VIII JORNADAS DOCENTES

Viernes 23 y sábado 24 de septiembre

PACIENTES EN FRACASO EN NUESTRAS CONSULTAS. MANEJO ACTUAL Y POSIBLE MANEJO FUTURO

Roger Paredes

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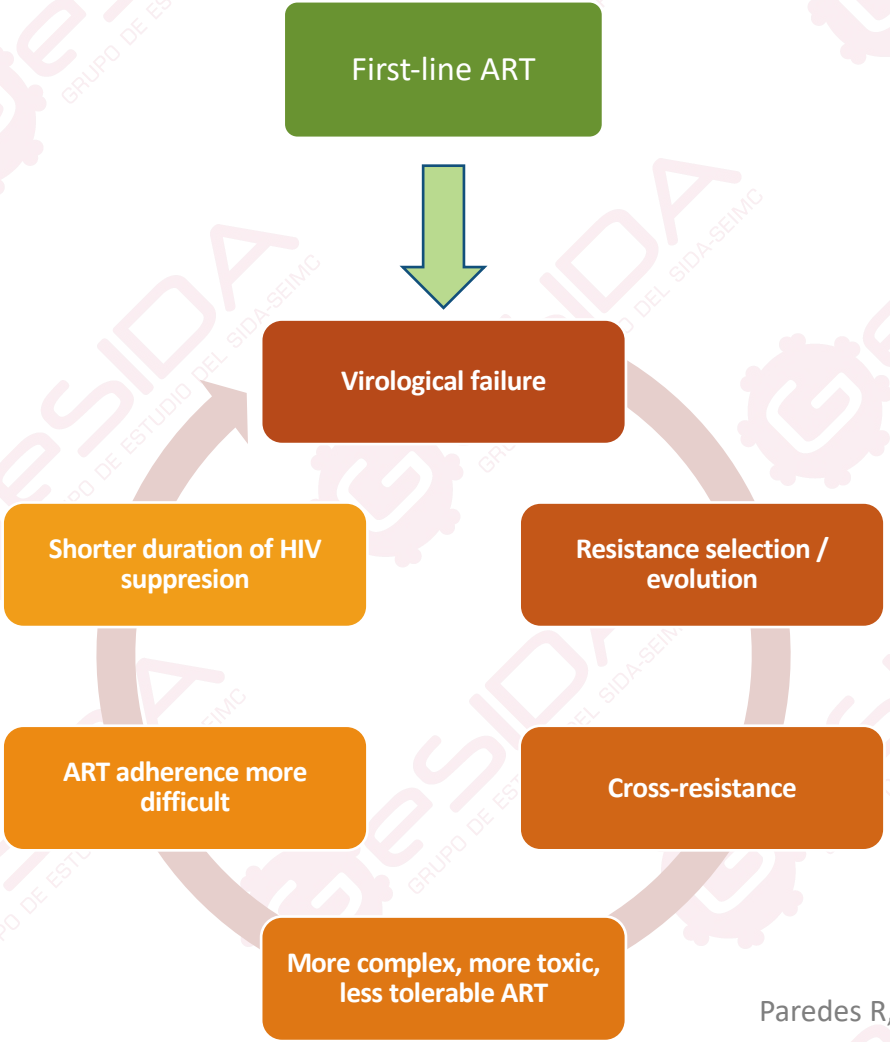
Failure leads to more failure



Paredes R, Clotet B, Antiviral Res 2010

Definiciones (GeSIDA)

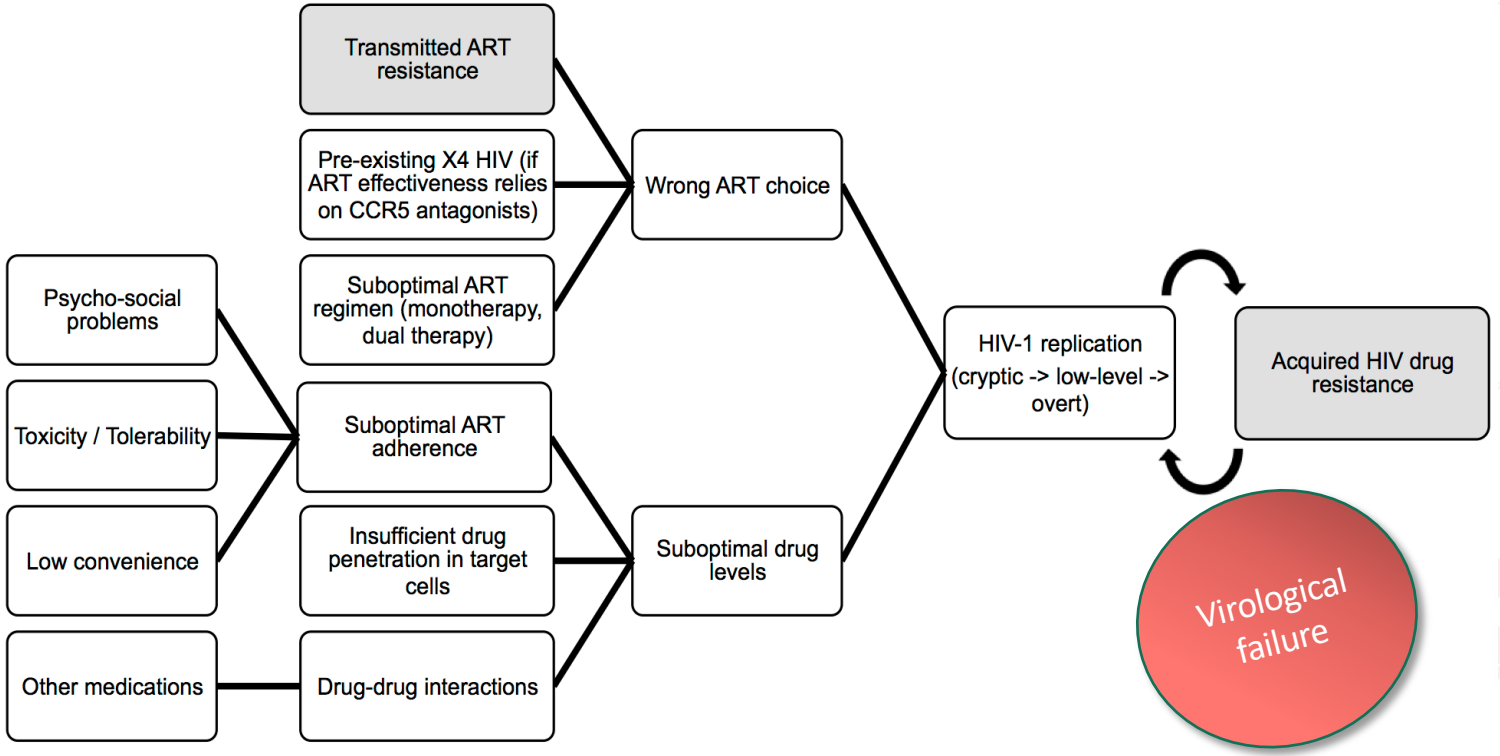
- **Fracaso virológico (FV):** CV >200 cop/mL transcurridas 24 semanas desde el inicio del TAR, confirmada en una muestra consecutiva.

    - ***Viremia de bajo nivel (VBN):*** CVP 50-1000 cop/mL en al menos dos muestras consecutivas. Estas viremias se pueden dividir en dos subgrupos:

        - CV 50-200: Impacto clínico incierto
        - CV 200-1000: Riesgo de fracaso

- **Blip:** CV 50 - 1000 cop/mL, con CVP previa y posterior <50 cop/mL.

How does viral failure happen?

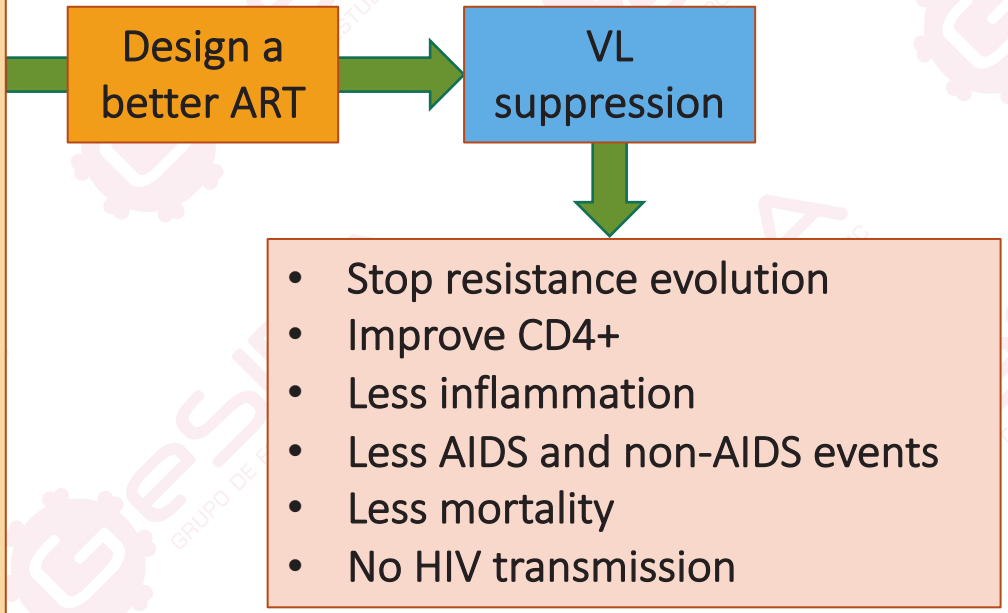


- CCR5, C-C chemokine receptor type 5

Casadellà M, Paredes R, Virus Res 2017;239:69–81

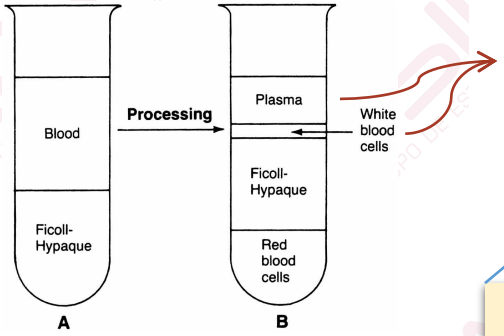
What should we do?

