¿Efavirenz debe seguir siendo tratamiento preferente de primera línea en guías mexicanas?

Votación

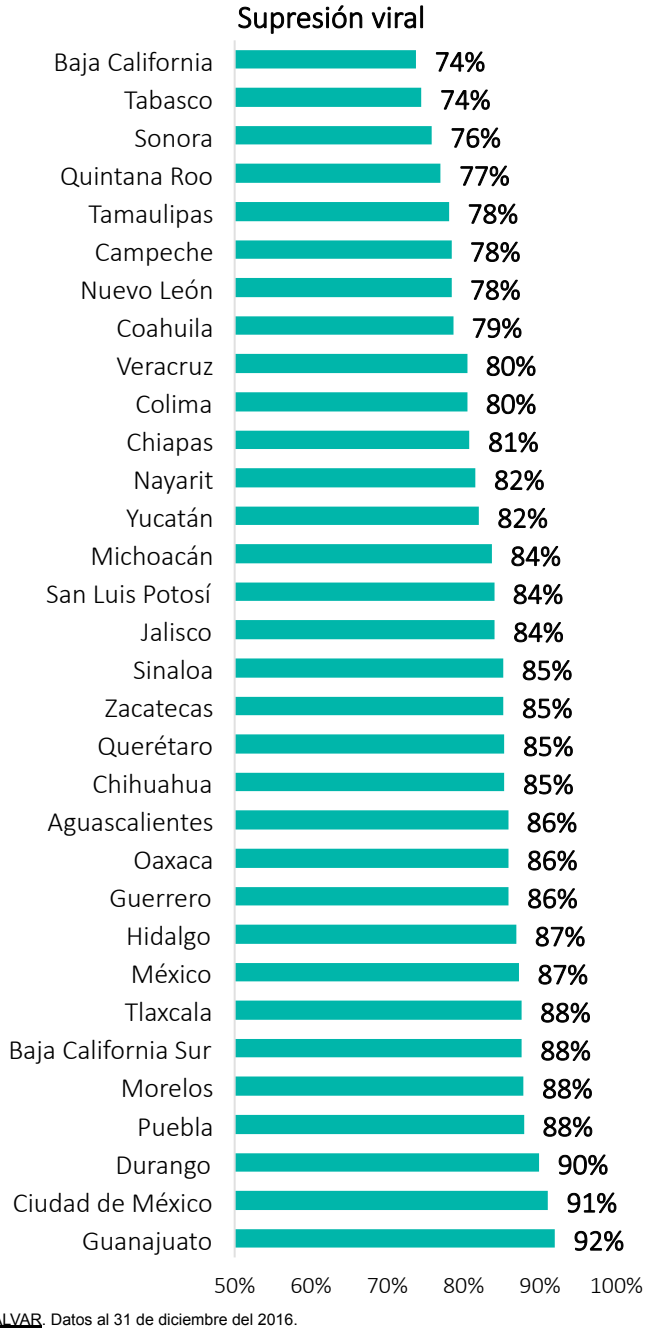
Uso de esquemas basados en efavirenz vs esquemas basados en inhibidores de integrasa

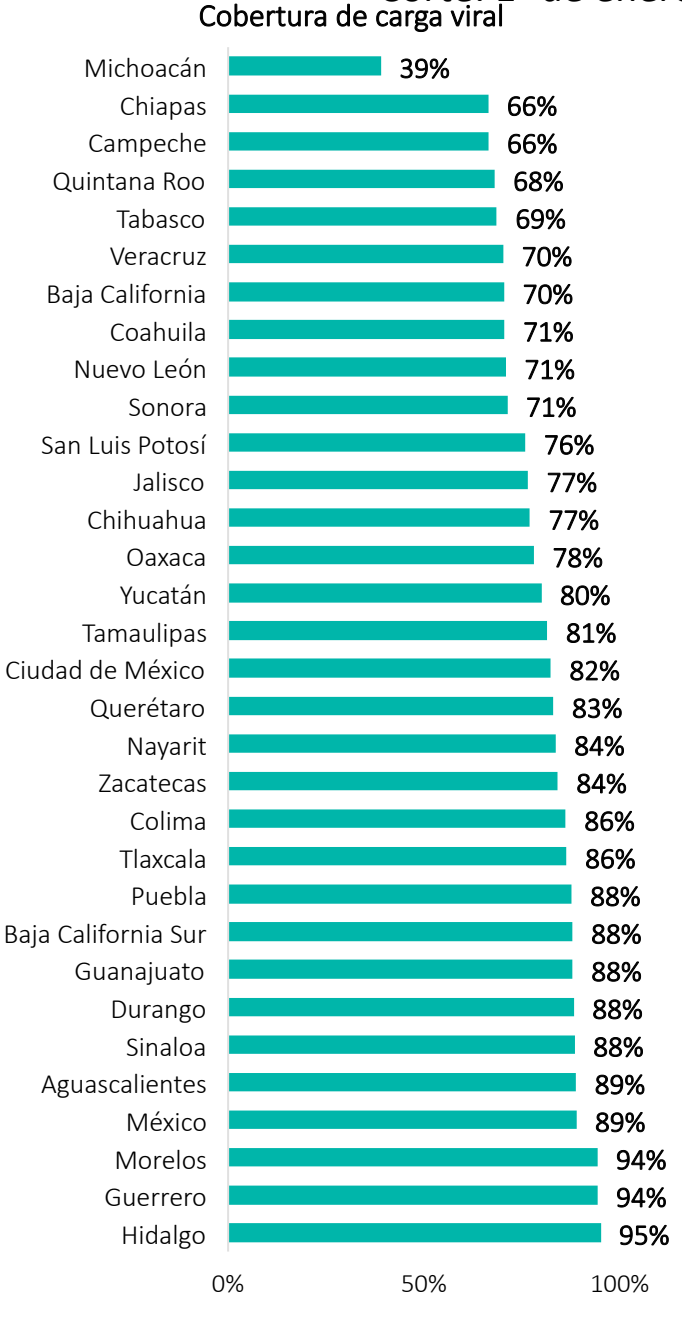
Dr. Juan Luis Mosqueda

Pues con inhibidores de integrasa¡¡¡

Indicadores para evaluar la calidad de la atención

Corte: 1° de enero de 2017

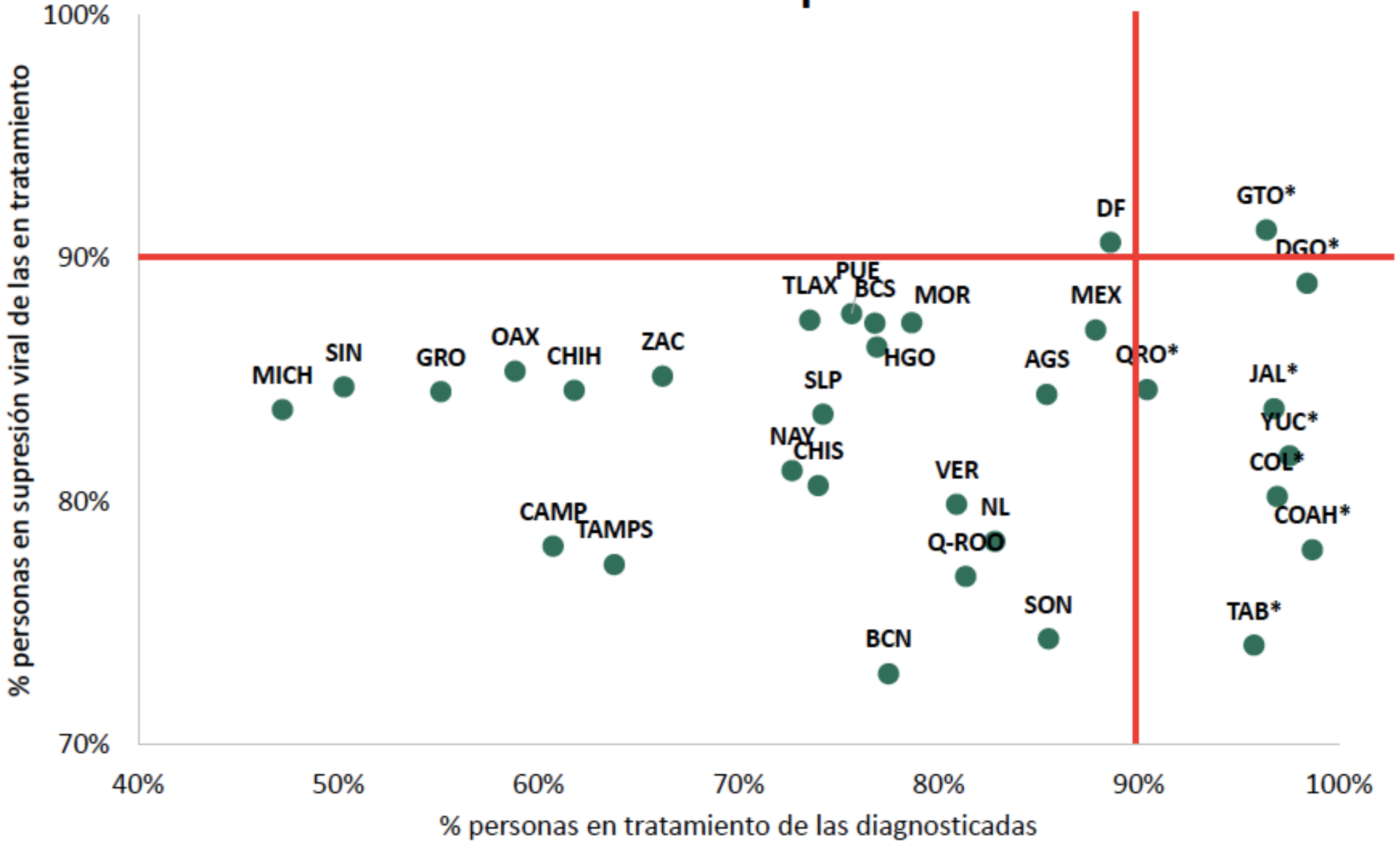




Fuente: SS/Censida. SALVAR. Datos al 31 de diciembre del 2016.

