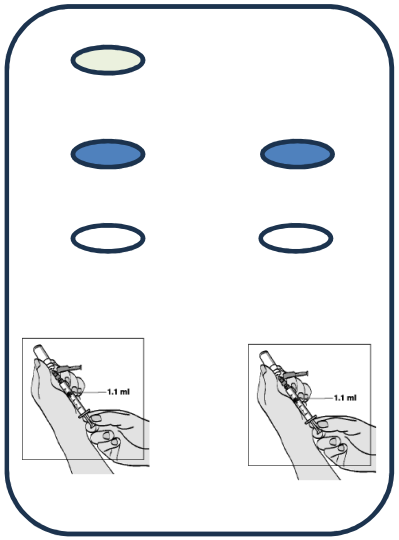
Simpler regimens for MDR patients

DRV 600mg

rtv 100mg

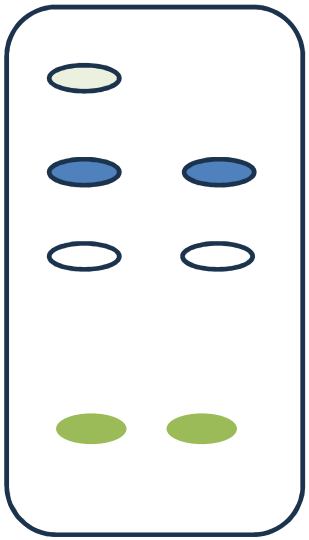


8am 8pm



RAL 400mg

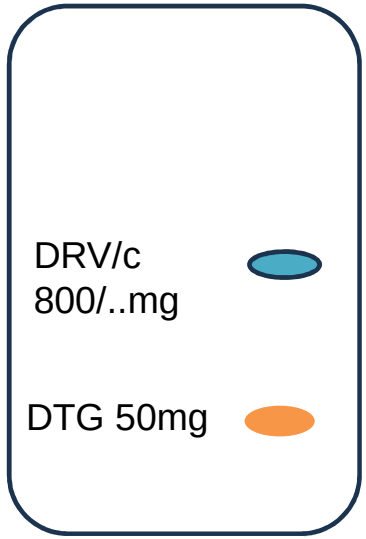
8am 8pm



8am 8pm

DRV/c 800/..mg

DTG 50mg



Boosted PI + (X) in clinical practice

Study	Design	Study arm (N. of pts)	Historical genotype resistance	Follow up weeks	HIV RNA < 50 c/ml (%)	New resistance mutations (VF)
Navarro J [1] (DARIL study)	retrospective, any viral load	DRV/r **+ RPV** (84)	In 41 pts: NRTI: 87% NNRTI: 44% PI: 23%, II: 7%	48 wks	87.7	0 (4 VF)
Castagna [2] (DAU study)	retrospective **switch**	uATV + DTG (151)	?	median: 62 wks	90	0 (2 VF)
Jabłonowska [3]	retrospective, any viral load	DRV/r + DTG (76)	?	48 wks	92	0 (1 VF)
Capetti A [4]	retrospective, any viral load	DRV/r + DTG (130)	118 with resistance to 1–5 ARV classes.	96 wks	95	0 (2 VF)
Hawkins KL [5]	retrospective, any viral load	DRV/r + DTG (65)	DRV primary mutations: 8%	median: 419 days	94	0 (0 VF)
Navarro J [6]	retrospective, **switch**	DRV/r + DTG (50)	In 41 pts: NRTI: 93.2% NNRTI: 72.7% PI: 15%	median: 25 mos	98	0 (1 VF)
Vizcarra P [7]	retrospective, **switch**	DRV/r + DTG (51)	NRTI: mean 1.2 NNRTI: mean 2.4 PI: mean 3.5	48 wks	90	0 (0 VF)

1. Navarro J et al. 2020; 2 Castagna et al. AIDS 2019; 3. Jabłonowska E et al Plos One 2018; 4. Capetti A et al. HIV Clin Trials 2018; 5. Hawkins KL et al. Antivir Ther. 2019; 5. Navarro J et al. Pharmacotherapy. 2019; Vizcarra P et al. Antivir Ther 2019

Switching to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) plus darunavir/cobicistat in heavily antiretroviral-experienced, virologically suppressed HIV-infected adults receiving complex regimens