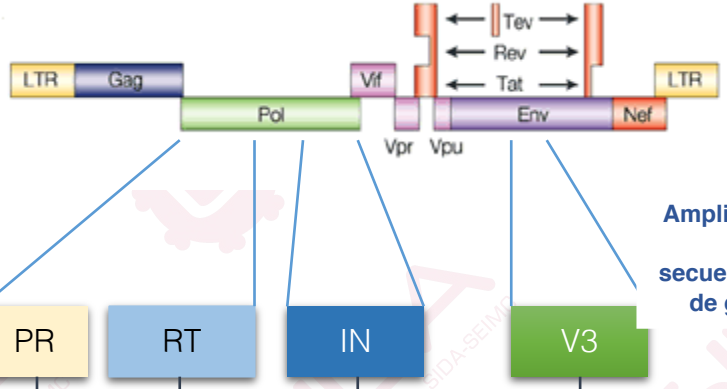
- Evaluate & promote adherence
- Check for drug-drug interactions
- Evaluate the barrier to resistance of current drugs
- Resistance testing --> Cumulative interpretation
- Viral tropism
- Drug levels?



HIV RESISTANCE GENOTYPING

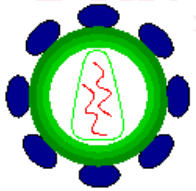
Separación de plasma y PBMCs





Amplificación y secuenciación de genes

STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

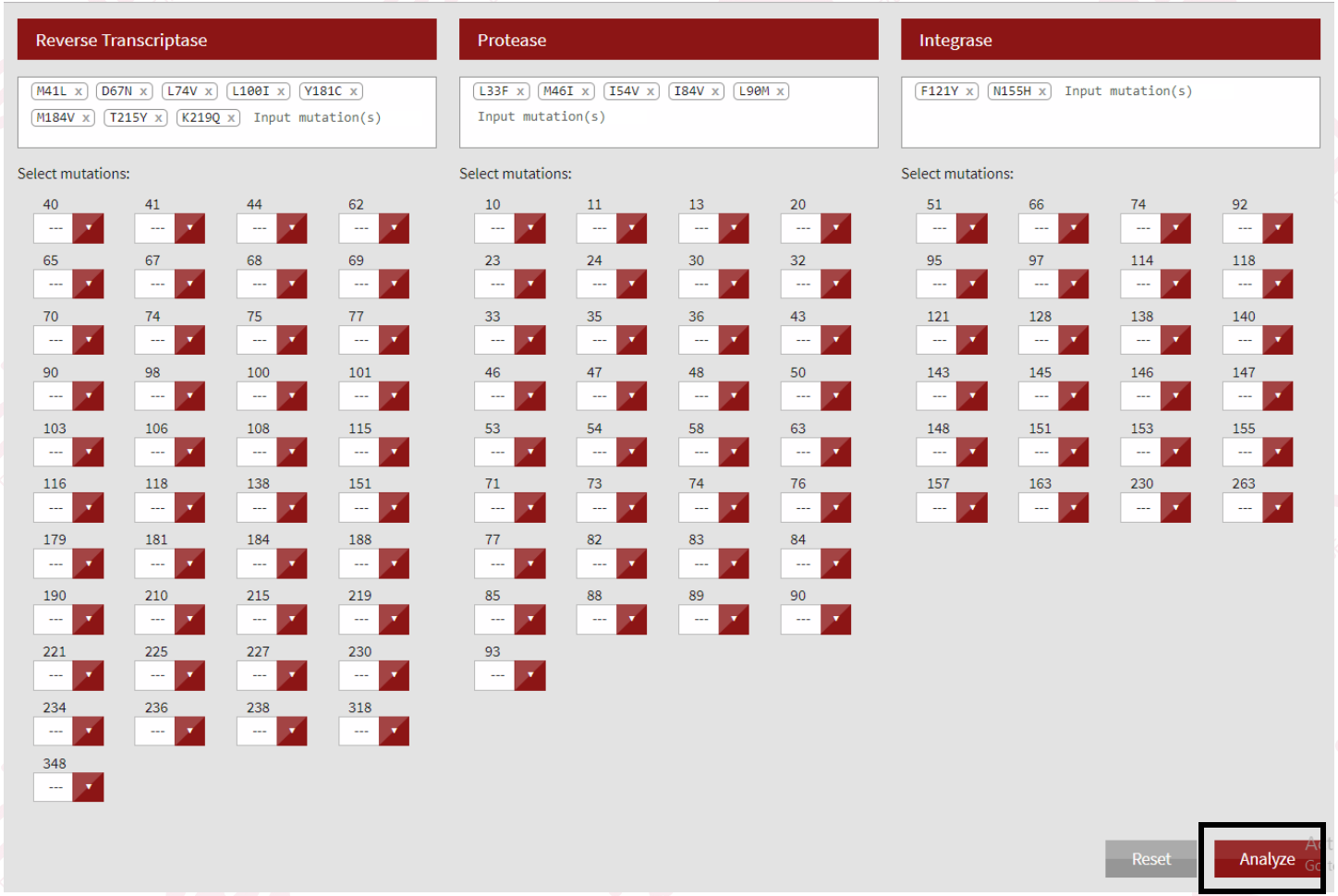


Interpretación fenotípica de las secuencias

Geno2pheno [coreceptor]

Who and When to Test – IAS-USA 2018

Recommendations	When to Test	Comments
All individuals with HIV infection if:		
• Newly diagnosed and presumably ART-naïve	As soon as an individual is diagnosed with HIV-1 infection. In any case, before ART is started.	To detect transmitted RAM. Early testing increases the chances of detecting TDR before mutations are potentially replaced by wild-type virus (particularly relevant for high–fitness cost mutations, eg, M184V, K65R, T215Y, and others). Many resistance mutations can still be detected even years after infection; in particular, low–fitness cost mutations (eg, K103N, L90M, etc). InSTI TDR is currently rare.
• On ART, with confirmed plasma HIV RNA >200 copies/mL after HIV RNA <50 copies/mL	Preferably while on failing ART	To detect acquired drug resistance in patients who initially responded to ART and, later on, failed. InSTI RAM should be tested in all treatment failures.
• Do not achieve full virus suppression after initiating ART	≥6 months after ART initiation	To detect acquired drug resistance in patients who did not achieve successful viral suppression to antiretroviral treatment. InSTI RAM should be tested in all treatment failures.
• Interrupted ART containing an NNRTI with a long half-life (eg, efavirenz)	As soon as virus rebounds > 500 HIV-RNA copies/ mL, respectively, before re-initiation of ART.	Treatment interruption of such regimens can lead to virtual monotherapy with rapid emergence of NNRTI resistance.
• who have a significant increase in viral load in a drug-naive individual not on treatment.	After confirmation of increase in plasma viremia.	Superinfection with drug-resistant virus may occur


Reverse Transcriptase
M41L x D67N x L74V x L100I x Y181C x M184V x T215Y x K219Q x Input mutation(s)
Select mutations:
40 41 44 62
65 67 68 69
70 74 75 77
90 98 100 101
103 106 108 115
116 118 138 151
179 181 184 188
190 210 215 219
221 225 227 230
234 236 238 318
348
Protease
L33F x M46I x I54V x I84V x L90M x
Input mutation(s)
Select mutations:
10 11 13 20
23 24 30 32
33 35 36 43
46 47 48 50
53 54 58 63
71 73 74 76
77 82 83 84
85 88 89 90
93
Integrase
F121Y x N155H x Input mutation(s)
Select mutations:
51 66 74 92
95 97 114 118
121 128 138 140
143 145 146 147
148 151 153 155
157 163 230 263
Reset
Analyze

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M41L, D67N, L74V, M184V, T215Y, K219Q**
NNRTI Resistance Mutations:	**L100I, Y181C**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	High-Level Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Low-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	High-Level Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	High-Level Resistance

Drug Resistance Interpretation: IN

IN Major Resistance Mutations:	**F121Y, N155H**
IN Accessory Resistance Mutations:	None
Other Mutations:	None

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Low-Level Resistance
dolutegravir (DTG)	Low-Level Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	**M46I, I54V, I84V, L90M**
PI Accessory Resistance Mutations:	**L33F**
Other Mutations:	None

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Low-Level Resistance
lopinavir/r (LPV/r)	High-Level Resistance

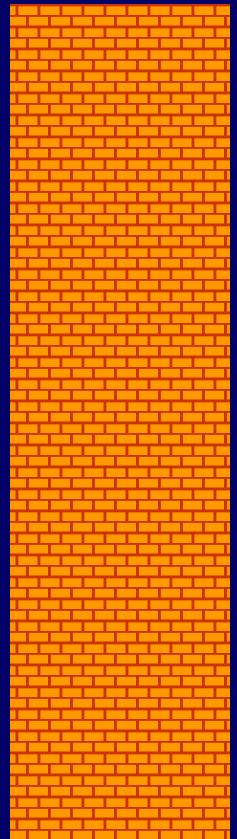
Stanford Drug Resistance Database

Resistance Test Interpretation Scores:

- Susceptible: Total score 0 to 9
- Potential low-level resistance: Total score 10 to 14
- Low-level resistance: Total score 15 to 29
- Intermediate resistance: Total score 30 to 59
- High-level resistance: Total score >= 60

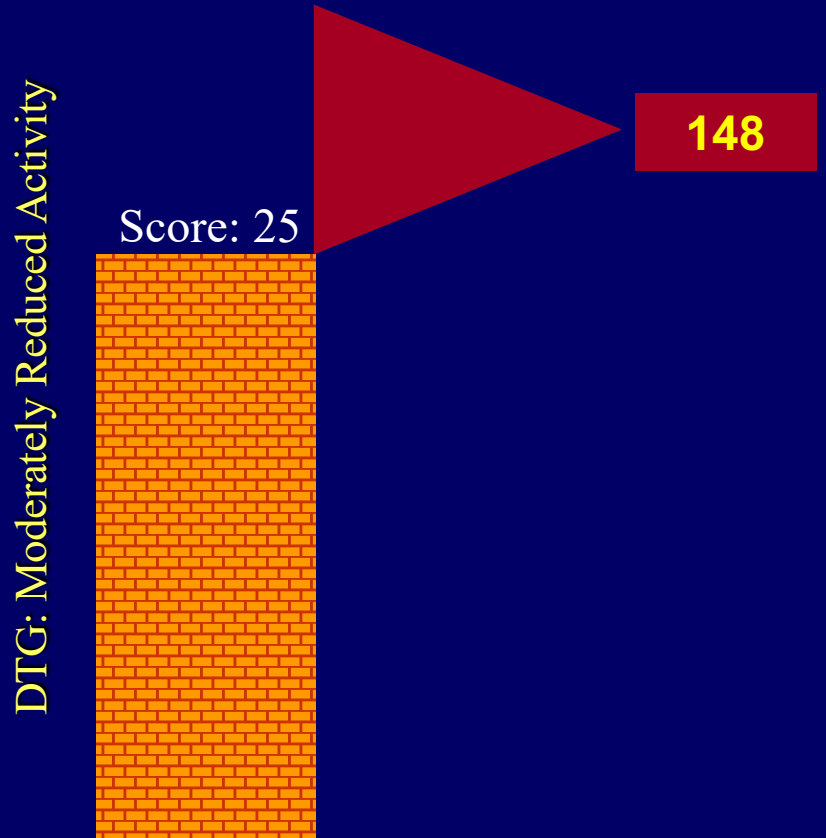
Accumulating Mutations Increase Stanford Scores
Example: Dolutegravir

Score: 0



DTG: Fully Active

Accumulating Mutations Increase Stanford Scores
Example: Dolutegravir



Accumulating Mutations Increase Stanford Scores
Example: Dolutegravir

DTG: Substantially Reduced Activity

Score: 45

148 + 140

Accumulating Mutations Increase Stanford Scores
Example: Dolutegravir

DTG: Severely Reduced Activity

Score: 80

148 + 140 + 138

Accumulating Mutations Increase Stanford Scores
Example: Dolutegravir

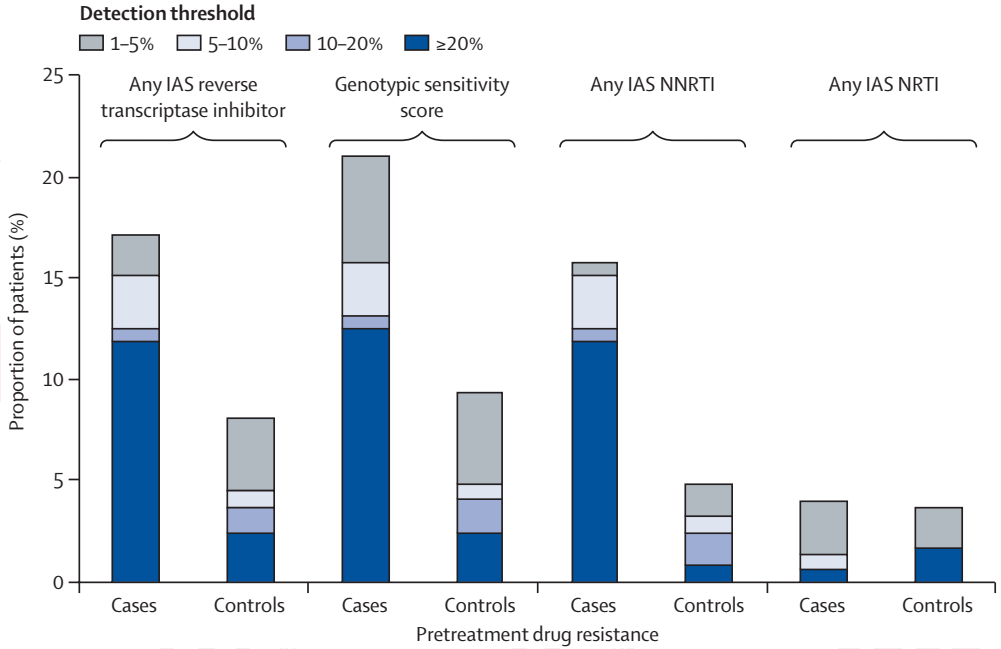
DTG: Severely Reduced Activity

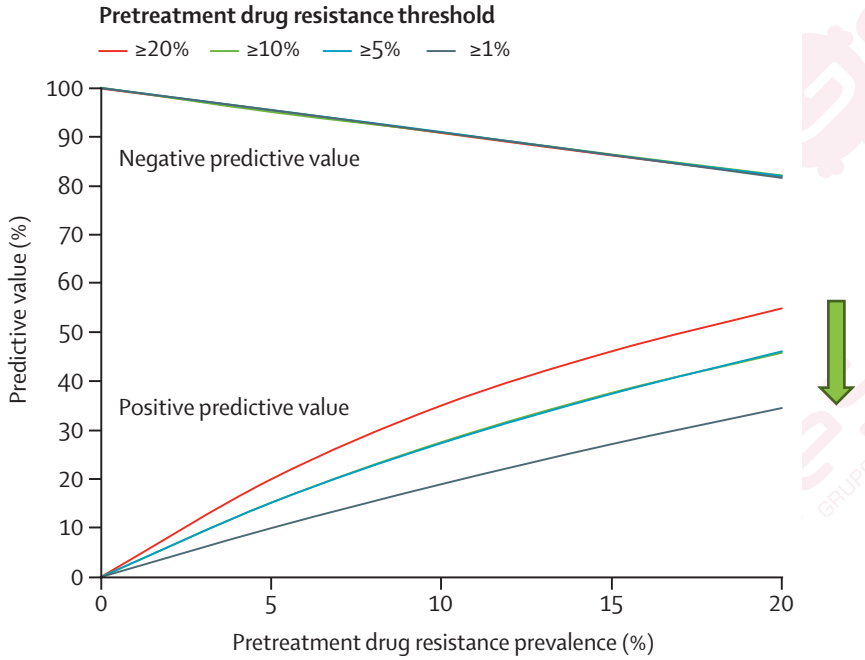
148 + 140 + 138

Score of 60

Score: 80

A “Sanger-like” cut-off for NGS is just fine: NNRTIs





Inzhaule S et al. Lancet HIV 2018

Co-Receptor Tropism Assays - DHHS

Perform a tropism test:

- Whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**
- For patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**
- Phenotypic is preferred **(AI)**
- Genotypic tropism assay as an alternative tropism test **(BII)**
- Proviral DNA tropism assay can be used in aviremic patients (BII)

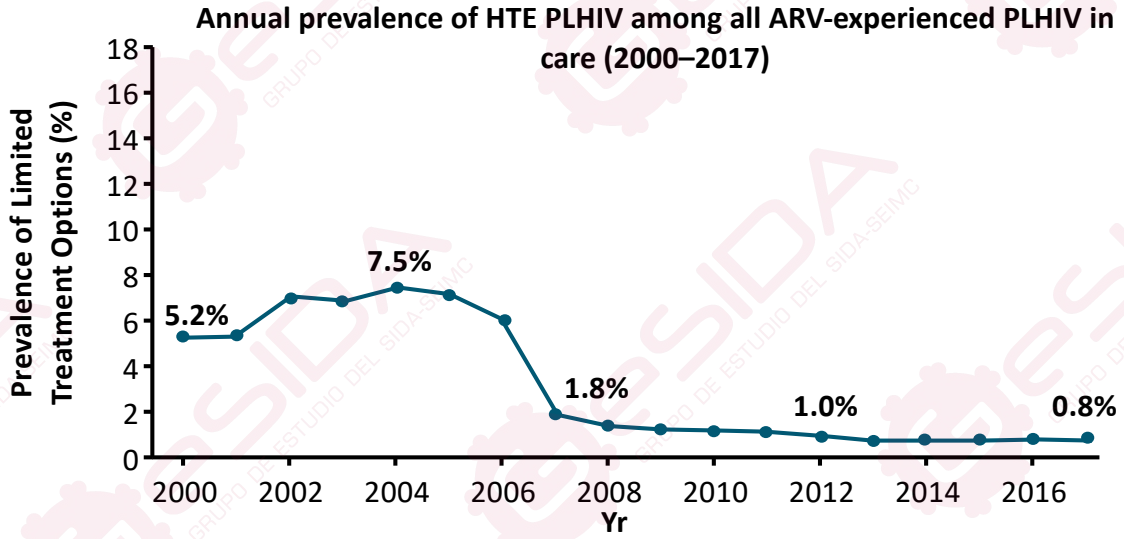
Preventing DR accumulation

- REGAIN virus suppression quickly

ARV drugs during non suppression	Tolerable VL	When should ART be changed	ART change
TXF / XTC	200 /mL	ASAP	No need to switch the backbone
NNRTIs	None	Immediately	2nd gen INSTIs
bPIs	200 /mL	ASAP	DRV + 2nd gen INSTIs
RAL / ELV	None	Immediately	2nd gen INSTIs
DTG / BIC	None	Immediately	DRV + 2nd gen INSTIs