SALUD
SECRETARÍA DE SALUD

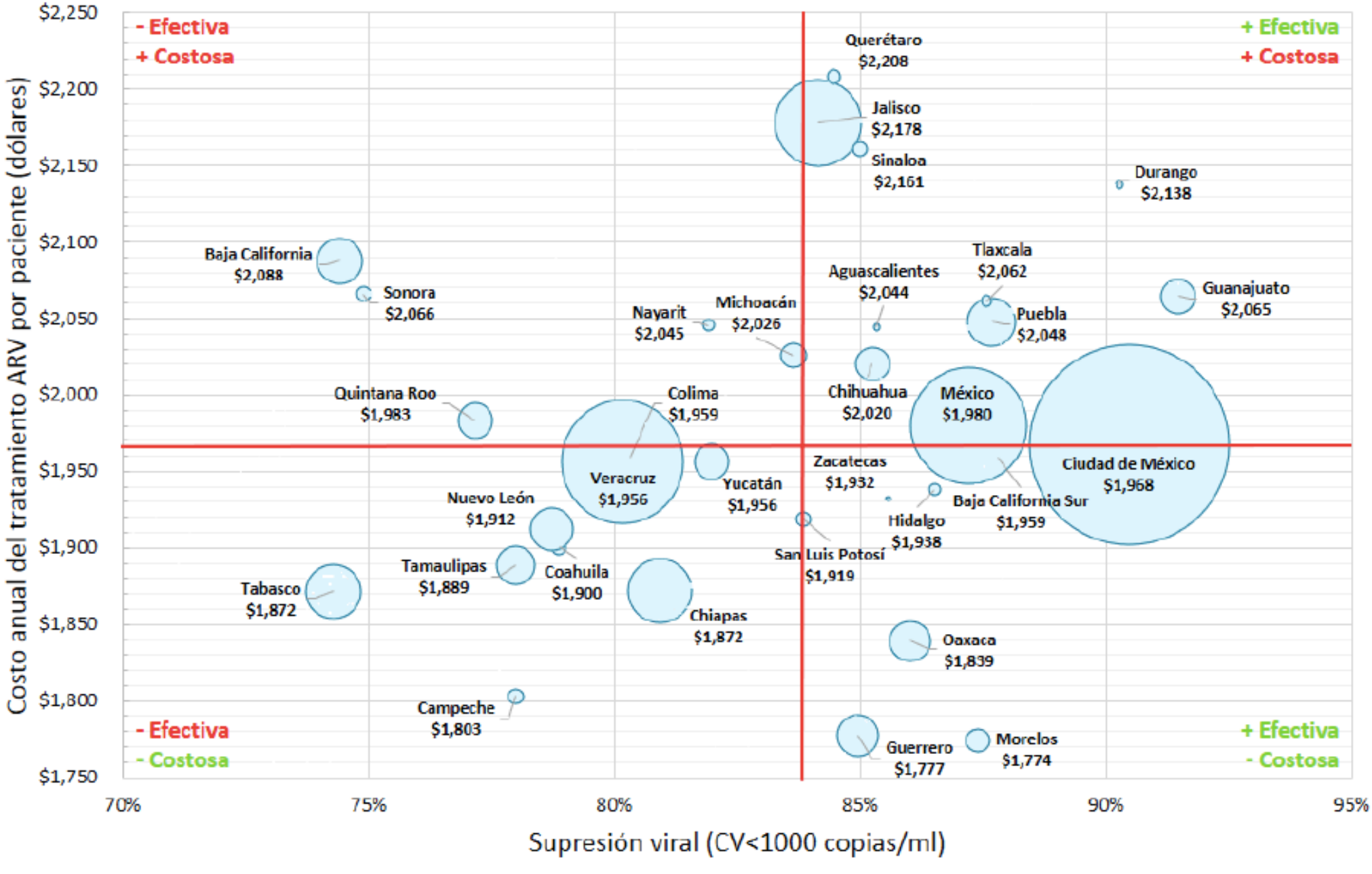
Meta 2 vs. Meta 3: % de personas en TAR de las diagnosticadas vs. % de personas en supresión viral de las en TAR



Fuente: SS/CENSIDA. SALVAR. Datos al 31 de diciembre de 2016.
Personas diagnosticadas vivas (SSA, otras, privado) por entidad de residencia. RNC. DGE/Secretaría de Salud. Datos al 31 de diciembre de 2016.
*Se utilizó el número de personas en atención en SALVAR, por ser mayor al número de personas notificadas en la entidad.

SALUD
SECRETARÍA DE SALUD

Porcentaje de supresión viral y costo anual del tratamiento ARV por paciente



Fuente: SS/CENSIDA. SALVAR. Datos al 31 de diciembre de 2016.

Agenda

- Eficacia y tolerabilidad
- Perfil metabólico
- Resistencia
- Mujeres, mujeres embarazadas
- Costos

Agenda

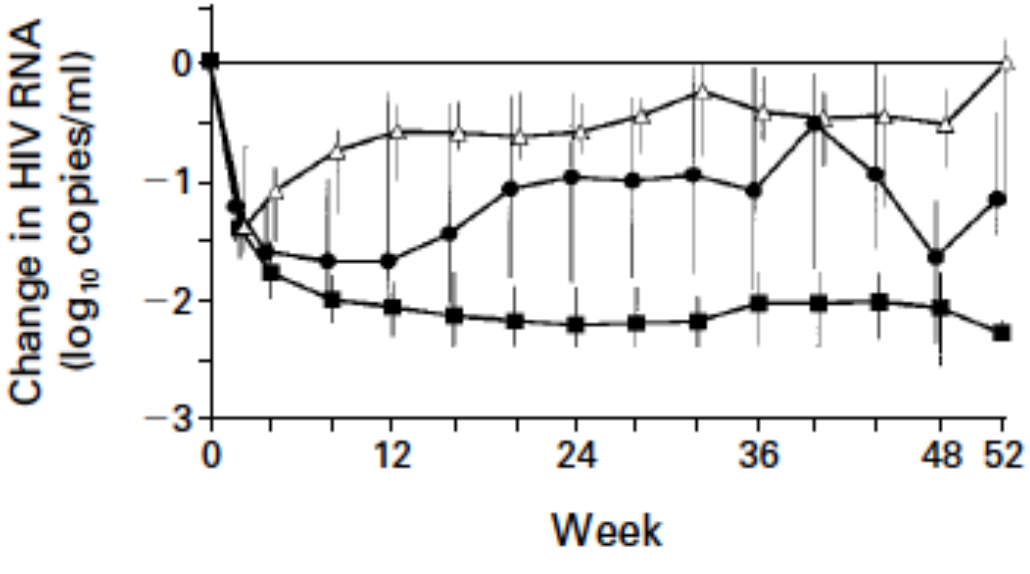
- Eficacia y tolerabilidad
- Perfil metabólico
- Resistencia
- Mujeres, mujeres embarazadas
- Costos

….1996

The New England Journal of Medicine

TREATMENT WITH INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE IN ADULTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND PRIOR ANTIRETROVIRAL THERAPY

ROY M. GULICK, M.D., M.P.H., JOHN W. MELLORS, M.D., DIANE HAVLIR, M.D., JOSEPH J. ERON, M.D., CHARLES GONZALEZ, M.D., DEBORAH MCMAHON, M.D., DOUGLAS D. RICHMAN, M.D., FRED T. VALENTINE, M.D., LESLIE JONAS, B.S., ANNE MEIBOHM, PH.D., EMILIO A. EMINI, PH.D., AND JEFFREY A. CHODAKEWITZ, M.D.



No. of Patients Studied					
■ Three drugs	30	30	25	10	5
● Indinavir	31	28	25	8	5
△ Zidovudine–lamivudine	33	30	25	9	5

Conceptos importantes

- En la era actual de ARV, los resultados de eficacia son condicionados principalmente por tolerabilidad