Daniel Podzamczer[1]*, Arkaitz Imaz [2], Ana Lopez-Lirola[3], Hernando Knobel[4], Mar Masiá [5], Chiara Fanciulli[6], Cristina Hernández[7], María Lagarde[8], Angela Gutierrez[9], Adrià Curran[10], Luis Morano[11], Marta Montero-Alonso[12], Jesús Troya [13], Raúl Rigo[2], María Casadellà[14], Antonio Navarro-Alcaraz[14], Fernando Ardila[2], Mariona Parera[14], Enrique Bernal[15], Patricia Echeverria[16], Vicente Estrada[17], Carmen Hidalgo-Tenorio[18], Juan Macias [19], Paula Prieto[20], Joaquín Portilla[21], Eulalia Valencia[22], María Jesús Vivancos[23] and Antonio Rivero[24,25]

Pilot study
switch study
63 patients
median N. of pills: 4 (3-10)
33/39 resistance mutations (DNA)
HIV RNA <50 c/ml at week 48: 95%

BIC/FTC/TAF + DRV-c

Podzamczer D et al JAC 2023

What’s next for oral therapy?

Managing Highly Treatment Experienced (HTE) patients

Efficacy and Safety of Fostemsavir Plus Optimized Background Therapy in Heavily Treatment-Experienced Adults With HIV-1: Week 240 Results of the Phase 3 BRIGHTE Study

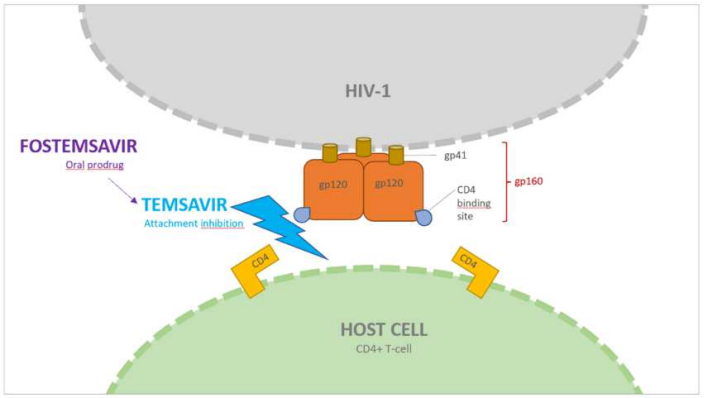
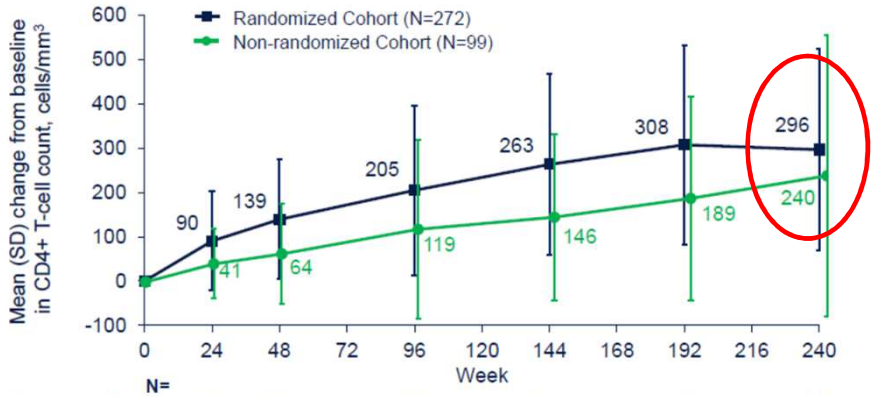
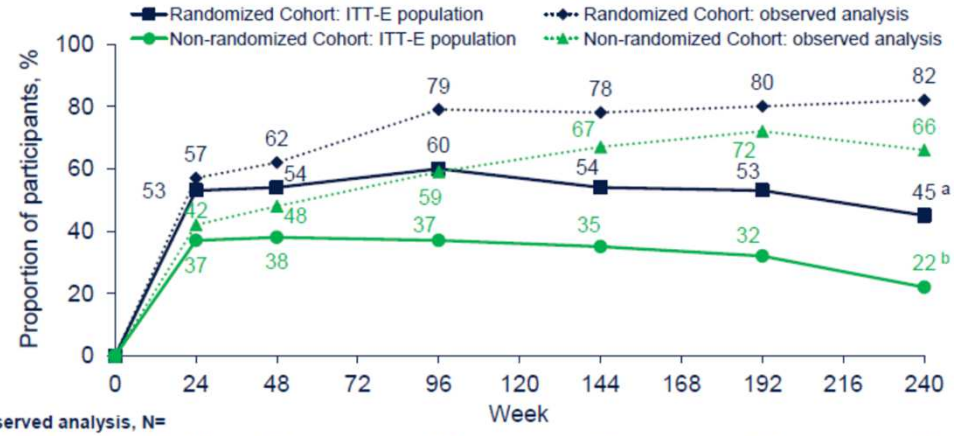


