GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults HIV-1 (DRIVE-FORWARD): 48- week results of a randomised, double-blind, phase 3, non inferiority trial

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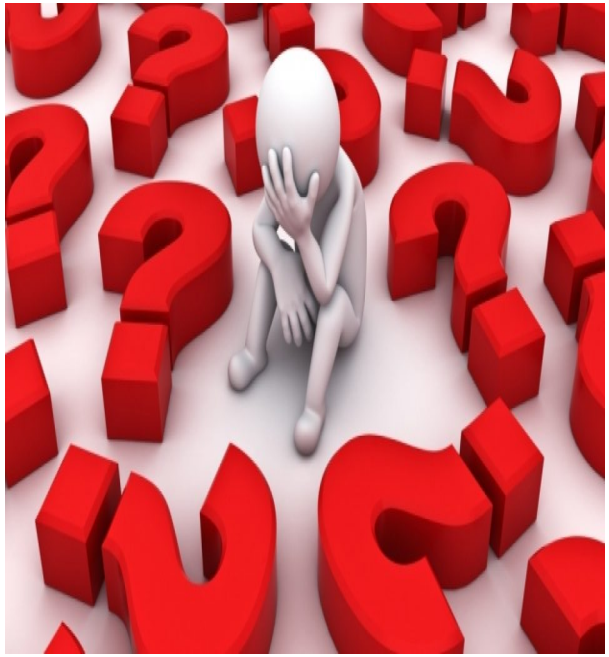
Pongámonos en contexto (I)

- ITINAN:
  - EFV: SNC, rash, lípidos, ¿ideación suicida?
  - RPV: eficacia, comida, IBP
  - NVP: toxicidad dermatológica y hepática, warning CD4
  - ETV: BID, no aprobada en naive



Pongámonos en contexto (II)

REGIMEN	nb	%
3TC ABC DTG	132	39
DTG ETC TDF	78	23
DRV ETC RTV TDF	25	7
ETC RPV TDF	22	7
ETC EVG TDF	19	6
EFV ETC TDF	16	5

Datos Cohorte Suiza 2015. Disponible en http://www.shcs.ch/228-3-antiretroviral-treatment último acceso 05.05.2018

Pongámonos en contexto (III)

		Virological/ Immunological	TOXICITY					Patient wish	Physician decision	Simplification	Other	No. of Regimen*
			GI	Liver	Kidney	CNS	Other					
2015	DRV ETC RTV TDF	9	14	1	22	3	26	36	69	75	45	289
2015	EFV ETC TDF	2	1	4	13	108	25	12	58	20	45	286
2015	DTG ETC TDF	1	3	5	13	6	7	21	29	101	18	202
2015	ATV ETC TDF	5	2	2	24	1	17	20	39	45	23	169
2015	3TC ABC DRV RTV	1	5	0	0	0	19	14	28	67	13	145

3.9.6: The five frequently discontinued regimens in 2015, by reason, number[0]

Datos Cohorte Suiza 2015. Disponible en http://www.shcs.ch/228-3-antiretroviral-treatment último acceso 05.05.2018

Pongámonos en contexto (y IV)

- Doravirina:
  - Alta potencia (IC_{50} 12 nM en WT)
  - Activo con mutaciones clásicas ITINAN (103, 138, 181)
  - Sustrato de citocromo P450
  - No afectado por ingesta