  Dr. Juan Sierra Madero

  24 de agosto de 2017

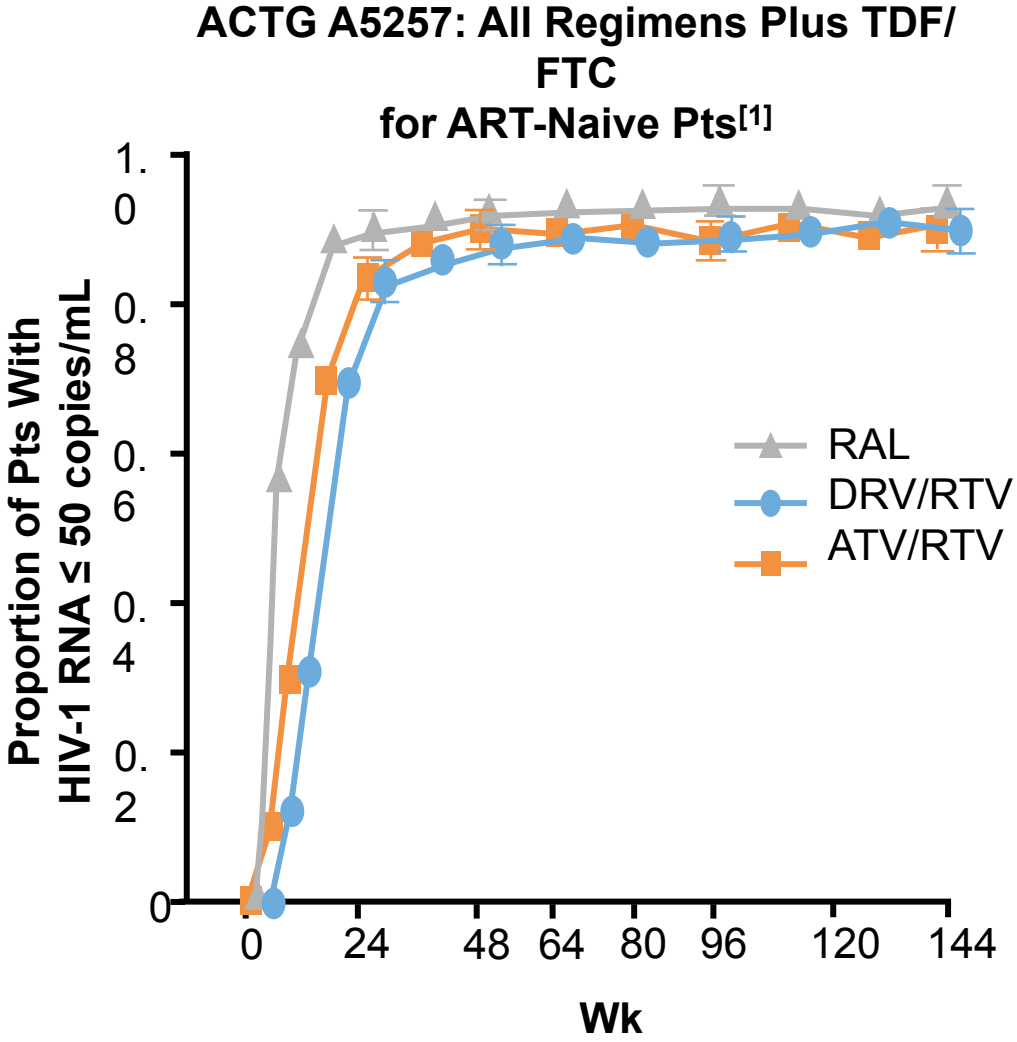
- No podemos esperar que algún regimen ARV muestre superioridad ante los INSTI

  Dr. Emilio Fumero

  25 de agosto de 2017

Efficacy of Initial HIV Therapy: The Flat Part of an Asymptotic Function

- Rates of virologic suppression can barely be improved further
- Most pts in clinical trials *and* clinical practice who are not suppressed are not receiving ART
- A small fraction has multiclass resistance

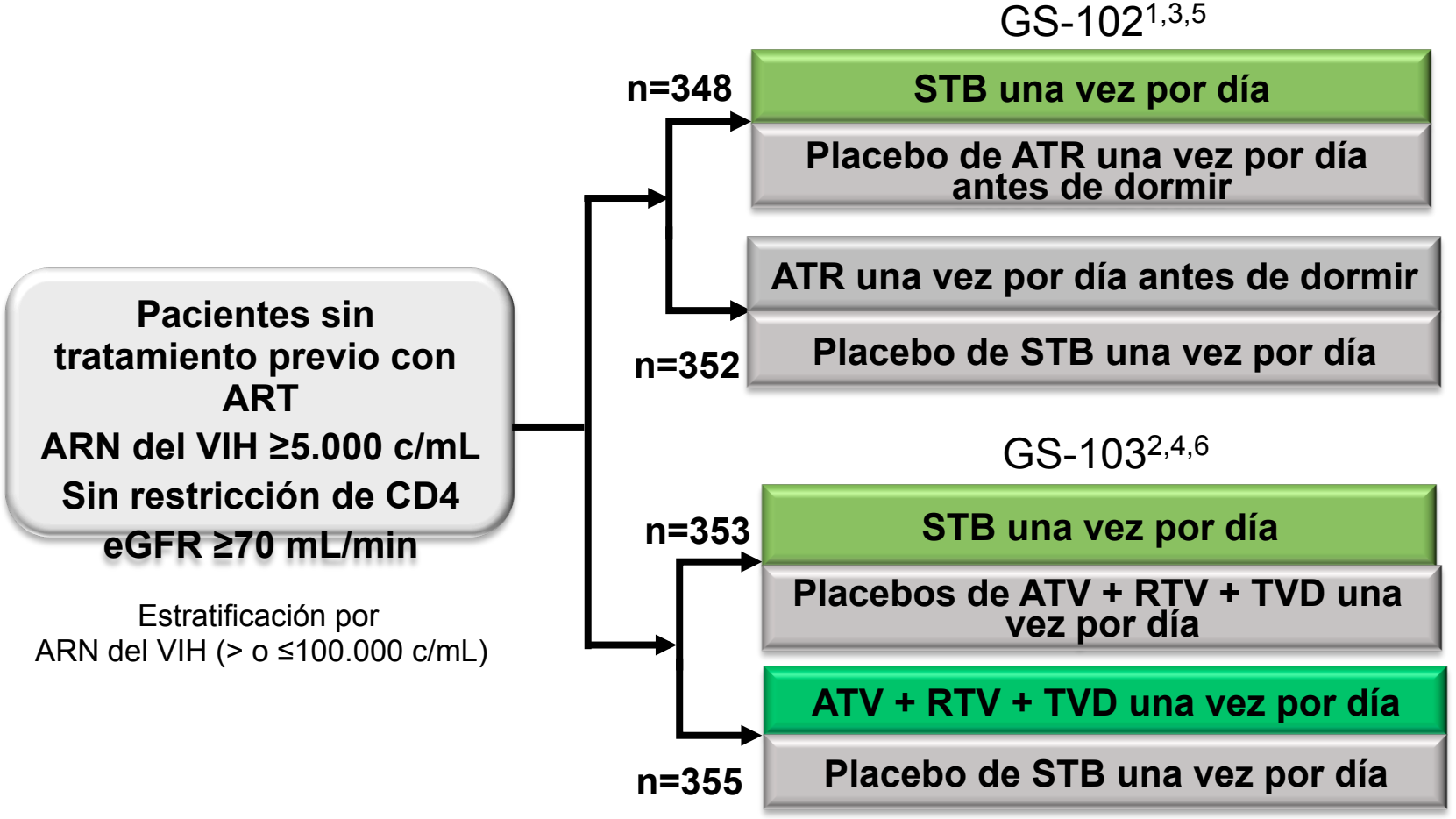


1. Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

Slide credit: clinicaloptions.com

Estudios 102 y 103 (STB en comparación con ATR y ATV+RTV+TVD)

Estudio aleatorizado, doble ciego, con doble simulación y control activo



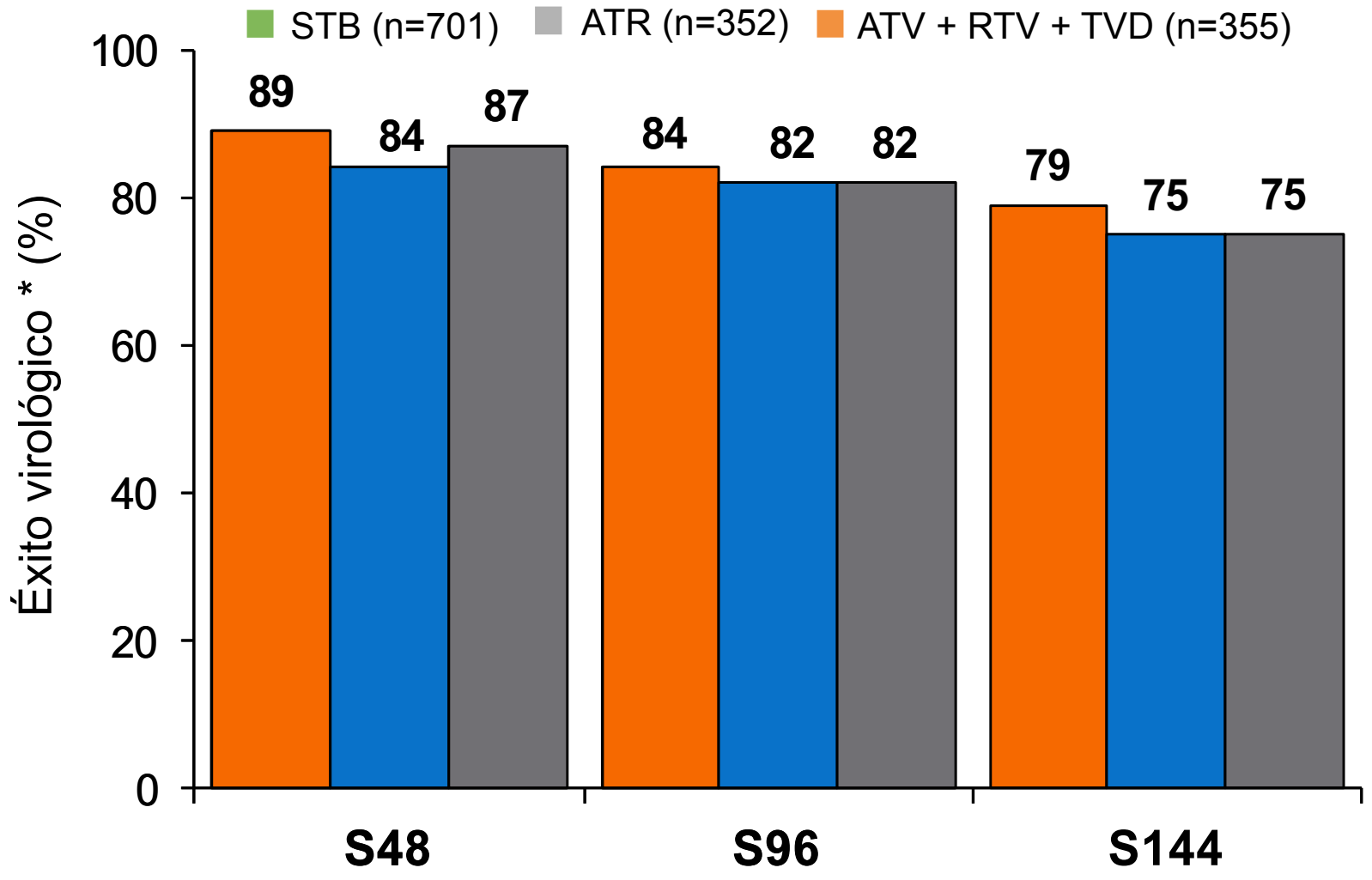
Criterio de valoración principal: No inferioridad (margen de 12 %) de STB respecto del grupo comparador para alcanzar el ARN del VIH-1 <50 copias/mL a las 48 semanas (análisis snapshot de la FDA) [1,2]