Figure 4. Change in CD4+ T-Cell Count From Baseline to Week 240 (Observed Analysis)



N=						
Randomized Cohort	248	228	213	197	179	139
Non-randomized Cohort	87	83	65	53	45	31

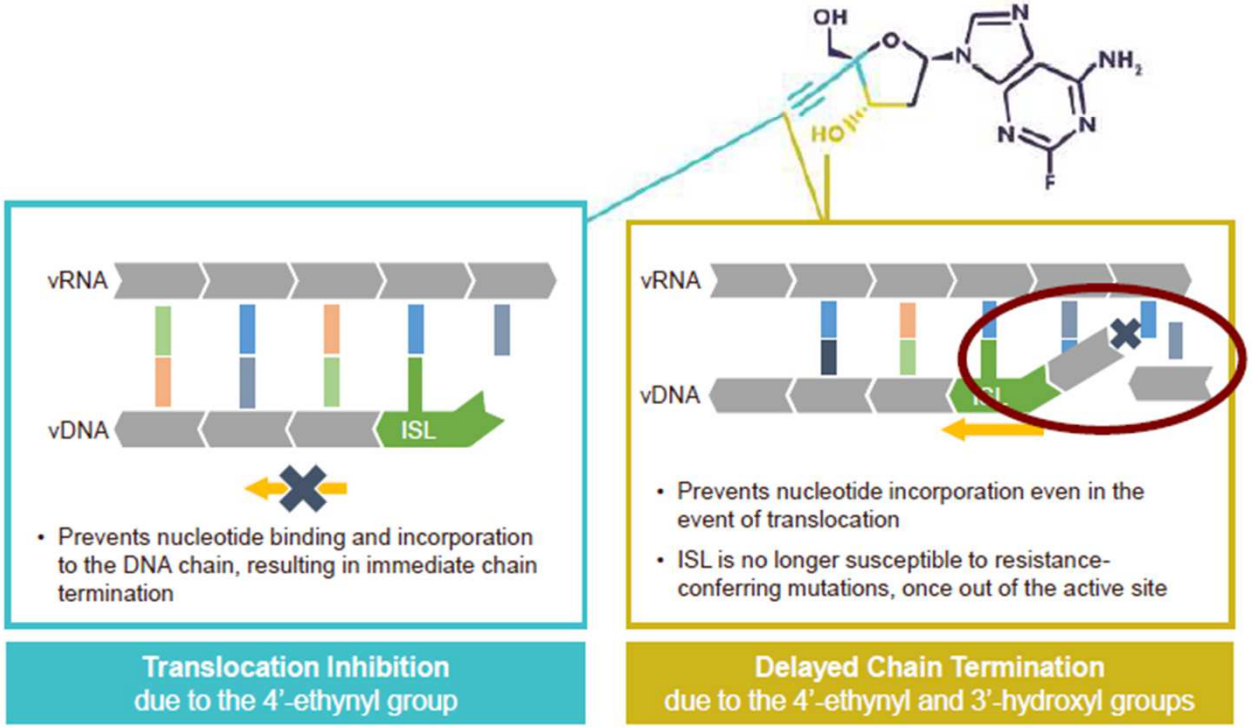
Figure 3. HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis



Observed analysis, N=						
Randomized Cohort	247	233	214	206	195	164
Non-randomized Cohort	89	83	66	57	50	35