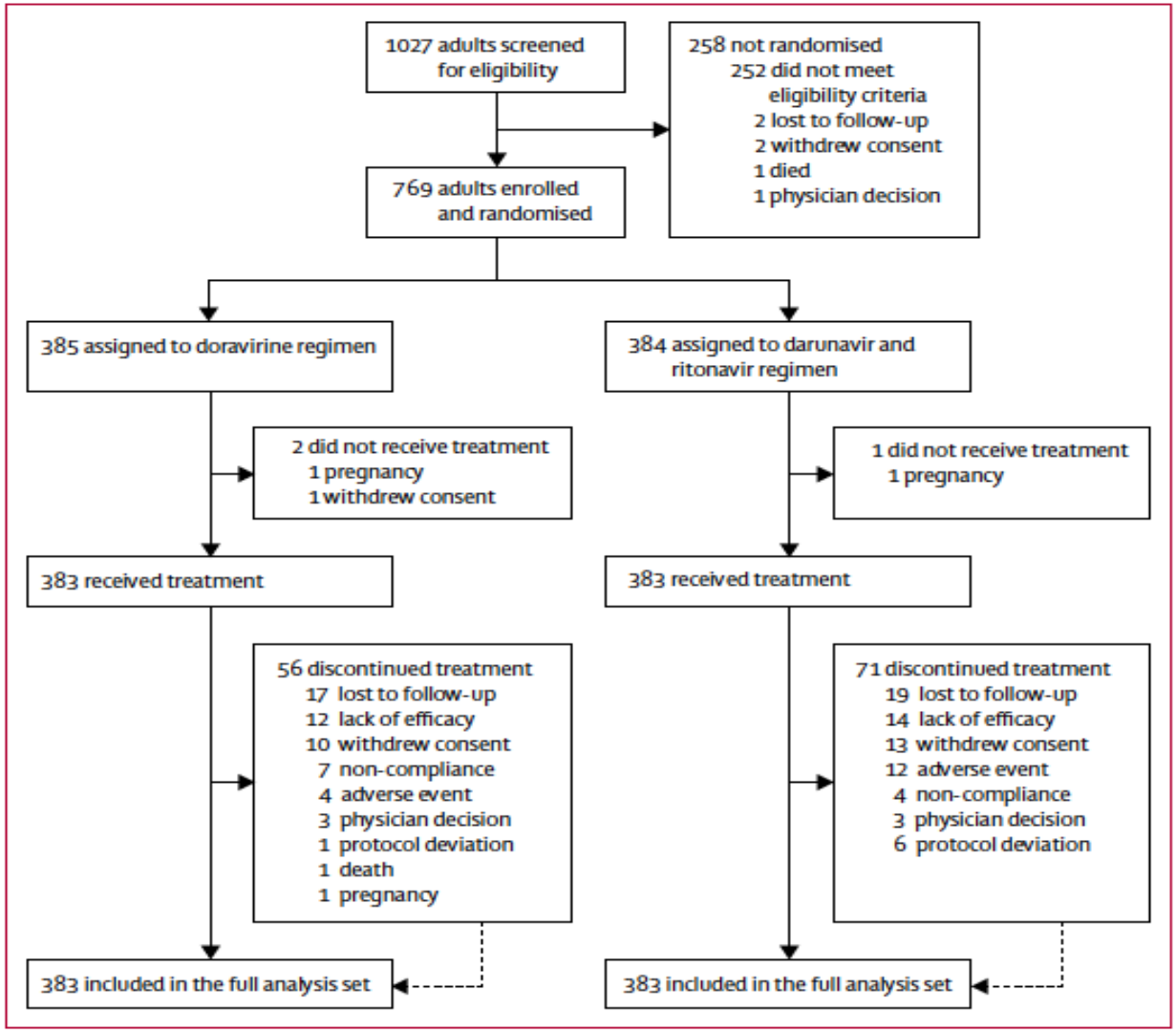
Métodos (I)

- Fase 3, aleatorizado 1:1, controlado con placebo, doble ciego, de no inferioridad
- 2 ITIAN +:
  - DRV-rtv QD
  - DOR (100 mg)
- ITIAN:
  - TDF+FTC
  - ABC+3TC
  - Libre elección
- Placebo
- 4 cp/día

Métodos (II)

- Estratificación:
  - Pareja de análogos
  - CV (10^5 copias/mL)
- FV:
  - >200 cp 24 o 36 s
  - >50 cp 48 s
  - Rebrote
  - Muestra confirmación 1-4 s
  - Cambio AN pasada s 2 con cv>50 cp/mL
- Objetivo Primario:
  - CV<50 cp/mL 48 s snapshot
- Tamaño estimado: 680
- Análisis interinos:
  - Efectos SNC (200, 8 s)
  - Eficacia (300, 24 s)

Población


1027 adults screened for eligibility
258 not randomised
252 did not meet eligibility criteria
2 lost to follow-up
2 withdrew consent
1 died
1 physician decision
769 adults enrolled and randomised
385 assigned to doravirine regimen
384 assigned to darunavir and ritonavir regimen
2 did not receive treatment
1 pregnancy
1 withdrew consent
1 did not receive treatment
1 pregnancy
383 received treatment
383 received treatment
56 discontinued treatment
17 lost to follow-up
12 lack of efficacy
10 withdrew consent
7 non-compliance
4 adverse event
3 physician decision
1 protocol deviation
1 death
1 pregnancy
71 discontinued treatment
19 lost to follow-up
14 lack of efficacy
13 withdrew consent
12 adverse event
4 non-compliance
3 physician decision
6 protocol deviation
383 included in the full analysis set
383 included in the full analysis set

Características basales

	Doravirine regimen (n=383)	Darunavir and ritonavir regimen (n=383)
Sex		
Men	319 (83%)	326 (85%)
Race		
White	280 (73%)	280 (73%)
Median age, years	33·0 (27–41)	34·0 (27–43)
Median CD4 count (cells per µL)	410 (299–550)	393 (257–547)
CD4 count (cells per µL)		
≤200	42 (11%)	67 (17%)
>200	341 (89%)	316 (83%)
Median HIV-1 RNA $\log_{10}$ copies per mL	4·4 (4·0–4·9)	4·4 (4·0–4·8)
HIV-1 RNA concentration†		
≤100 000 copies per mL	300 (78%)	308 (80%)
>100 000 copies per mL	83 (22%)	74 (19%)
Previous AIDS diagnosis	36 (9%)	37 (10%)
NRTI component†		
Tenofovir and emtricitabine	333 (87%)	335 (87%)
Abacavir and lamivudine	50 (13%)	48 (13%)