MDR HIV

- Susceptible to ≤2 drug classes with ≤2 active drugs per class, according to a resistance test
- CNICS Cohort: >26,000 ARV-treated adults in the US



- Bajema K, et al. IAS 2019. Abstract MOPEB246

ARV, antiretroviral; CNICS, CFAR Network of Integrated Clinical System

MDR HIV in rich countries

- Adolescents with perinatal infection
- Adults infected early in the epidemic with successive virtual mono/dual ART

Dr Paredes – Personal Communication

- ART, antiretroviral therapy

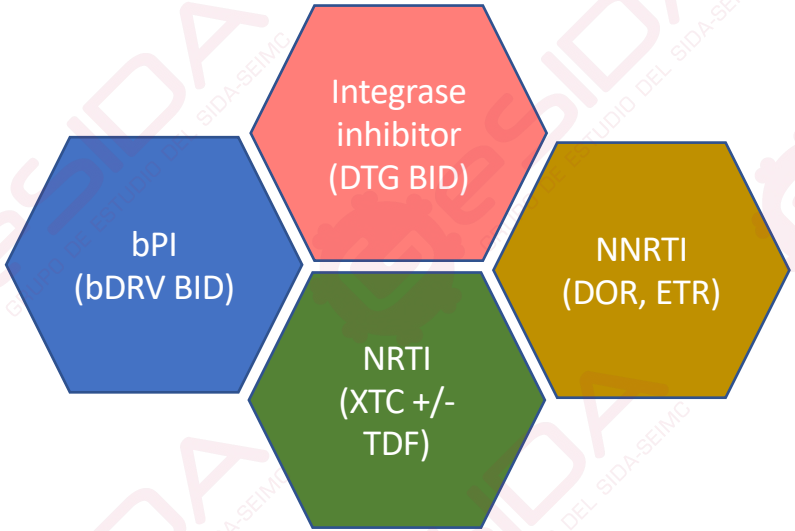
Images:ID 41629285 © Dontcut | Dreamstime.com (left) and Gfycat.com(right)

Management of DR HIV

- Management by an HIV DR expert
- Consider:
  - Adherence, adherence, adherence
  - Most VFs today are resolved with adherence reinforcement
  - Toxicity / tolerance
  - Treatment history → It is possible to predict resistance… although sometimes there are surprises!
  - Consider all previous genotypes → Resistance mutations do not disappear
  - Viral load and CD4+
    - Baseline VL predicts nadir CD4, residual viraemia, and risk of VF
    - Low CD4 + predicts VF
- **Hit hard and de-escalate when virus is suppressed**

• DR, drug resistance; VF, virologic failure

Basis for HIVDR (MDR) management



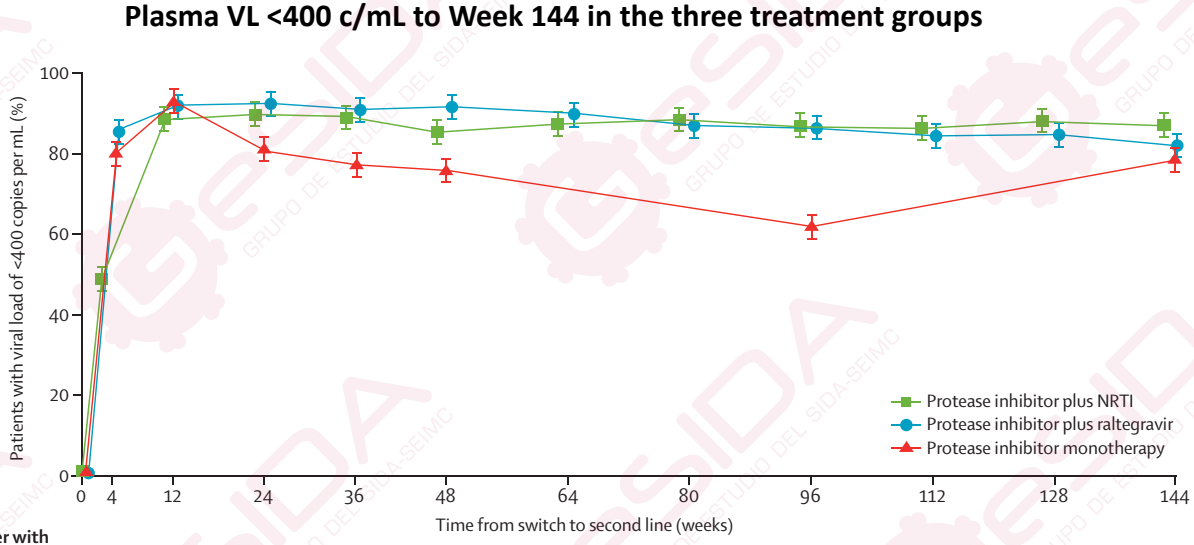
COMBINE CURRENT ART DRUGS
AIMING FOR RESIDUAL ACTIVITY

New ARVs
(often in clinical trials)
- Islatravir
- Fostemsavir
- Ibalizumab
- Lenacapavir

Drugs with residual use
- Maraviroc
- Enfuvirtide

bDRV, boosted darunavir; BID, twice daily; bPI, boosted protease inhibitor; DTG, dolutegravir; ETR, etravirine; Inh, isoniazid; NNRTI, non-nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; XTC, either emtricitabine FTC or lamivudine 3TC

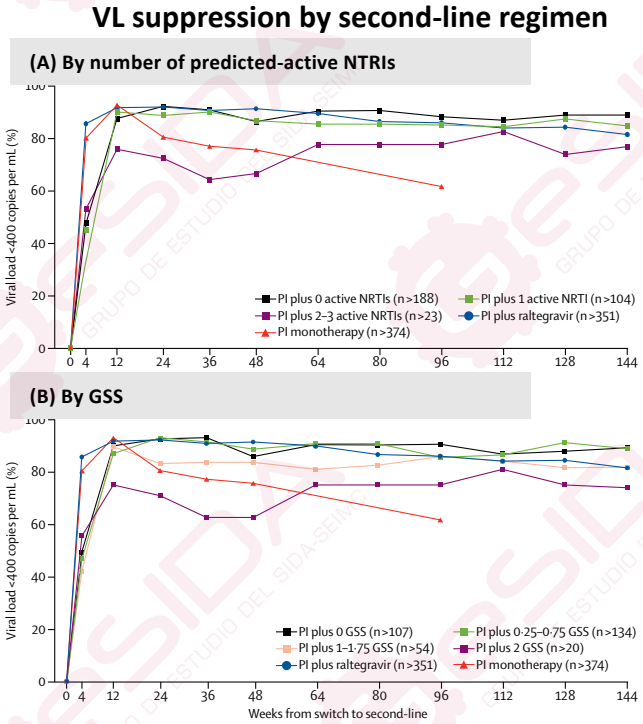
NRTIs retain antiviral activity in the presence of resistance (1)

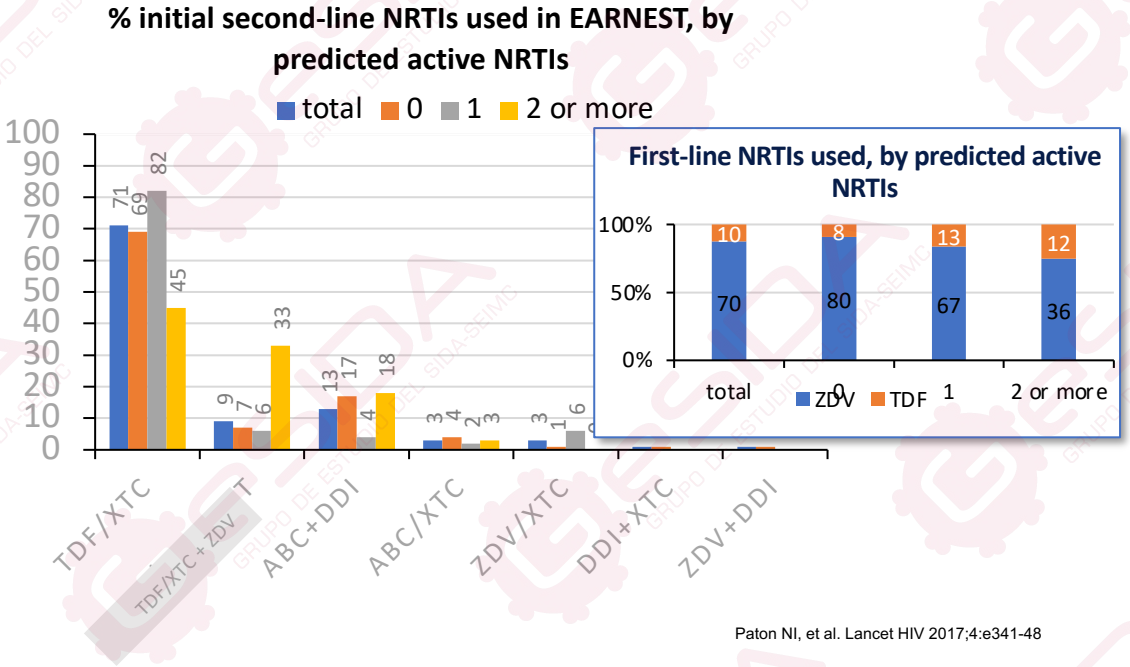


Number with viral-load result											
Protease inhibitor plus NRTI	426	374	381	382	386	395	382	370	379	351	342	367
Protease inhibitor plus raltegravir	433	389	394	389	382	400	392	378	391	369	351	383
Protease inhibitor monotherapy	481	374	385	378	379	389			380			375