Aberg J. et al. HIV Glasgow 2022: P061

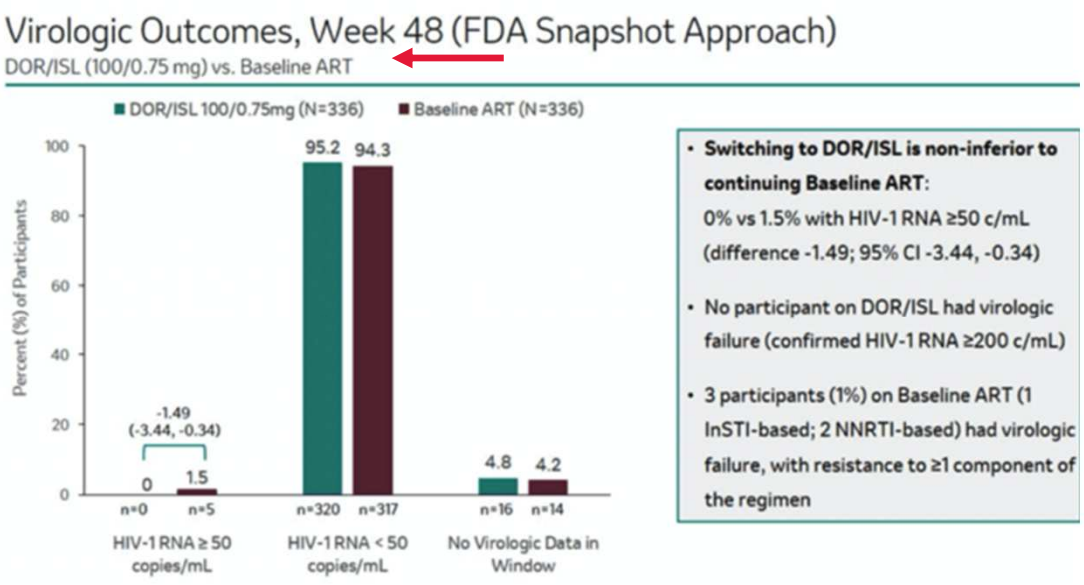
Islatravir (MK-8591): First-in-class NRTTI with Multiple Mechanisms of Action

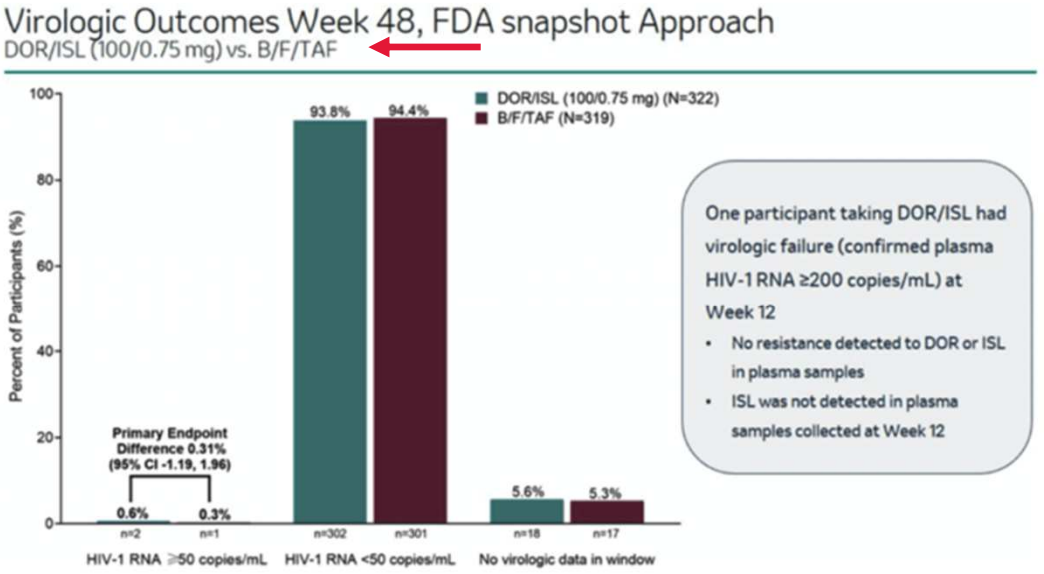


Multiple mechanisms contribute to the high potency of ISL against HIV-1 and drug-resistant variants as well as its high barrier to resistance

Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB and Poster #LBPED46.