Eficacia 48 s

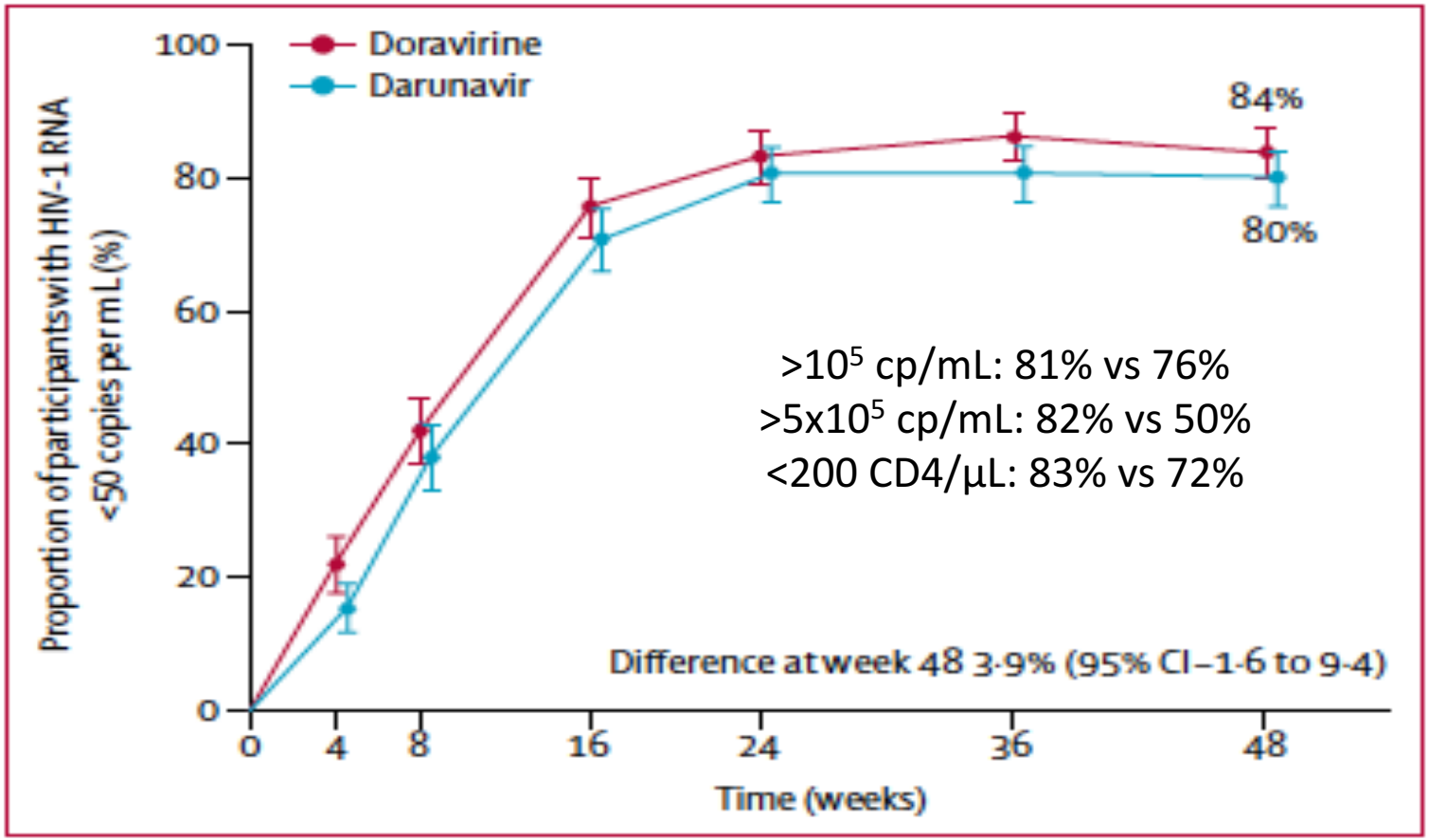


Figure 2: **Proportion of participants with HIV-1 RNA of less than 50 copies per mL by visit**

Δ CD4 48 s: 193 vs 186 cél/µL

Fracasos Virales

- 5% DOR vs 6% DRV
- Rebotes
- Test Genotípico:
  - 15/43 (7 vs 8)
- Sin R a DOR ni AN
- DRV-rtv: polimorfismos