Criterios de valoración secundarios: Eficacia, seguridad y tolerabilidad observada hasta la semana 96[3,4] y 144[5,6]

STB = Stribild® = EVG/COBI/TVD; ATR = Atripla® = EFV/TVD; TVD = Truvada® = FTC/TDF

1. Sax P, et al. Lancet 2012;379:2439-48
2. DeJesus E, et al. Lancet 2012;379:2429-38
3. Zolopa A, et al. JAIDS.2013;63:96-100
4. Rockstroh JK, et al. JAIDS 2013;62:484-486
5. Wohl D, et al. JAIDS 2014;65 (3):e118-121
6. Clumeck N, et al. JAIDS 2014;65:e121-124

Estudio 102 y Estudio 103 integrados: Semana 144

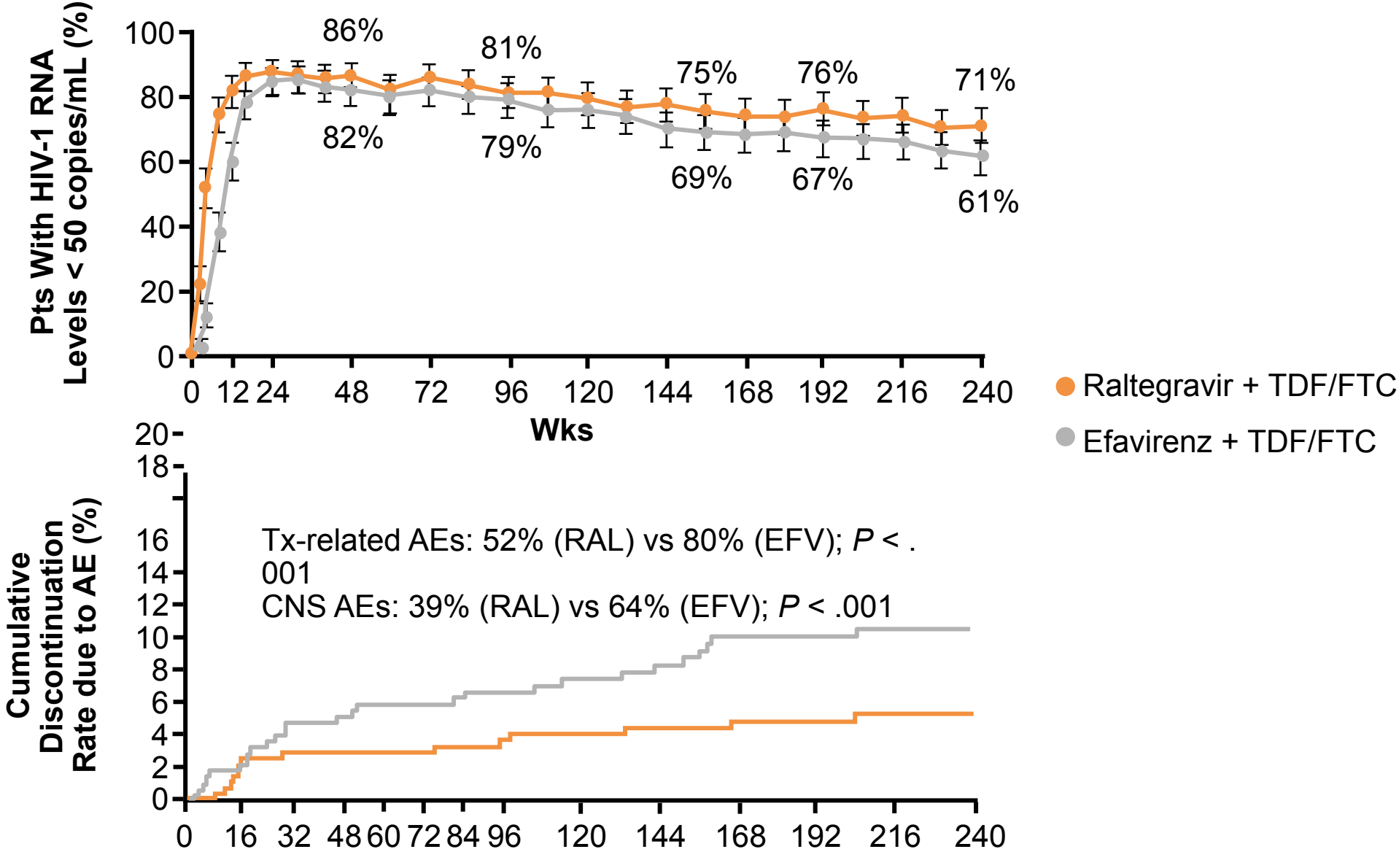


Los aumentos de CD4 (células/mm^3) fueron sólidos y comparables en la semana 144. STB (+300) en comparación con ATR (+300) en comparación con ATV+RTV+TVD (+293)

* Éxito virológico (ARN del VIH-1 <50 copias/mL) tal como lo define el algoritmo Snapshot de la FDA

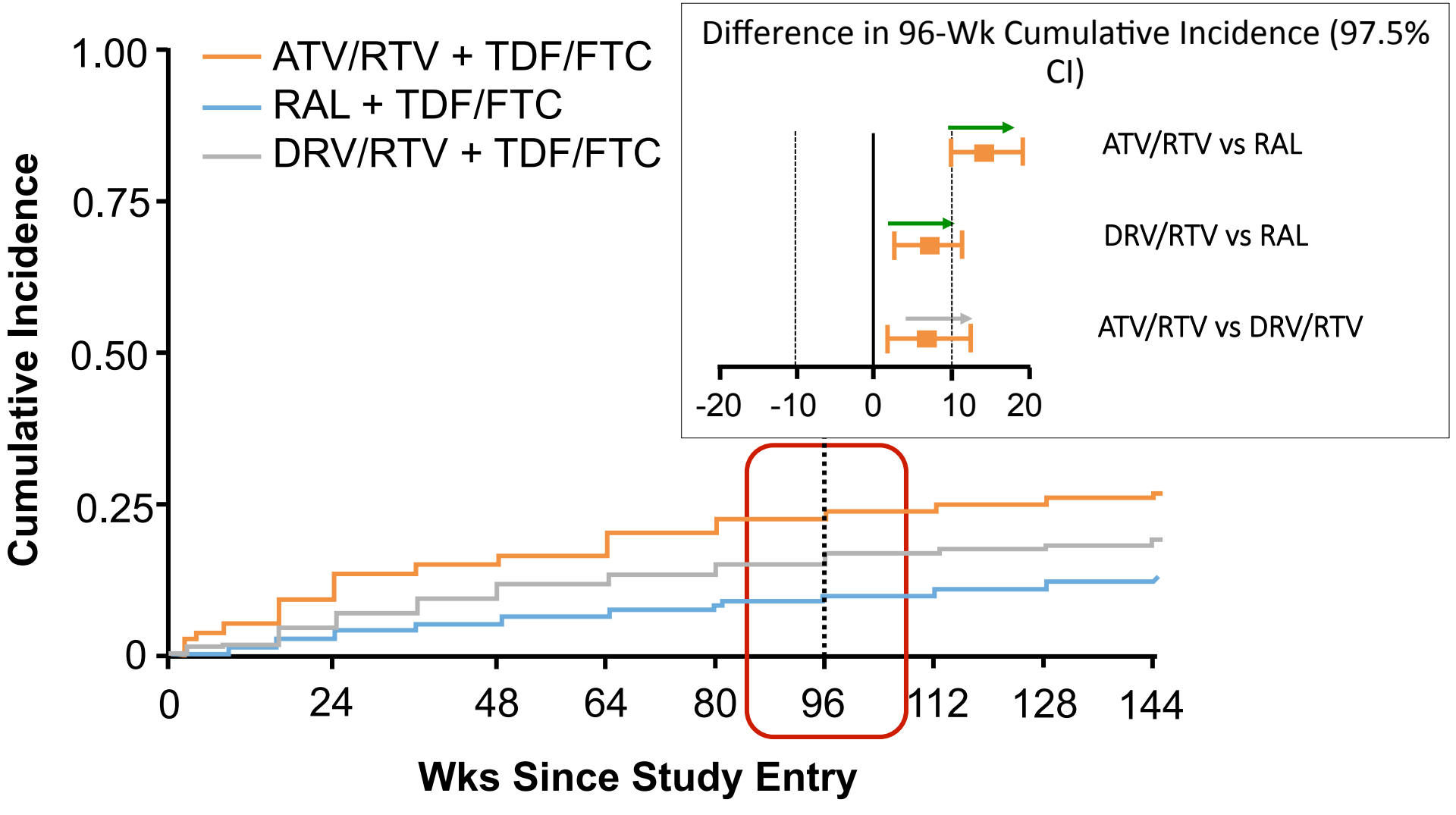
Elion R, et al. ICAAC 2014. Washington, DC. H-644

STARTMRK: Long-term Efficacy and Tolerability Data for RAL



Rockstroh JK, et al. J Acquir Immune Defic Syndr. 2013;63:77-85.