doravirine/islatravir (100mg/0.75mg) as switch strategy

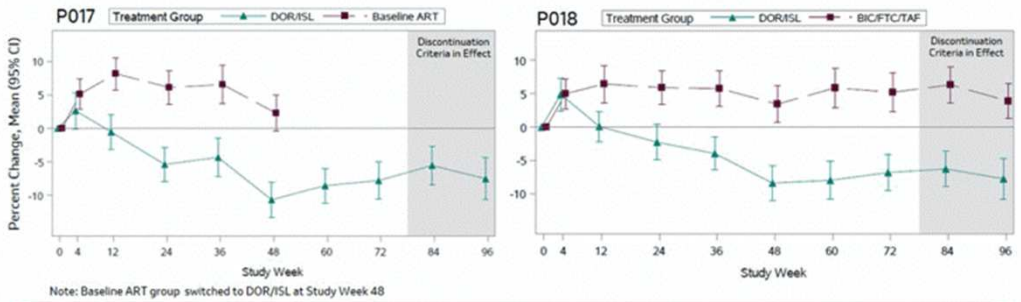




Molina JM et a. CROI 2023

Rockstroh JK et al. Doravirine/islatravir (100mg/0.75mg) once daily compared to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) as initial HIV-1 treatment: 48 week results from a double-blind phase 3 trial.
12th IAS Conference on HIV Science (IAS 2023), Brisbane, abstract OALBX0102, 2023.

Phase 3 DOR/ISL 100/0.75 mg QD in HIV-1 Switch (MK8591A-017/018)
Total Lymphocyte Count

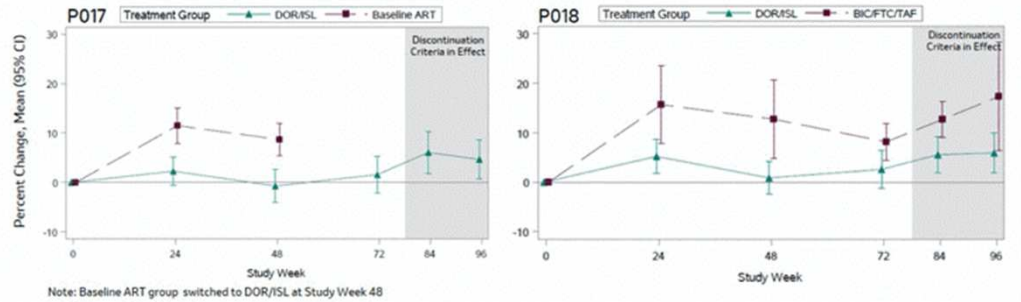


Note: Baseline ART group switched to DOR/ISL at Study Week 48

- Declines in total lymphocyte counts were observed in ISL-treated participants over 48 Weeks and subsequently stabilized on continued ISL 0.75 mg QD dosing
- Prior to implementation of total lymphocyte count discontinuation criteria (approximately at Week 84), the mean percent change from baseline in total lymphocyte count had declined from baseline in the ISL 0.75 mg group and increased in the comparator group

Mean values at baseline (10^9/L): P017, DOR/ISL 1.97; bART 1.95. P018, DOR/ISL 1.91; B/F/TAF 1.96.

Phase 3 DOR/ISL 100/0.75 mg QD in HIV-1 Switch (MK8591A-017/018)
CD4+ T-Cell Count



Note: Baseline ART group switched to DOR/ISL at Study Week 48

What's next for oral therapy?

March 2023, Phase 3 study in naive:

DOR/ISL 100/**0.25** mg orally once daily

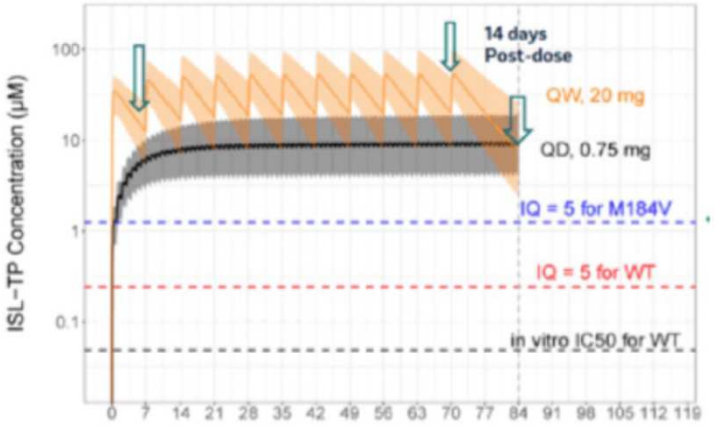
Squires KE et al. CROI 2023 Feb 20-23

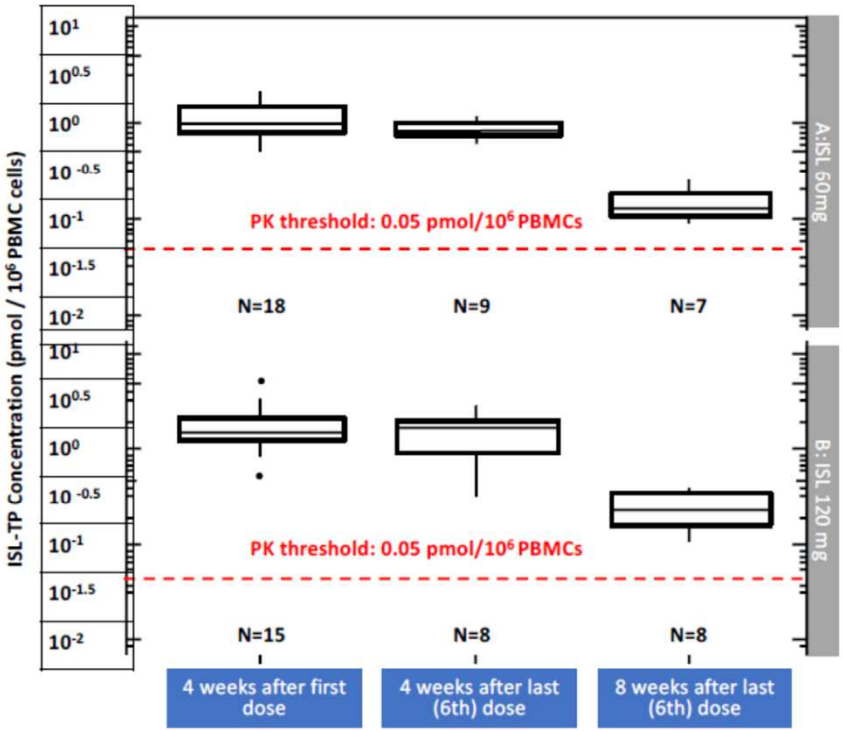
Persistent adherence to ARVs is always an issue

Long-acting oral therapy

ISL 2mg + LEN 300mg orally once weekly

Islatravir once-weekly for treatment and once-monthly for PrEP

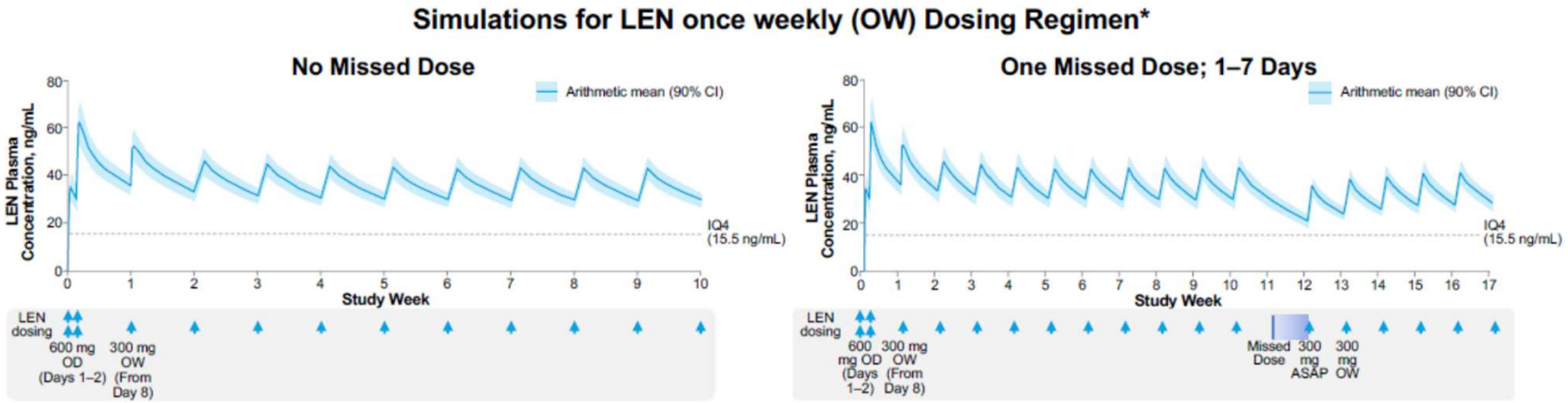




Kandala et al. CROI 2021; Hillier et al. IAS2021

Long acting – oral once weekly, including ISL

Simulations for Once-Weekly Dosing of Oral LEN



- Oral loading dose of 600 mg on Days 1 and 2 followed by oral 300 mg OW doses maintained the lower bound of the 90% CI of mean C_{trough} above IQ4 through the dosing interval
- If one oral LEN OW dose is missed, it should be taken ASAP and then normal dosing regimen can be resumed (i.e., taking one dose (300 mg) on scheduled day)

Simulations suggested that LEN 300 mg once weekly allows for a 7-day forgiveness window.