- Interrupción por otras causas:
  - 10% vs 14%
  - 1% en cada brazo cv>400 cp/mL
  - 1 DOR: V106I, H221T, Phe227C junto a M184V

Efectos Adversos

	Doravirine regimen (n=383)		Darunavir and ritonavir regimen (n=383)	
	All cause	Treatment-related	All cause	Treatment-related
Any adverse event	307 (80%)	117 (31%)	300 (78%)	123 (32%)
Serious adverse event	19 (5%)	1 (<1%)	23 (6%)	1 (<1%)
Discontinued due to adverse event*	6 (2%)	4 (1%)	12 (3%)	8 (2%)
Most common adverse events†				
Upper abdominal pain	19 (5%)	9 (2%)	10 (3%)	2 (1%)
Diarrhoea	54 (14%)	21 (5%)	86 (22%)	49 (13%)
Nausea	41 (11%)	25 (7%)	46 (12%)	29 (8%)
Fatigue	31 (8%)	18 (5%)	20 (5%)	8 (2%)
Nasopharyngitis	30 (8%)	0	39 (10%)	0
Upper respiratory infection	36 (9%)	0	23 (6%)	0
Back pain	21 (5%)	0	8 (2%)	0
Dizziness	19 (5%)	11 (3%)	15 (4%)	7 (2%)
Headache	53 (14%)	23 (6%)	41 (11%)	10 (3%)
Cough	19 (5%)	1 (<1%)	6 (2%)	0
Events of clinical interest				
Rash‡	28 (7%)	8 (2%)	32 (8%)	12 (3%)
Neuropsychiatric§	44 (11%)	22 (6%)	50 (13%)	19 (5%)

Incidencia de anomalías de laboratorio 3-4 similares

Lípidos

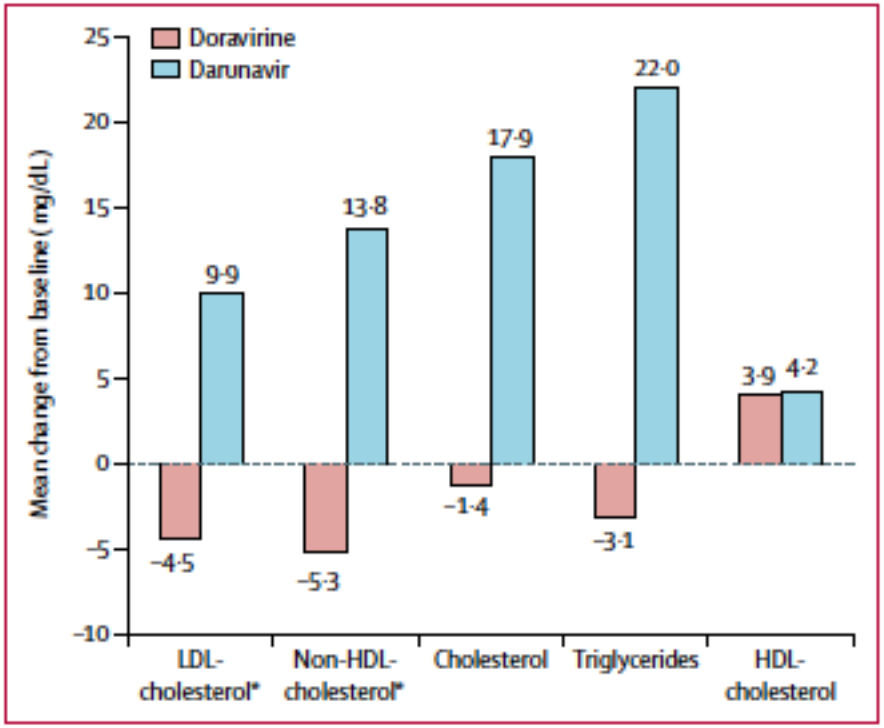


***Figure 3*: Change from baseline in fasting lipid concentrations at week 48**
Statistical analyses were not prespecified for cholesterol, triglyceride, or HDL-cholesterol. *p<0·0001 for between-group comparison.

Conclusiones (I)

- Se demuestra la no inferioridad de DOR vs DRV-rtv a 48 s
  - CV> 10^5 cop/mL
  - CD4<200
  - Ascenso de CD4 similar
  - Similar con TDF/FTC y ABC/3TC
- DOR: eficacia similar a RPV y EFV
- DRV-rtv: eficacia menor
  - Más penalizado por interrupciones
  - Definición y protocolo de fracaso viral

Conclusiones (II)

- Fracasos virales:
  - DOR: mutaciones resistencias 0.3% (1/383)
- Perfil lipídico favorable
- Rash y SNC:
  - Similares a RPV (ECHO, THRIVE)