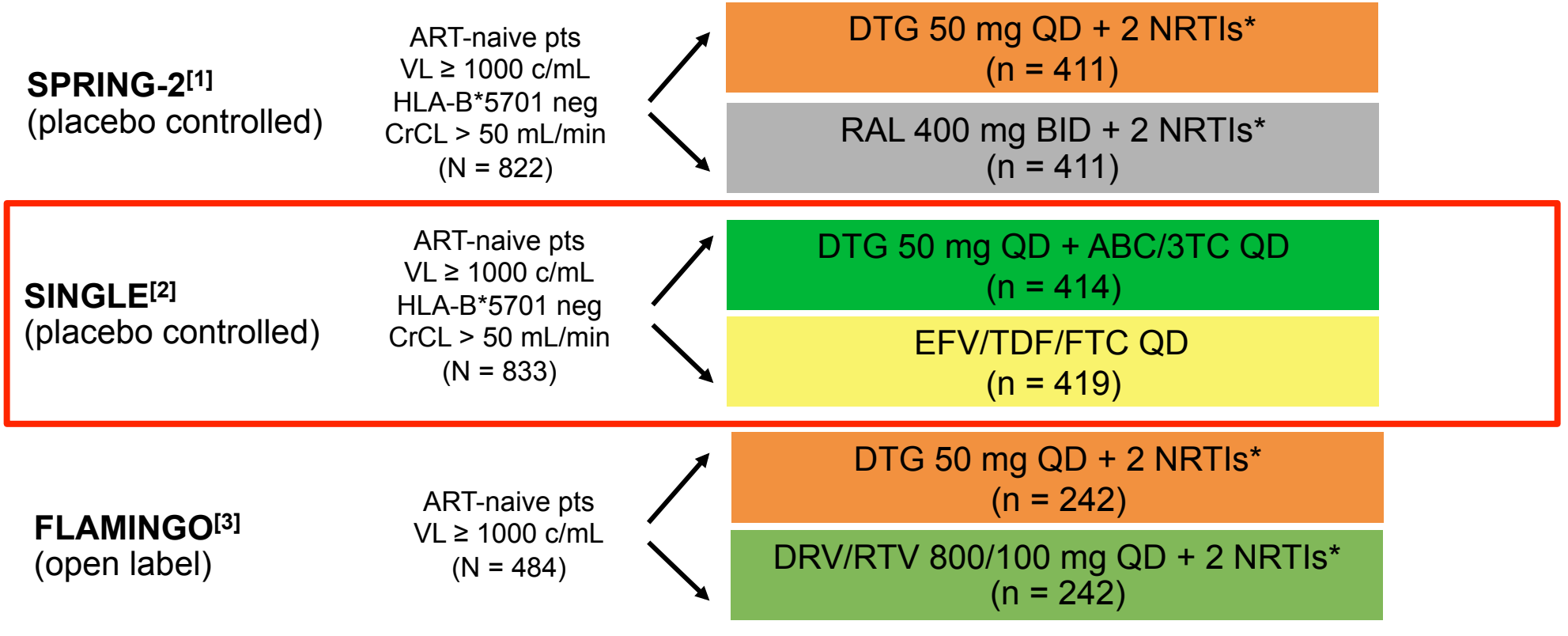
ACTG 5257: Cumulative Incidence of Virologic or Tolerability Failure at Wk 96



Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

SINGLE: Dolutegravir + ABC/3TC vs EFV/TDF/FTC in Naive Pts: 96-Wk Report

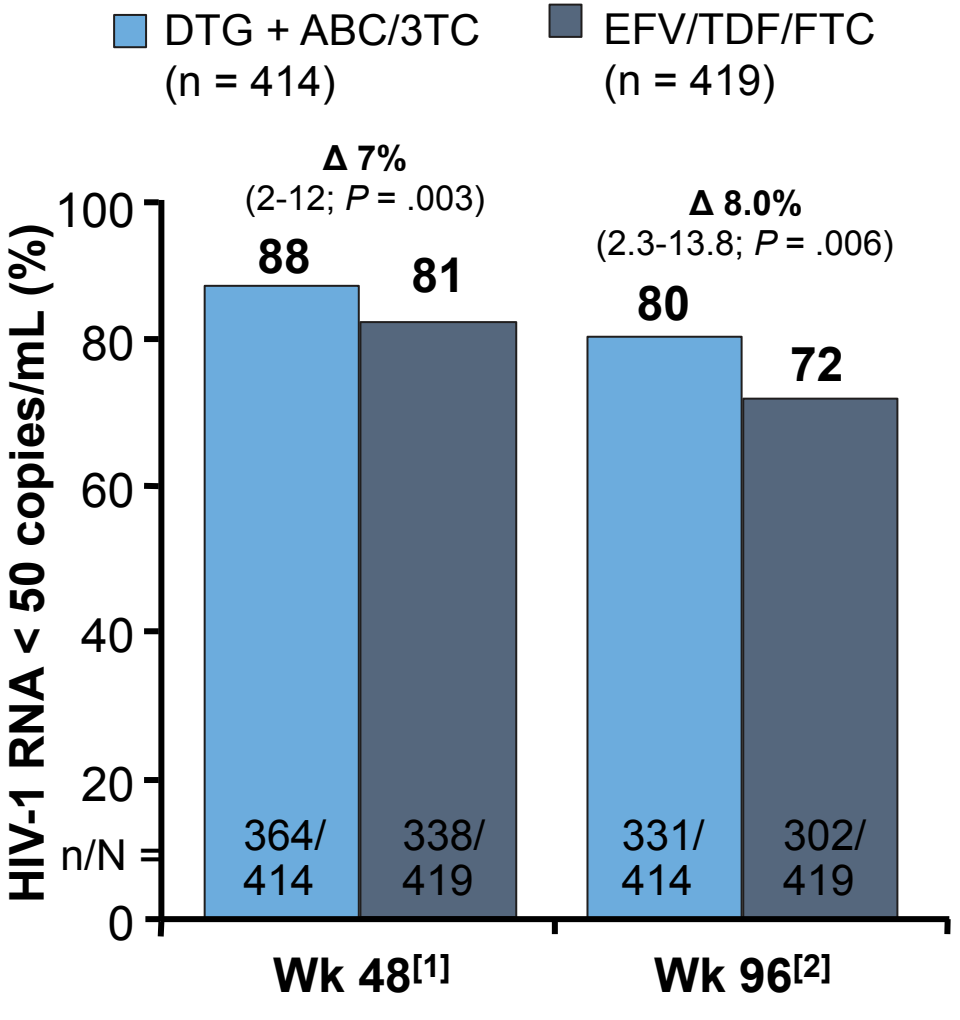
- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.
3. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

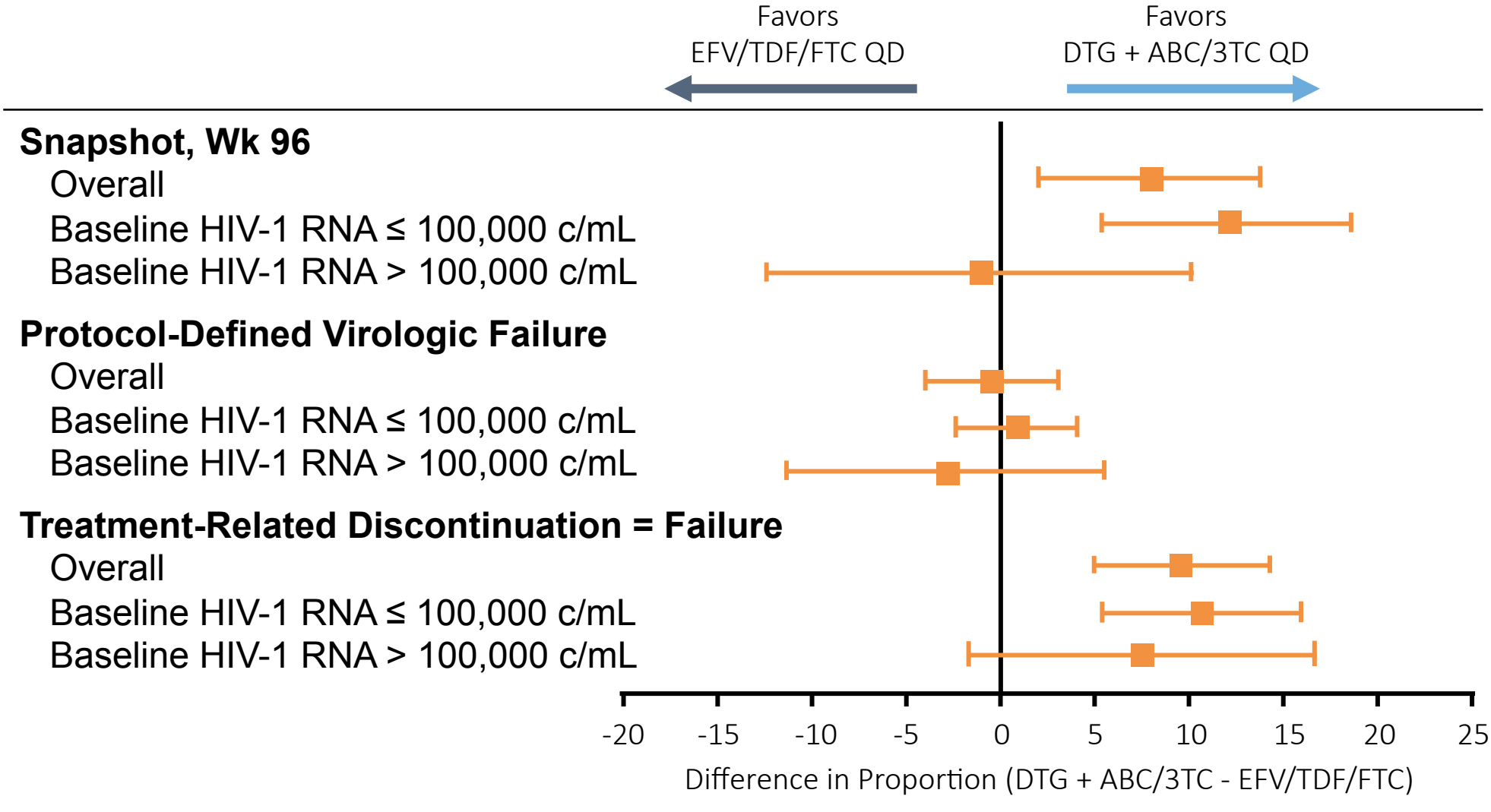
SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC at Both Wk 48 and 96