*Oral loading 600 mg QD on Days 1–2, then 300 mg QW from Day 8

ASAP, as soon as possible; C_{trough}, concentration at end of dosing interval; IQ, inhibitory quotient; OD, once daily; OW, once weekly; PK, pharmacokinetic(s)

Shaik N, et al. AIDS 2022, Poster PESUB23

Modern oral HAART

- ✓ high potency
- ✓ high genetic barrier
- ✓ higher tolerability
- ✓ longer forgiveness
- ✓ STR
- ✓ 2DR
- ✓ lower toxicity
- ✓ simpler Rx for MDR and HTE

Will long-acting options put an end to oral therapy?

- ➢ **dislike** for injections
- ➢ **Oral Lead In** for LA to assess early toxicity/tolerability
- ➢ managing coinfections and **ddIs**
- ➢ **oral bridging:** missed injections of LA
- ➢ **challenges with LA**: «injection schedules» and «in hospital delivery»
- ➢ specific settings: i.e. **pregnancy**
- ➢ **barriers to** transfer this option into all Countries?

Managing planned missed injections (with oral bridging): Q2M

- CAB and RPV oral tablets QD can be used to replace CAB + RPV LA injections for up to 2 months[1,2]
  - For oral therapy durations greater than 2 months, an alternative oral regimen is recommended[1,2]
- The 1st dose of oral therapy should be taken on the target date for injection (±7 days)[1,2]
- It is recommended to resume injection dosing on the target treatment date. Oral dosing completes on the same day as injections restart[3]

Resumption of injections after planned missed injections (with oral bridging)[1,2]

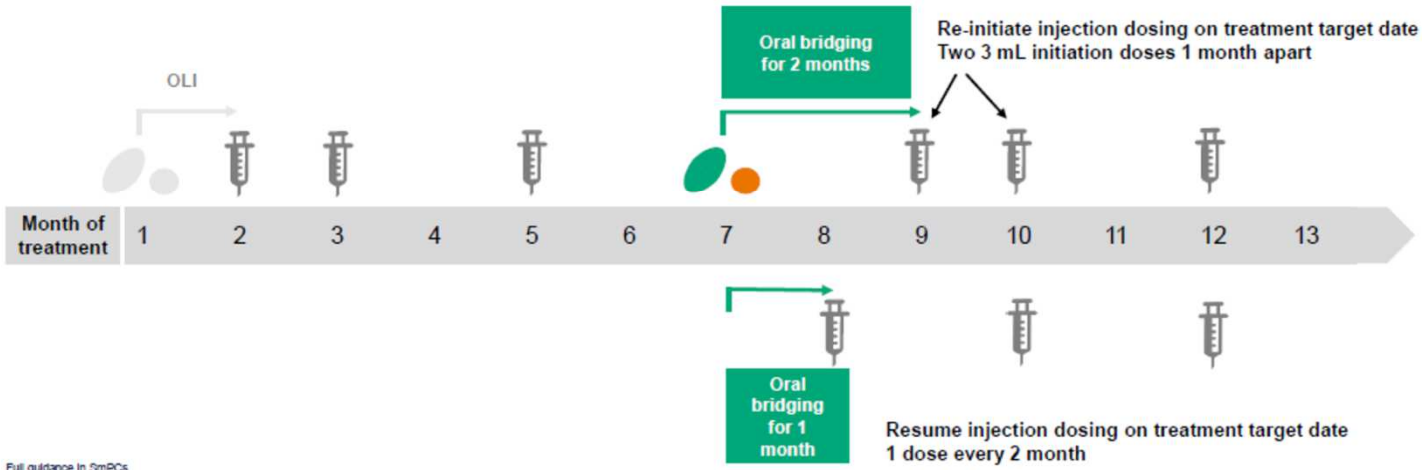
Time since MISSED injection date	Injection dosing recommendation
≤1 month	Continue with every 2 month (3 mL, 600 mg CAB LA and 900 mg RPV LA) IM injections dosing schedule as soon as possible
>1 month	Re-initiate injections (3 mL, 600 mg CAB LA and 900 mg RPV LA): two initiation injections 1 month apart, then every 2 months thereafter