Hakim JG, et al. Lancet Infect Dis 2018;18:47–57

NRTIs retain antiviral activity in the presence of resistance (2)





Paton NI, et al. Lancet HIV 2017;4:e341-48

- ABC, abacavir; DDI, drug–drug interaction; GSS, genotypic susceptibility score; PI, protease inhibitor; ZDV, zidovudine

NRTIs retain antiviral activity in the presence of resistance (3)

	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Genomic susceptibility score of second-line regimen (per 0·5 higher)	0·78 (0·61–0·99)	0·04	0·61 (0·46–0·81)	0·001
Proportion of non-adherent visits (per 10% higher)*	0·66 (0·55–0·79)	<0·0001	0·61 (0·49–0·77)	<0·0001
Unemployed or student *vs* employed	0·39 (0·21–0·72)	0·003	0·22 (0·07–0·63)	0·005
Hours worked by employed and students (per 10 h higher)	1·03 (0·92–1·17)	0·6	0·83 (0·70–0·99)	0·04
Baseline viral load per doubling	0·82 (0·70–0·95)	0·01	0·80 (0·67–0·97)	0·02
Baseline CD4 cell count per doubling	1·24 (1·02–1·50)	0·03	1·33 (1·04–1·71)	0·02

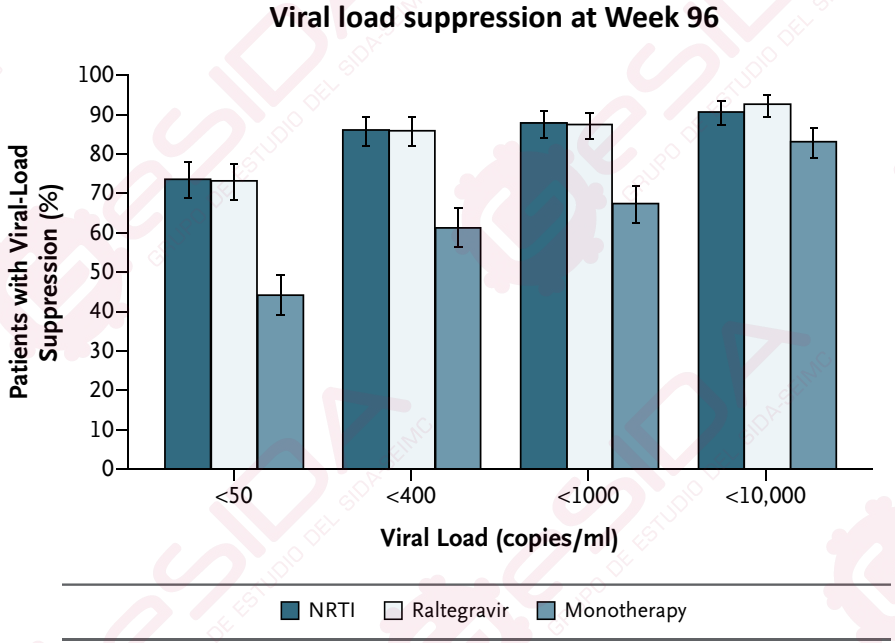
n=317, excluding those with missing week 144 viral load, baseline genotype or baseline employment status. Baseline refers to switch to second-line therapy (enrolment into the trial). Univariable analyses are in the appendix. Adjusted odds ratio adjusted for the factors given in the table. Factors not selected (p>0·05): sex, age, viral subtype, years on first-line antiretroviral treatment, diabetes, family history of cardiovascular disease, previous CNS disease, previous tuberculosis, smoking, alcohol consumption, household income, food availability, years of education, estimated glomerular filtration rate, haemoglobin, glucose, presence of individual mutations in the baseline genotype (where >10% prevalence), presence of combinations of 2 mutations in the baseline genotype (where >10% prevalence). *Scheduled visit that was either missed or where the participant self-reported missing pills since the last visit.

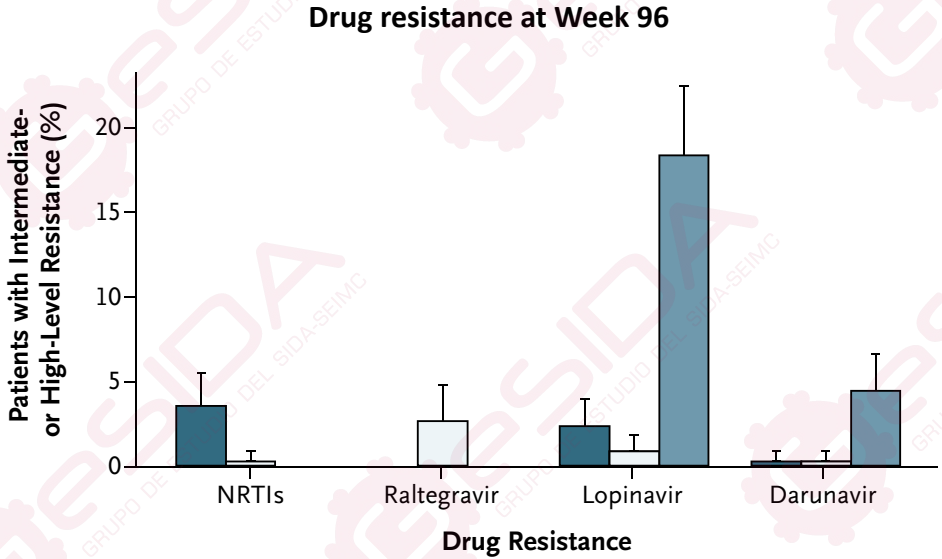
***Table 2*: Multivariable model for viral load <400 copies per mL at week 144 in protease inhibitor and nucleoside reverse-transcriptase inhibitor group**