- Treatment-related study d/c: 3% in DTG vs 11% in EFV arm
  - No new treatment-related AEs in either arm btwn Wks 48-96
- VF at Wk 96: 25 (6%) in each arm
- 0 pts with resistance in DTG arm; 1 pt with NRTI and 6 pts with NNRTI resistance in EFV arm
- CD4+ count increase at Wk 96 greater with DTG: +325 vs +281 cells/mm^3 (P = .004)

1. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.
2. Walmsley S, et al. CROI 2014. Abstract 543.

SINGLE: HIV-1 RNA < 50 c/mL at Wk 96 by Baseline HIV-1 RNA



Walmsley S, et al. CROI 2014. Abstract 543. Reproduced with permission.

Agenda

- Eficacia y tolerabilidad
- Perfil metabólico
- Resistencia
- Mujeres, mujeres embarazadas
- Costos

ART and Effects on Lipids

TDF

RAL
DTG

RPV

ABC

EFV

ATV/RTV or ATV/COBI
DRV/RTV or DRV/COBI
EVG/COBI

Agenda

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- Mujeres, mujeres embarazadas
- Costos

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**

Lancet HIV 2016

Avila-Rios S. Lancet HIV 2016(12):e579-e591.

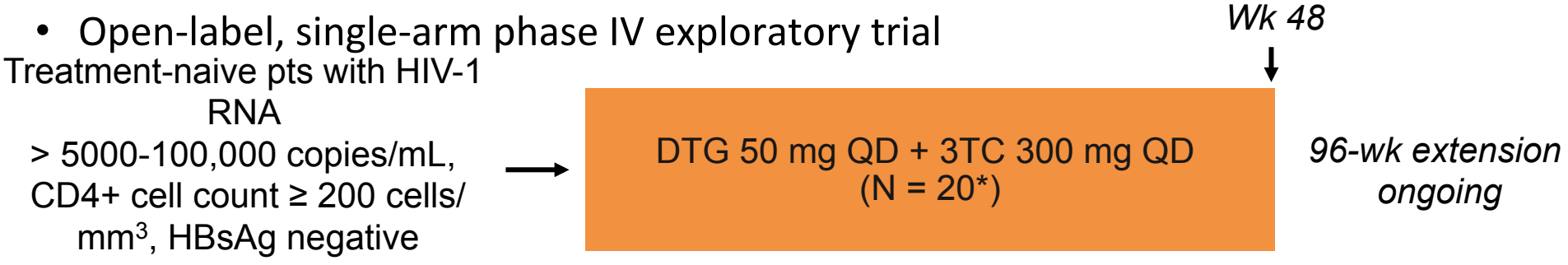
Resistencia primaria

	Sanger method*† (n=264)	Next-generation sequencing *‡ (n=264)
Any antiretroviral drug	41 (16%, 11·4–20·5)	38 (14%, 10·4–19·2)
NRTI	15 (6%, 3·2–9·2)	13 (5%, 2·6–8·3)
NNRTI	28 (11%, 7·2–15·0)	26 (10%, 6·5–14·1)
Protease inhibitors	7 (3%, 1·1–5·4)	8 (3%, 1·3–5·9)

Avila-Rios S. Lancet HIV 2016(12):e579-e591.

PADDLE: Dolutegravir + Lamivudine for Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial



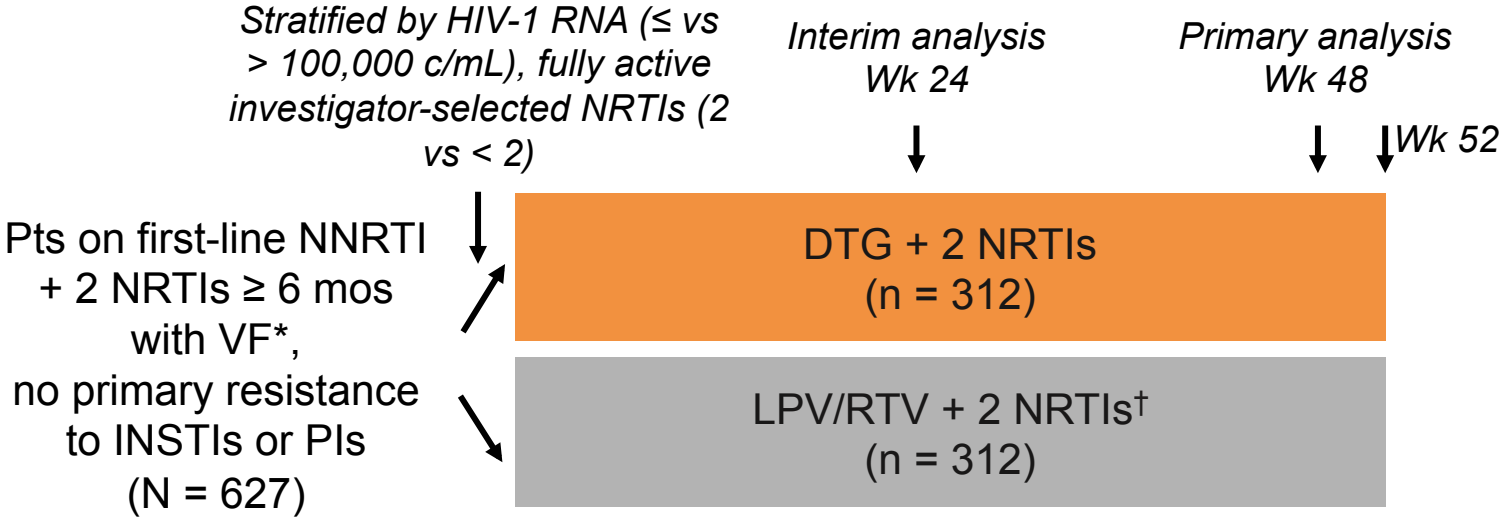
*10 pts enrolled initially; additional 10 pts enrolled after confirming virologic success of first cohort at Wk 8.

- 18/20 pts achieved HIV-1 RNA < 50 copies/mL at Wk 48 (primary endpoint)
  - 1 pt committed suicide (deemed unrelated to study drugs)
  - 1 pt experienced PDVF at Wk 36 (BL HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit (Wk 52)
  - 3 other pts with BL HIV-1 RNA > 100,000 copies/mL suppressed at Wk 48

Cahn P, et al. IAC 2016. Abstract FRAB0104LB.

DAWNING: Second-line DTG vs LPV/RTV + 2 NRTIs in Pts With Virologic Failure

- Interim results of an international, randomized, open-label phase IIIb study (N = 627)
  - Most frequent enrolment sites: South Africa (27%), Peru, Ukraine, Brazil, Thailand, China (8% to 10% each)



*HIV-1 RNA ≥ 400 copies/mL on 2 occasions. †After preplanned analysis (all Wk 24 and subsets of Wks 36/48 data), it was recommended that LPV/RTV be discontinued due to differences in virologic nonresponse and PDVF favoring DTG arm. Protocol amendment allowed pts on LPV/RTV to switch to DTG.

- Baseline characteristics (DTG vs LPV/RTV): female, 37% vs 33%; African heritage, 42% vs 36%; HIV-1 RNA > 100,000 copies/mL, 22% vs 20%

Aboud M, et al. IAS 2017. Abstract TUAB0105LB. ClinicalTrials.gov. NCT02227238.

DAWNING: Key Findings

Virologic Outcome at Wk 24, n (%)	DTG + 2 NRTIs (n = 312)	LPV/ RTV + 2 NRTIs (n = 312)	Treatment Difference, % (95% CI)
Success*	257 (82)	215 (69)	13.8 (7.3-20.3; *P* < .001)
Nonresponse	37 (12)	77 (25)	NR
No data	18 (6)	20 (6)	NR

- Virologic withdrawal†: DTG arm, n = 10 (3%); LPV/RTV arm, n = 28 (9%)
- In pts with virologic withdrawal:
  - No pts in DTG arm developed INSTI or NRTI RAMs
  - n = 3 in LPV/RTV arm developed NRTI RAMs
- AEs, DTG vs LPV/RTV
  - Drug related, 15% vs 36%
  - Serious/death, 5% vs 6%
  - Leading to withdrawal, 2% vs 5%

ITT-E population. *HIV-1 RNA < 50 copies/mL.