IM, intramuscular

1. Vocabria EU SmPC, Jul 2021; 2. Rekambys Available from: https://gskpro.com/content/dam/global/hcpportal/_FI/unprotected/pdf/hcp-p

Managing planned missed injections (with oral bridging): Q2M

- Re-initiate injection dosing on treatment target date
- Two 3 mL initiation doses 1 month apart



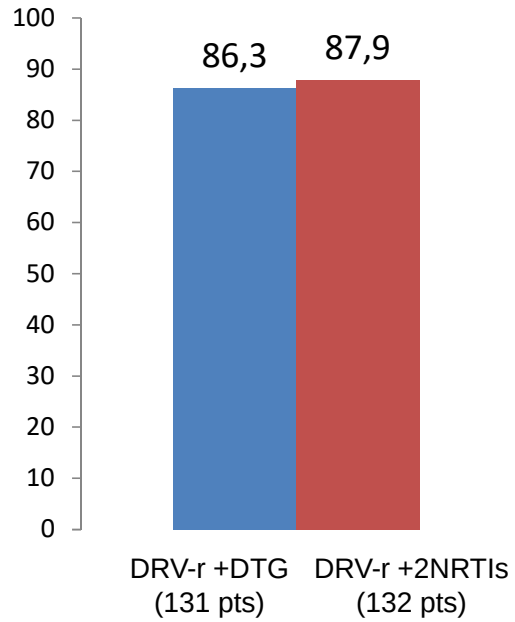
Full guidance in SmPCs
SmPC, Summary of Product Characteristic

Grazie per l'attenzione

Back up slides

Darunavir-r + DTG

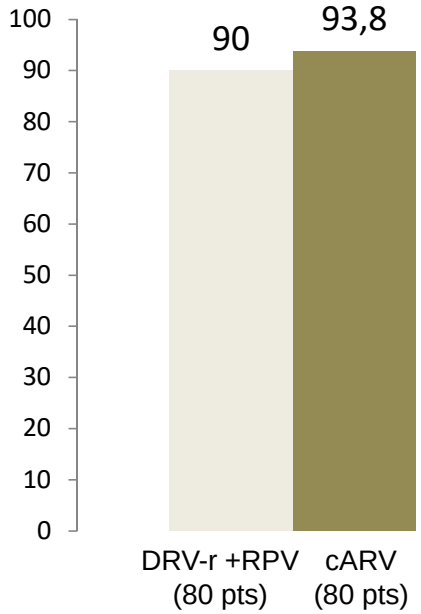
48-week data, randomized, switch trial (DUALIS), HIV RNA < 50 c/ml



No emergence of resistance

Darunavir-r + RPV

24-week data, randomized, switch trial (PROBE-2), HIV RNA < 50 c/ml

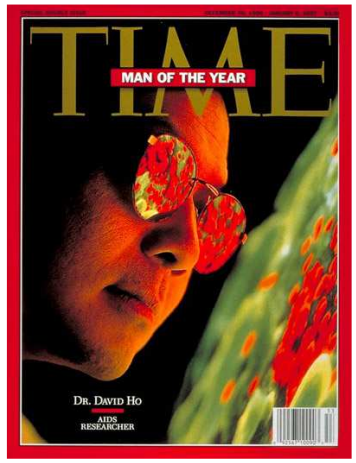


Spinner CD et al. Open Forum Infect Dis 2020;7:ofaa356

Maggiolo F et al. J Antimicrob Chemother. 2020;75:1332-1337.

THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 17, 1995

1996: Dr. David Ho, TIME



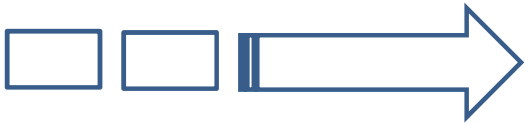
TIME TO HIT HIV, EARLY AND HARD

In the long run, effective treatment must instead force the virus to mutate simultaneously at multiple positions in one viral genome.

This is best achieved by using a combination of multiple, potent antiretroviral agents.

Improving HAART

«new agents»



Integrase inhibitors	
1 generation	RAL, EGV
2 generation	DTG, BIC

STOP and GO (CD4 driven)

Less Drug regimen

- Monotherapy
- NRTI-sparing
- Dual regimens