CNS, central nervous system

Paton NI, et al. Lancet HIV 2017;4:e341-48

NRTIs help prevent PI resistance

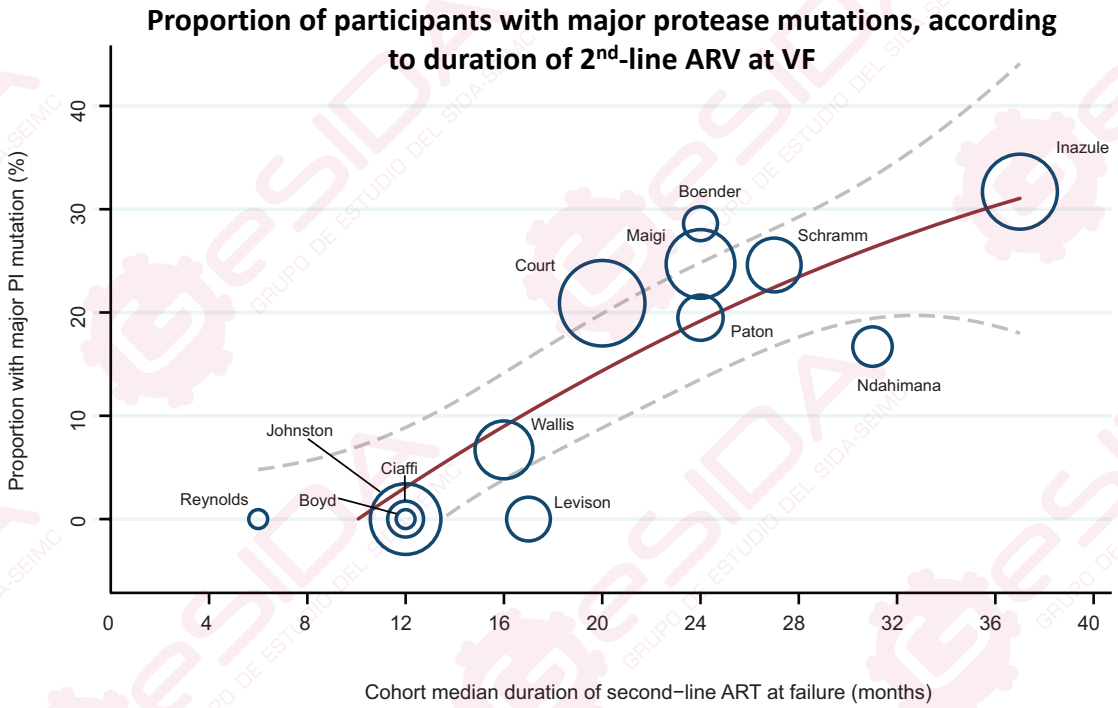




- In the above figures, I and T bars indicate 95% confidence intervals

Paton NI, et al. NEJM 2014;371:234-47

… but only to a certain extent



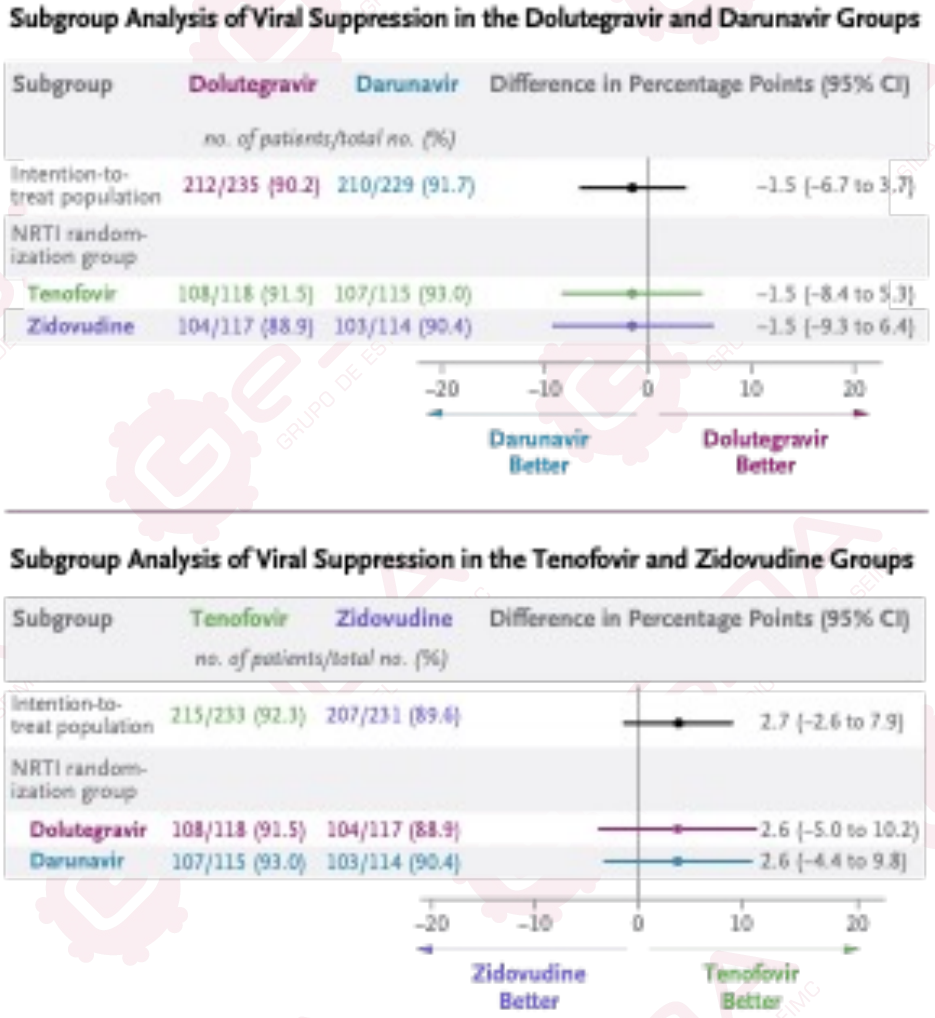
- Area of circles are proportional to size of cohort failing second-line treatment. Solid line and dashed line are quadratic line of best fit and 95% confidence interval, respectively

Stockdale AJ, et al. Clin Infect Dis 2018;66:1846-57

NADIA

No need to switch the NRTI backbone

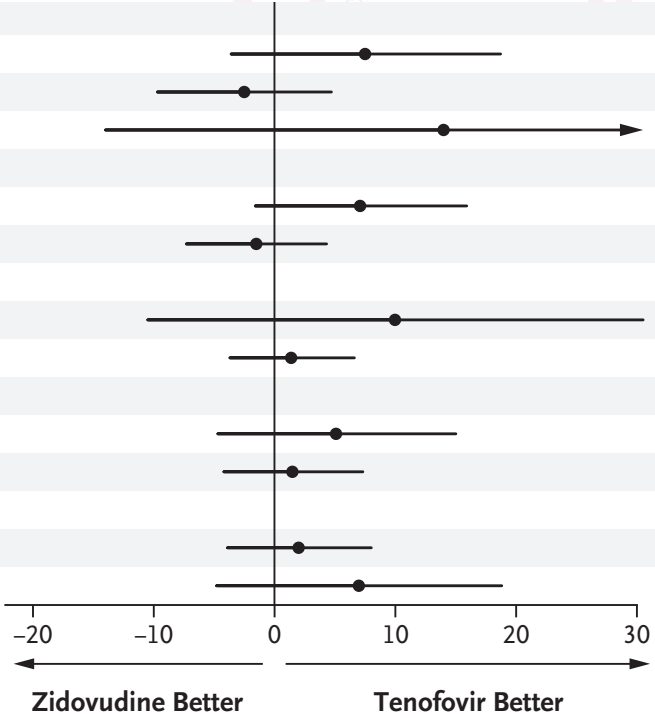
2 x 2 factorial, open-label, noninferiority trial, we randomly assigned patients for whom first-line therapy was failing (HIV-1 viral load, ≥1000 copies per milliliter) to receive dolutegravir or ritonavir-boosted darunavir and to receive te- nofovir or zidovudine; all patients received lamivudine.



Paton NI et al. NEJM 2021

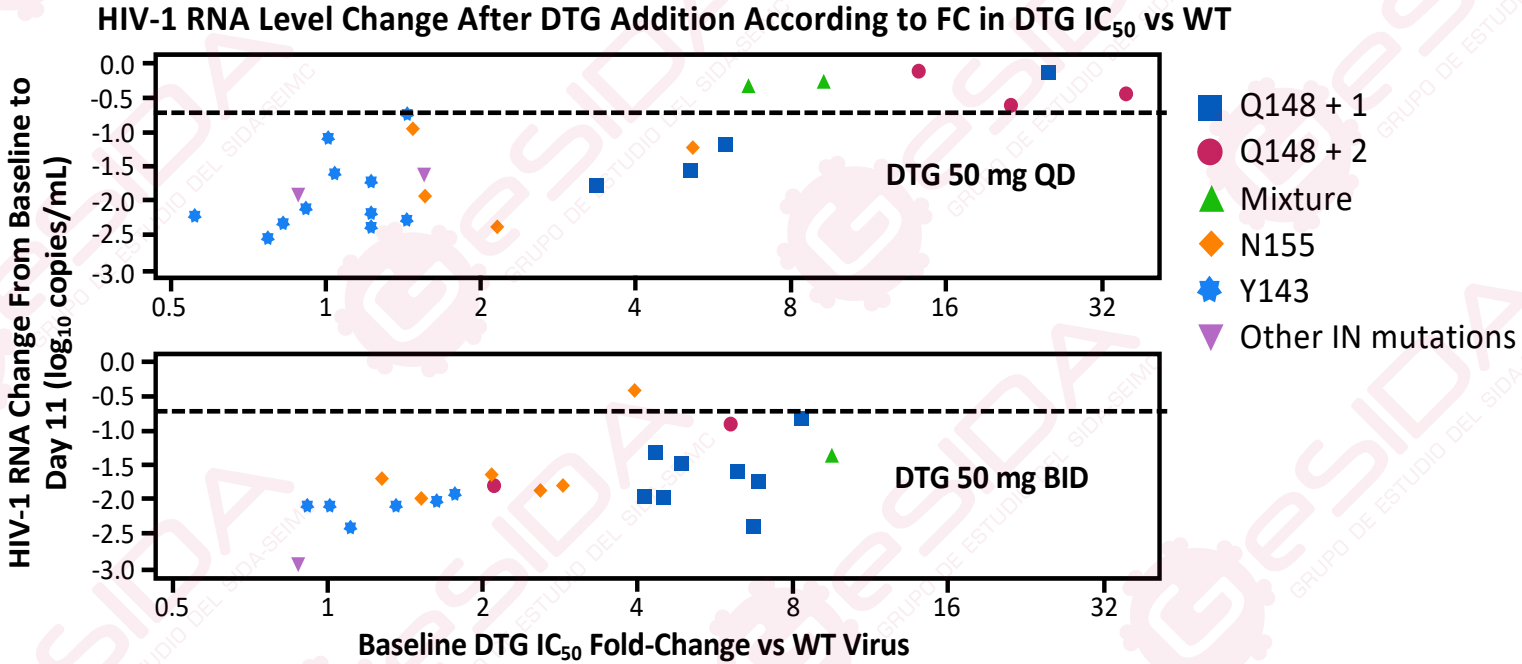
No need to switch the NRTI backbone

No. of predicted active NRTIs			
0	126/133 (94.7)	34/39 (87.2)	7.5 (–3.6 to 18.7)
1	73/80 (91.2)	150/160 (93.8)	–2.6 (–9.7 to 4.7)
≥2	13/17 (76.5)	15/24 (62.5)	14.0 (–14.0 to 41.9)
Presence of K65R/N at baseline			
No	103/114 (90.4)	94/113 (83.2)	7.2 (–1.6 to 15.9)
Yes	109/116 (94.0)	105/110 (95.5)	–1.5 (–7.3 to 4.3)
Presence of M184V/I at baseline			
No	24/29 (82.8)	24/33 (72.7)	10.0 (–10.5 to 30.5)
Yes	188/201 (93.5)	175/190 (92.1)	1.4 (–3.7 to 6.6)
Tenofovir resistance at baseline			
None or low level	86/97 (88.7)	76/91 (83.5)	5.1 (–4.8 to 15.0)
Intermediate or high level	126/133 (94.7)	123/132 (93.2)	1.5 (–4.2 to 7.3)
Zidovudine resistance at baseline			
None or low level	173/189 (91.5)	162/181 (89.5)	2.0 (–3.9 to 8.0)
Intermediate or high level	39/41 (95.1)	37/42 (88.1)	7.0 (–4.8 to 18.8)