†HIV-1 RNA decrease of < 1 $\log_{10}$ c/mL by Wk 16, increase to ≥ 400 c/mL after suppression, ≥ 400 c/mL at or after Wk 24.

Aboud M, et al. IAS 2017. Abstract TUAB0105LB.

Agenda

- Eficacia y tolerabilidad
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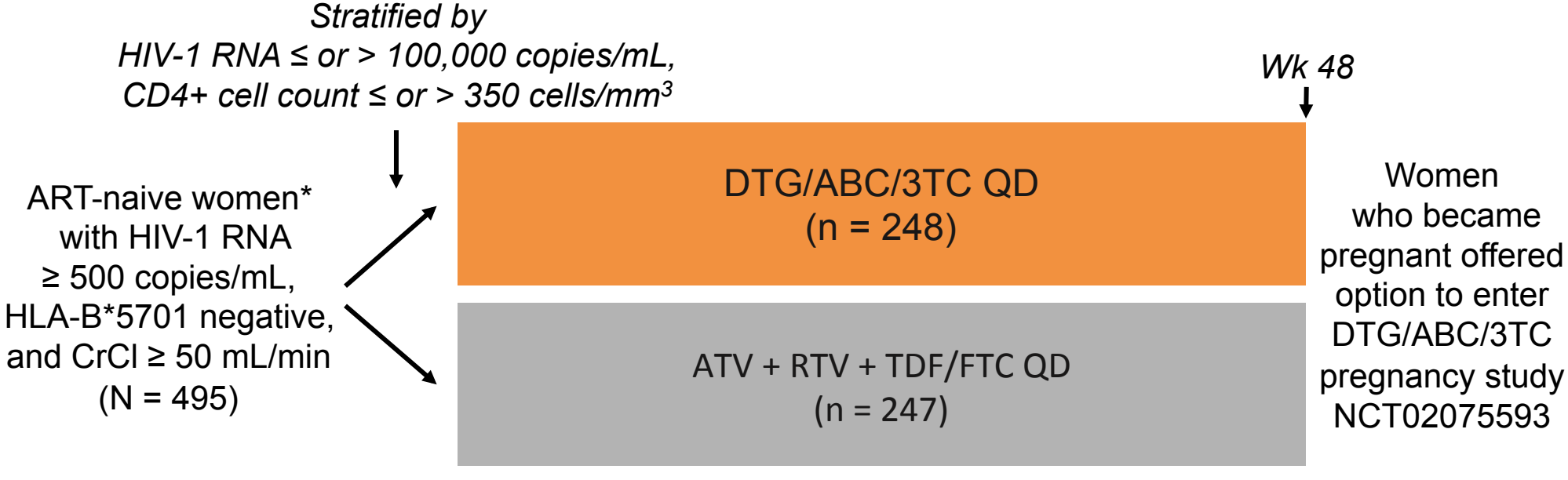
ARIA: DTG/ABC/3TC vs ATV + RTV + TDF/FTC in Treatment-Naive Women

- Multinational, randomized, open-label phase IIIb trial
  - Primary endpoint: Wk 48 HIV-1 RNA < 50 copies/mL



*Women enrolled in North America, European Union, Argentina, Puerto Rico, Russian Federation, South Africa, and Thailand.
Dosing: ATV 300 mg, RTV 100 mg, TDF/FTC 300/200 mg, DTG/ABC/3TC 50/600/300 mg.
After 48 wks, pts in the DTG/ABC/3TC arm could enter the continuation phase.

ARIA: DTG/ABC/3TC Superior to ATV + RTV + TDF/FTC at Wk 48

- Primary virologic outcomes (ITT-E analysis)

Outcome, % (n)	DTG/ABC/3TC (n = 248)	ATV + RTV + TDF/FTC (n = 247)	Treatment Difference (95% CI)	*P* Value
Virologic success (HIV-1 RNA < 50 copies/mL)	82 (203)	71 (176)	10.5 (3.1-17.8)	.005
Virologic nonresponse	6 (16)	14 (35)	--	--
No virologic data	12 (29)	15 (36)	--	--

- Virologic outcomes by baseline randomization strata (ITT-E analysis)

HIV-1 RNA < 50 copies/mL, %	DTG/ABC/3TC	ATV + RTV + TDF/FTC
Baseline HIV-1 RNA, copies/mL		
▪ ≤ 100,000	83	74
▪ > 100,000	80	64
Baseline CD4+ cell count, cells/mm³		
▪ ≤ 350	85	72
▪ > 350	78	71

Orrell C, et al. AIDS 2016. Abstract THAB0205LB.

Slide credit: clinicaloptions.com

DHHS Recommendations: Initial ART in Pregnant Women

- DHHS recommendations differ for *starting* vs *continuing* ART in pregnancy

Guideline Status	NRTIs	PIs	INSTIs	NNRTIs
Preferred	**3TC/ABC FTC/TDF 3TC + TDF**	**ATV/RTV* DRV/RTV*†**	**RAL*§**	
Alternative	3TC/ZDV	LPV/RTV*†		EFV* RPV*‡
Insufficient data to recommend	FTC/TAF	FPV	DTG EVG/COBI EVG/COBI	

*In addition to 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if pretreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm^3. §If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

DHHS Perinatal Guidelines. October 2016.

Slide credit: clinicaloptions.com

Tsepamo: Birth Outcomes When Initiating First-line DTG vs EFV in Pregnancy

- Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

Adverse Birth Outcomes (ABO), n (%)	DTG (n = 845)	EFV (n = 4593)	aRR* (95% CI)
Any	291 (34.4)	1606 (35.0)	1.0 (0.9-1.1)
▪ Severe	92 (10.9)	519 (11.3)	1.0 (0.8-1.2)
Stillbirth	18 (2.1)	105 (2.3)	0.9 (0.6-1.5)
Neonatal death (< 28 d)	11 (1.3)	60 (1.3)	1.0 (0.5-1.9)
Preterm birth (< 37 wks)	149 (17.8)	844 (18.5)	1.0 (0.8-1.1)
▪ Very preterm (< 32 wks)	35 (4.2)	160 (3.5)	1.2 (0.8-1.7)
SGA (< 10th percentile weight)	156 (18.7)	838 (18.5)	1.0 (0.9-1.2)
▪ Very SGA (< 3rd percentile weight)	51 (6.1)	302 (6.7)	0.9 (0.7-1.2)

- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396)
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- Investigators concluded ABO risks comparable when initiating first-line DTG vs EFV in pregnancy

Zash R, et al. IAS 2017. Abstract MOAX0202LB.