Paton NI et al. NEJM 2021

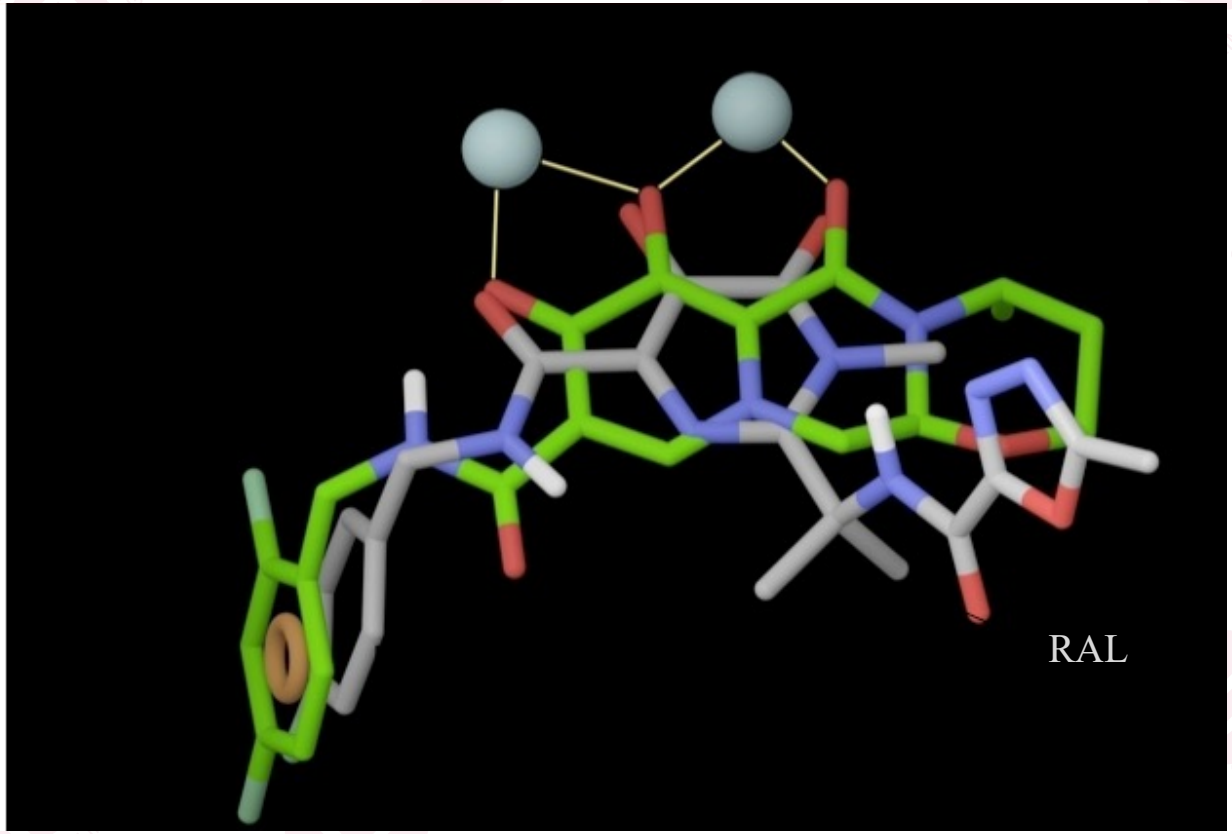
DTG activity in subjects with RAL resistance[1,2]



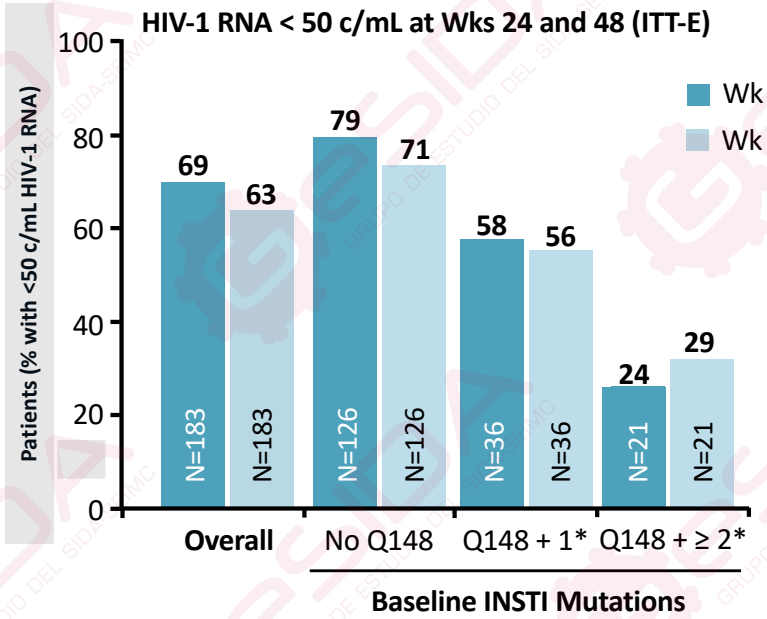
FC, fold change; IC_{50}, half maximal inhibitory concentration; IN, integrase; RAL, raltegravir; WT, wild type

1. Eron. JJ, et al. Infect Dis 2013;207:740–8
2. Soriano V et al.. EACS 2011. Abstr PS1/2LB.

DTG versus RAL alignment in active site



VIKING-3: DTG BID in subjects with RAL and EVG resistance



- 4 of 33 patients with N155H mutation at baseline had protocol-defined virologic failure

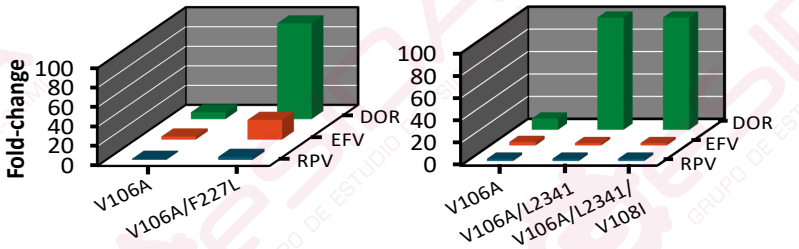
EVG, elvi

*Key secondary mutations were G140A/C/S, L74I and E138A/K/T.

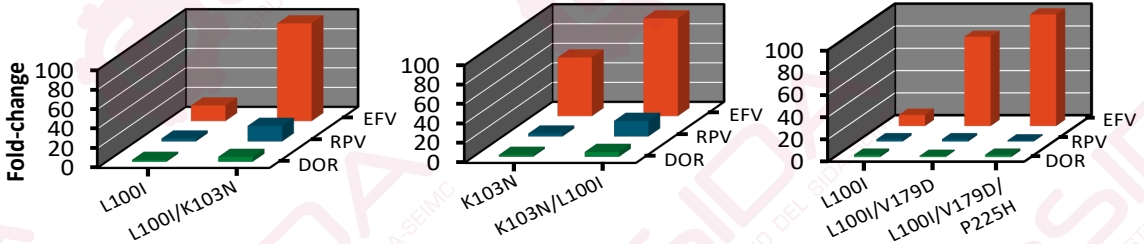
Castagna A. J Infect Dis 2014;210:354–62
Vavro CL, et al. EUDRW 2014. Abstr O_10.

DOR and NNRTI resistance

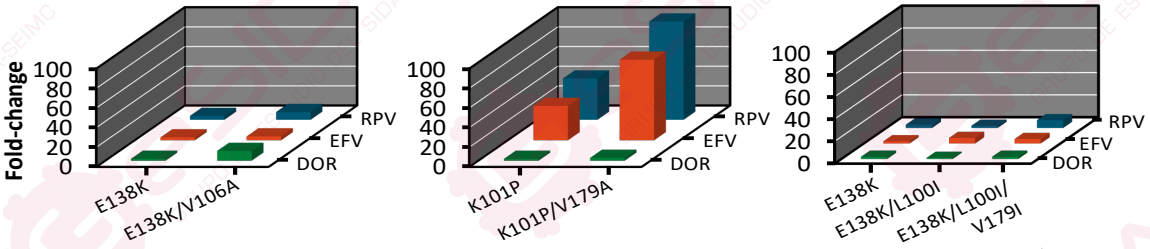
DOR-selected mutations (V106A, F227L, L234I, V108I)



EFV-selected mutations



RPV-selected mutations

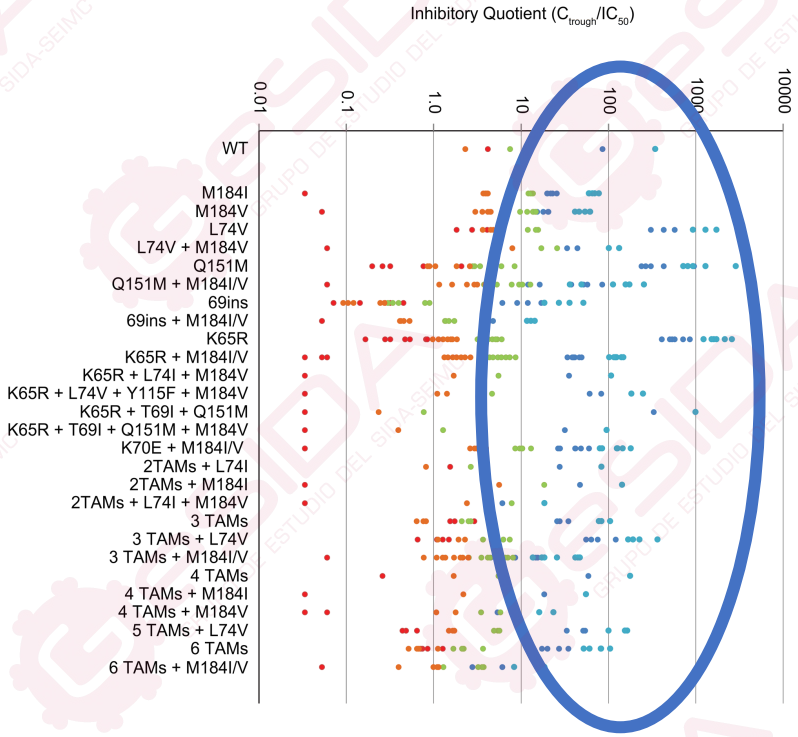


- EFV, efavirenz; RPV, rilpivirine

Feng M, et al. Antimicrob Agents Chemother 2015;59:590-8

ISLATRAVIR (MK-8951)

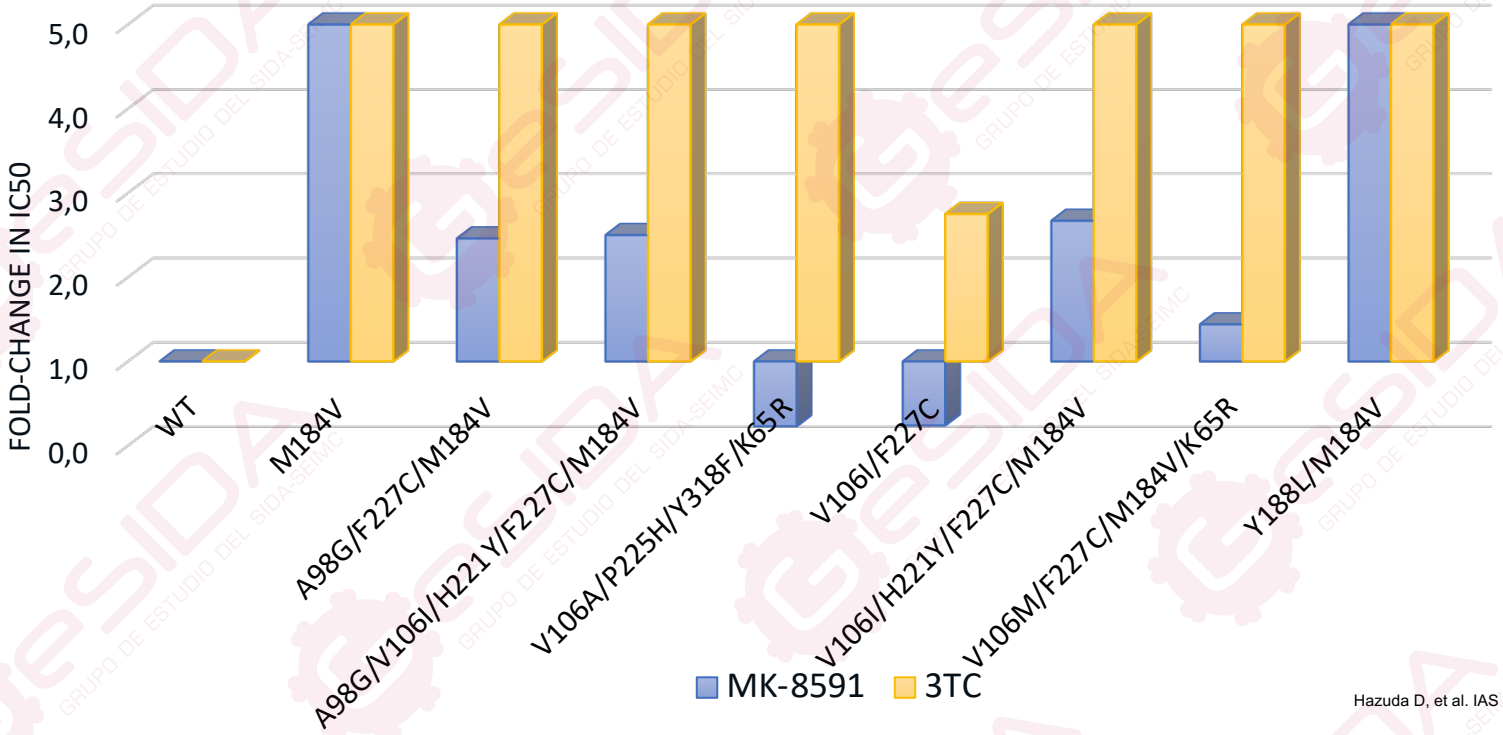
Inhibitory Quotients of MK-8591 and NRTIs Against Wild-Type and NRTI-Resistant HIV-1



QD, once daily

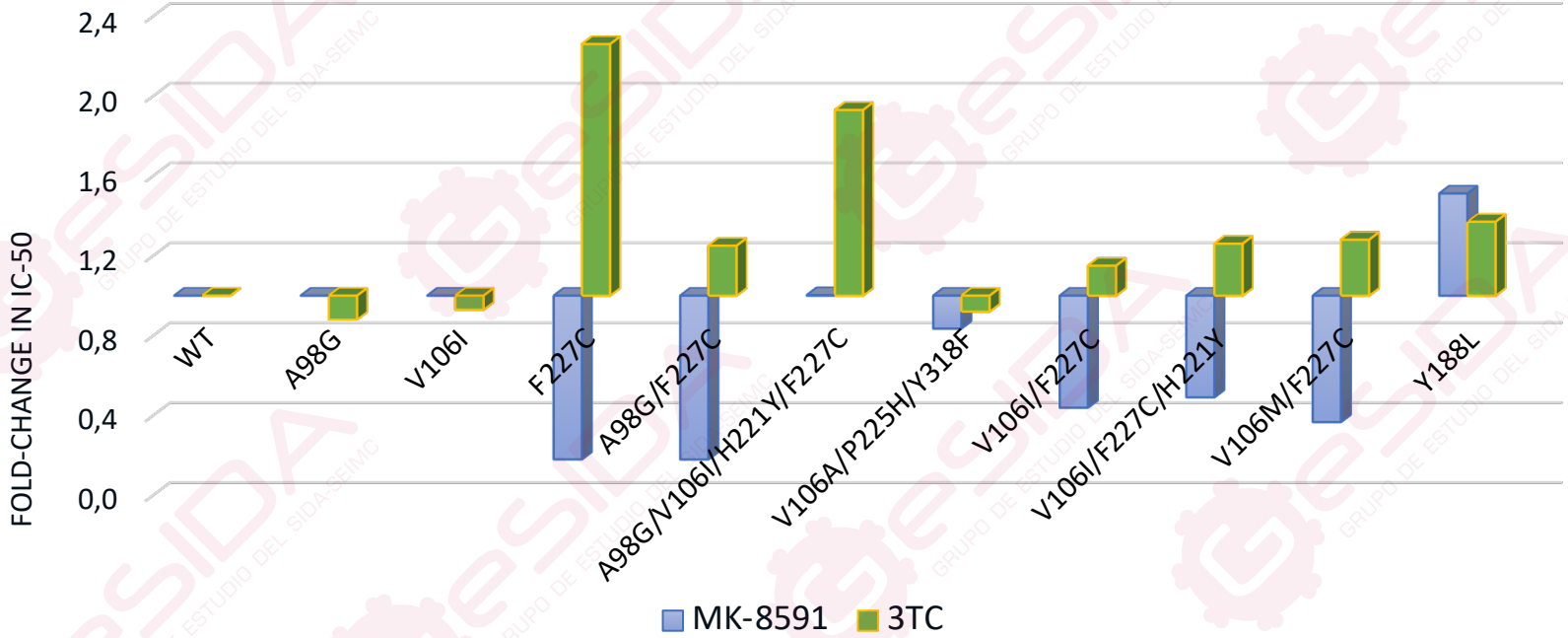
Grobler JA, et al. CROI 2021. Abstract 481 (P3530)

Susceptibility of DOR-resistant clinical isolates to ISL (MK-8591)



Hazuda D, et al. IAS 2018. Abstract THPEB068

Impact of DOR-associated mutations on susceptibility to ISL (MK-8591)



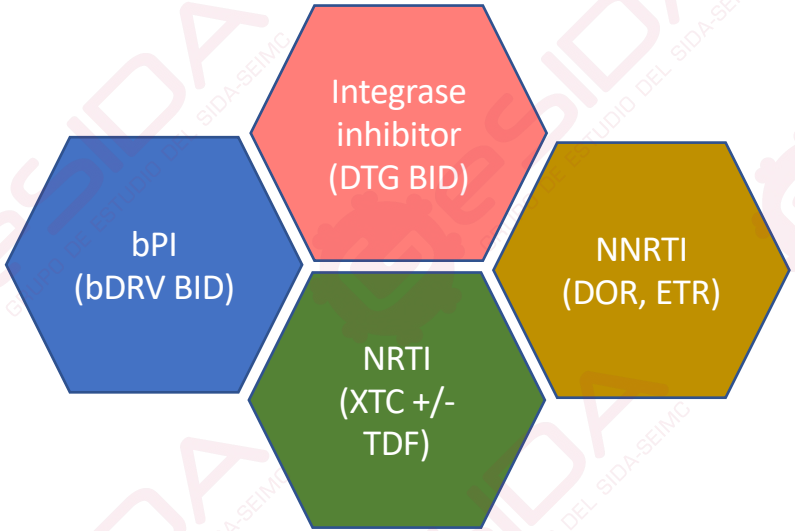
Hazuda D, et al. IAS 2018. Abstract THPEB068

GESIDA: Si no hay opciones

- **JAMÁS INTERRUMPIR EL TRATAMIENTO (AI)**
- Evitar la monoterapia funcional (A-III).
- Construr un **tratamiento "puente"** (A-III) hasta que sea possible un TAR supresor con 2-3 FAR activos (A-III).
- **Derivar al paciente** a un centro con experiencia y acceso a nuevos FAR (ensayos o programas de acceso expandido) (A-III).

Conclusions

HIV-RNA <50 c/ML
Never STOP ART



COMBINE CURRENT ART DRUGS
AIMING FOR RESIDUAL ACTIVITY

New ARVs
(often in clinical trials)
- Islatravir
- Fostemsavir
- Ibalizumab
- Lenacapavir

Drugs with residual use
- Maraviroc
- Enfuvirtide