Agenda

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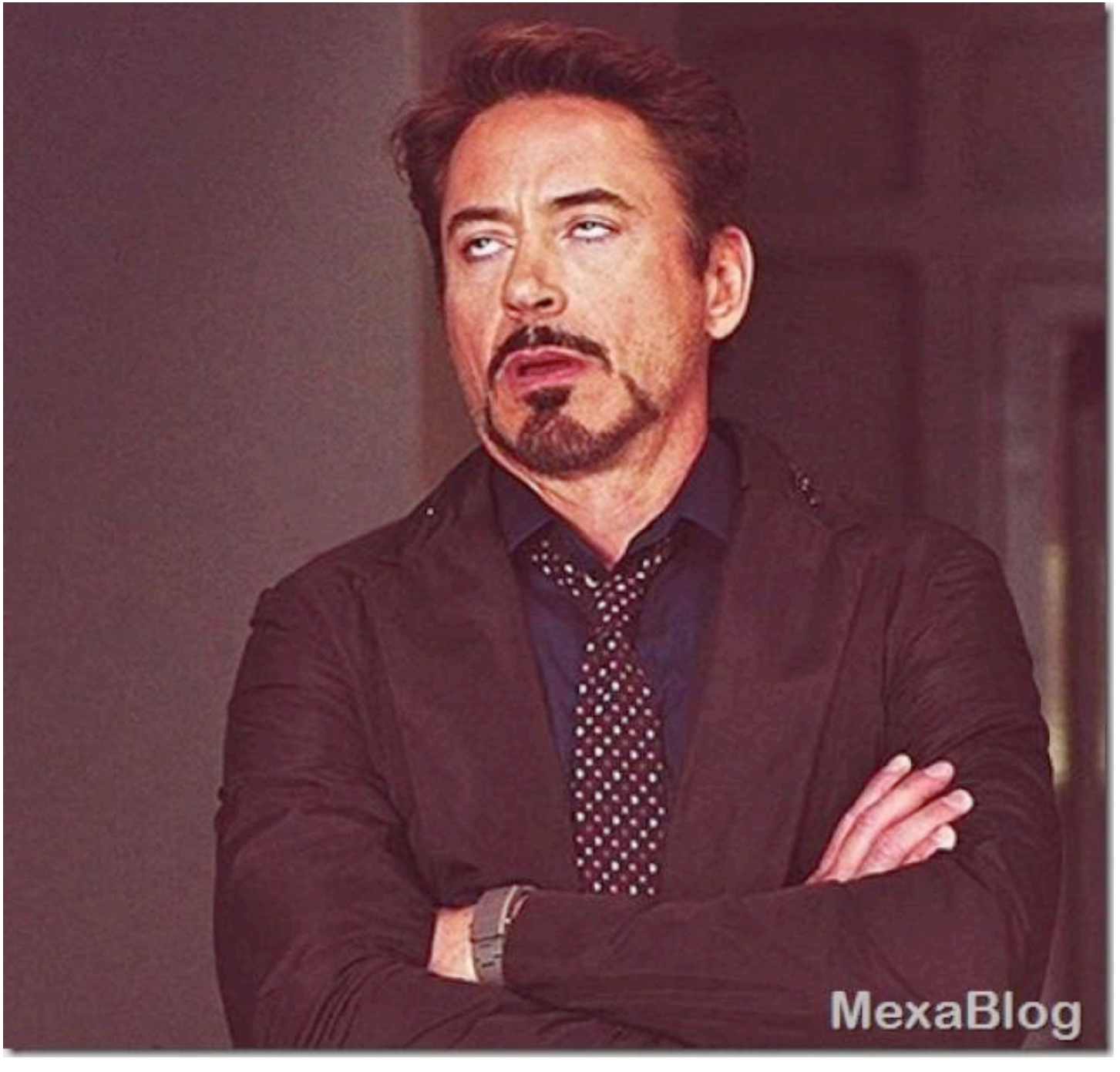
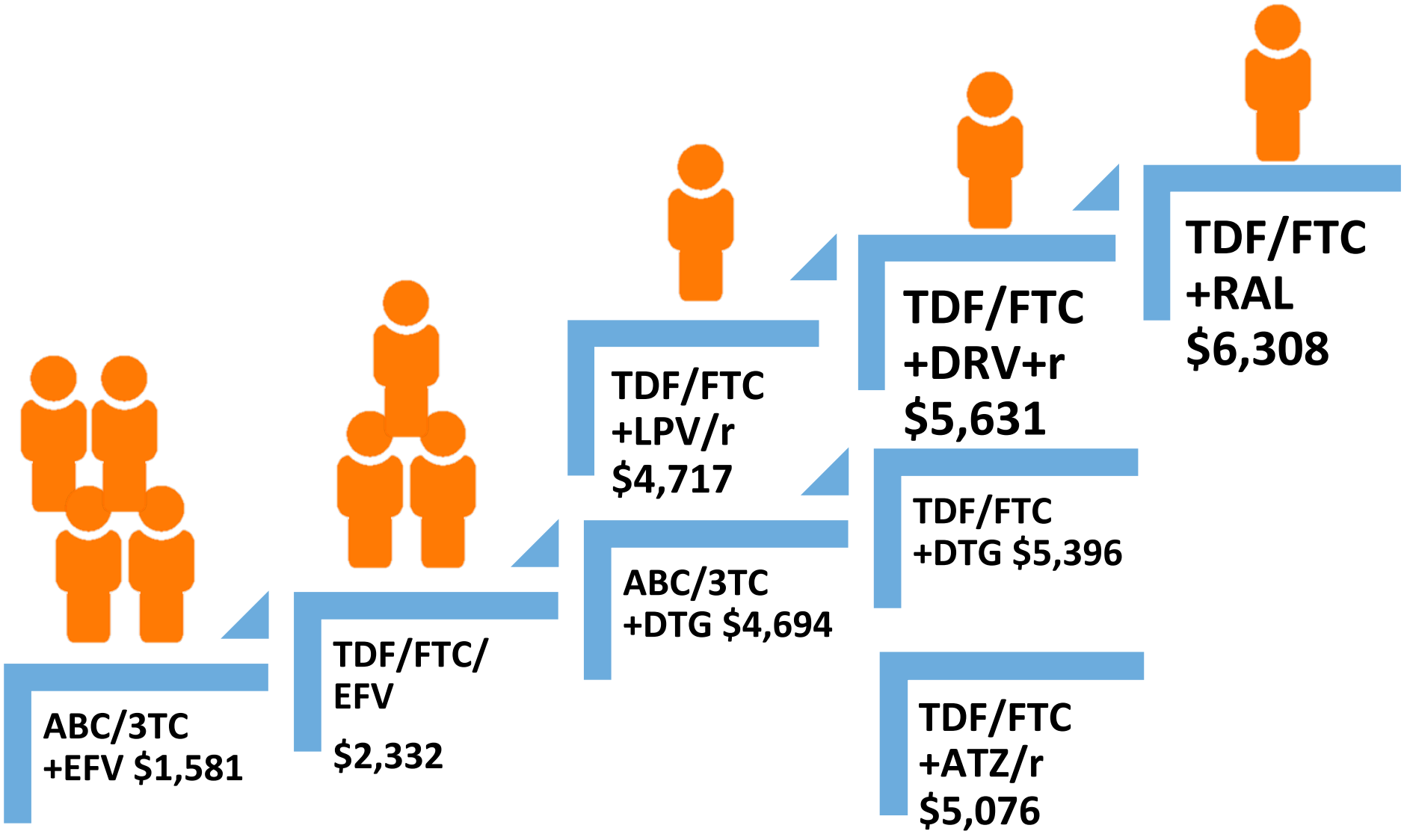
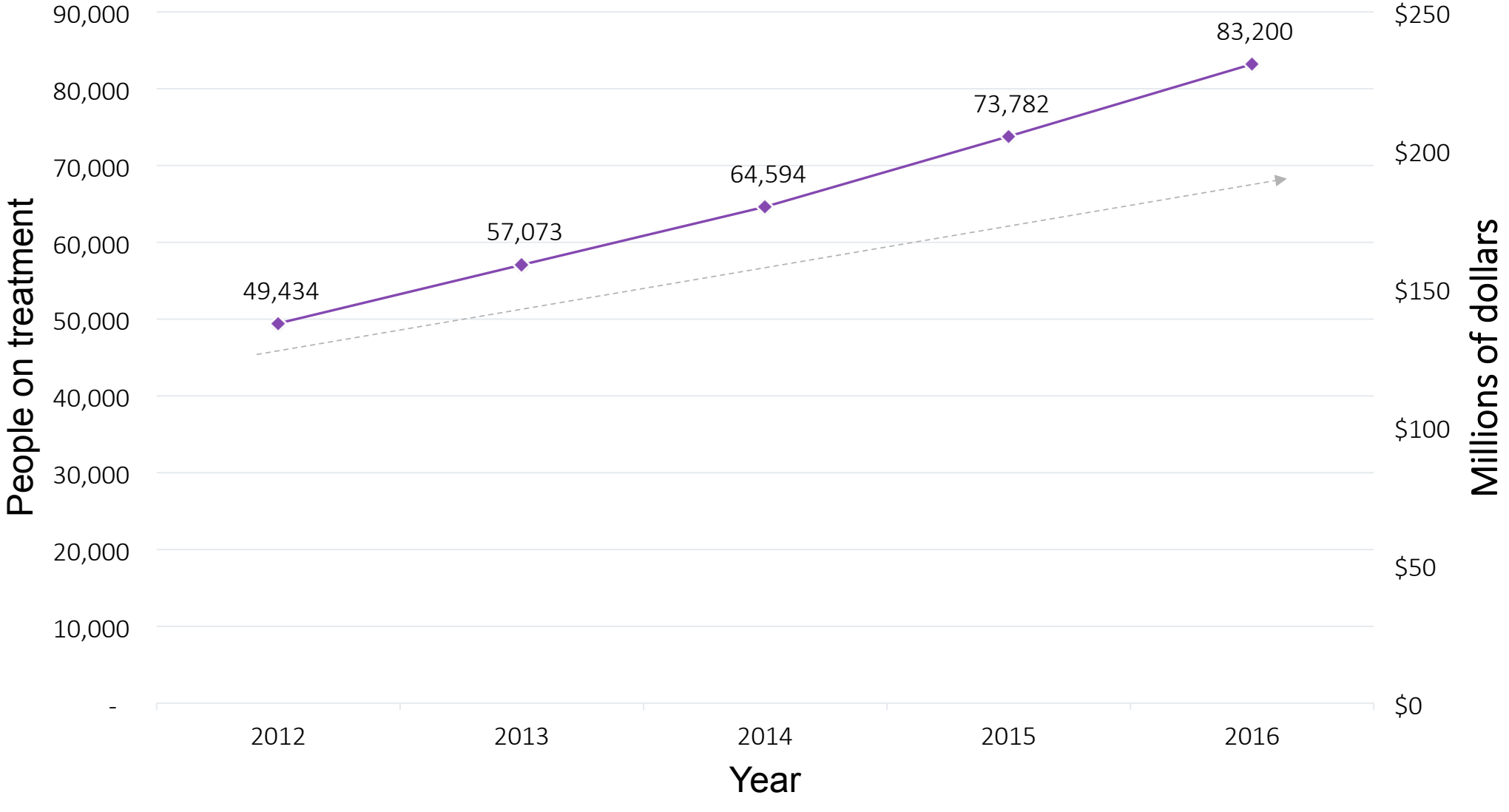
Costo de los medicamentos en México



Costo de los medicamentos en México



Personas recibiendo TARV en México



Slide courtesy of CENSIDA

Entonces el problema es el costo?

- En un futuro cercano, disponibilidad de STR basados en inhibidores de integrasa a costo de STR basado en efavirenz

- El ejemplo de Brasil, reducción de 70% del costo de dolutegravir. Costo aproximado de 500 dls por año.

Conclusions

- Debemos usar medicamentos con adecuada potencia y tolerabilidad, posología cómoda y un bajo número de tabletas.

- Nuestras guías no pueden dejar de lado los factores económicos, pues debe considerarse la sustentabilidad del programa.

Gracias

@doctormosqueda