WORKING ON BEHALF OF ViiV HEALTHCARE IN HIV

¿Qué te hace diferente en la era de las integrasas?

Beyond the Wall

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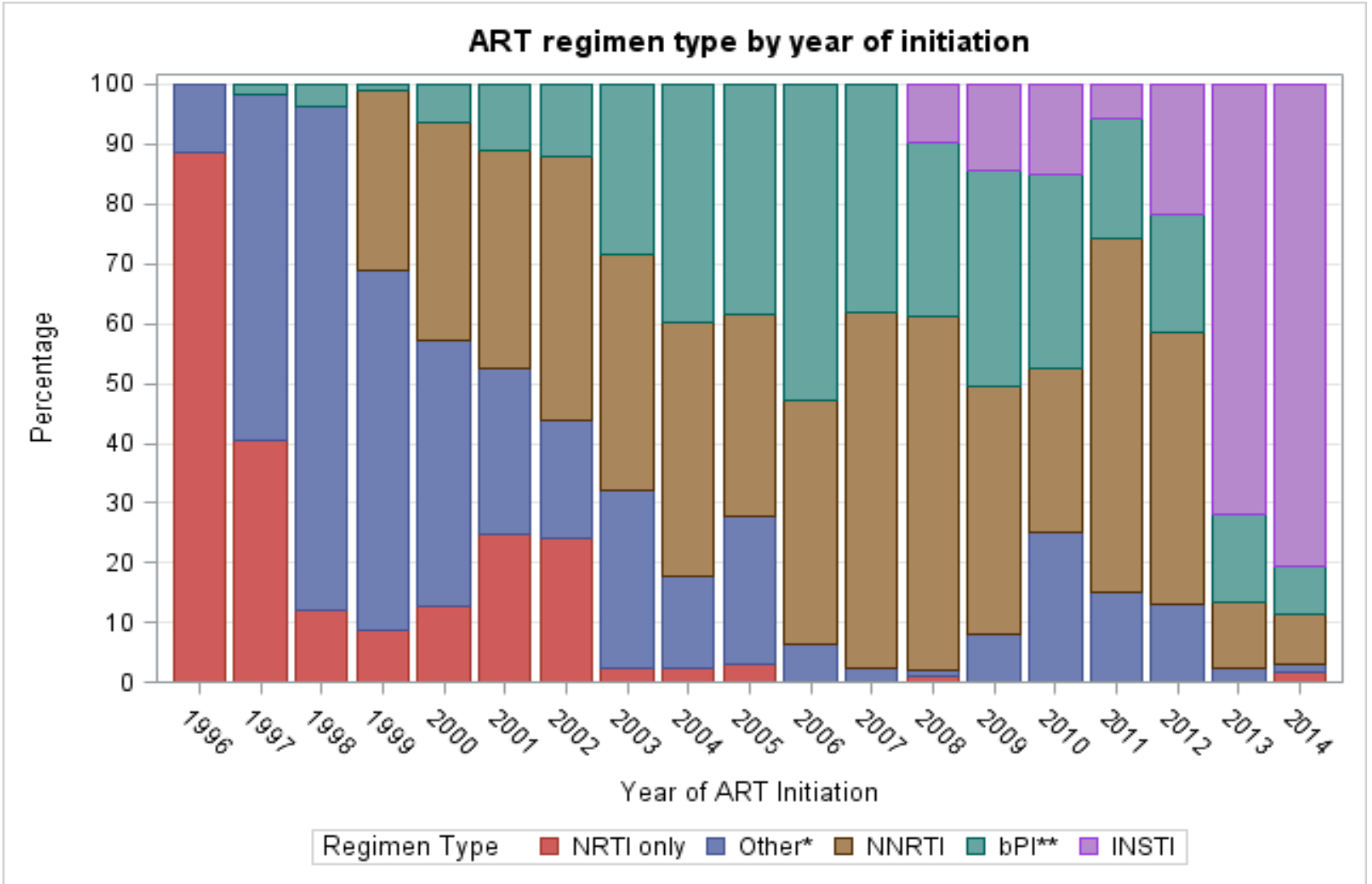
Global Director of Medical Virology and Early Drug Development, ViiV Healthcare

UCHCC: UNC CFAR
HIV Clinical Cohort

Shift To Integrase Inhibitor-based Therapy

Initial Antiretroviral Therapy

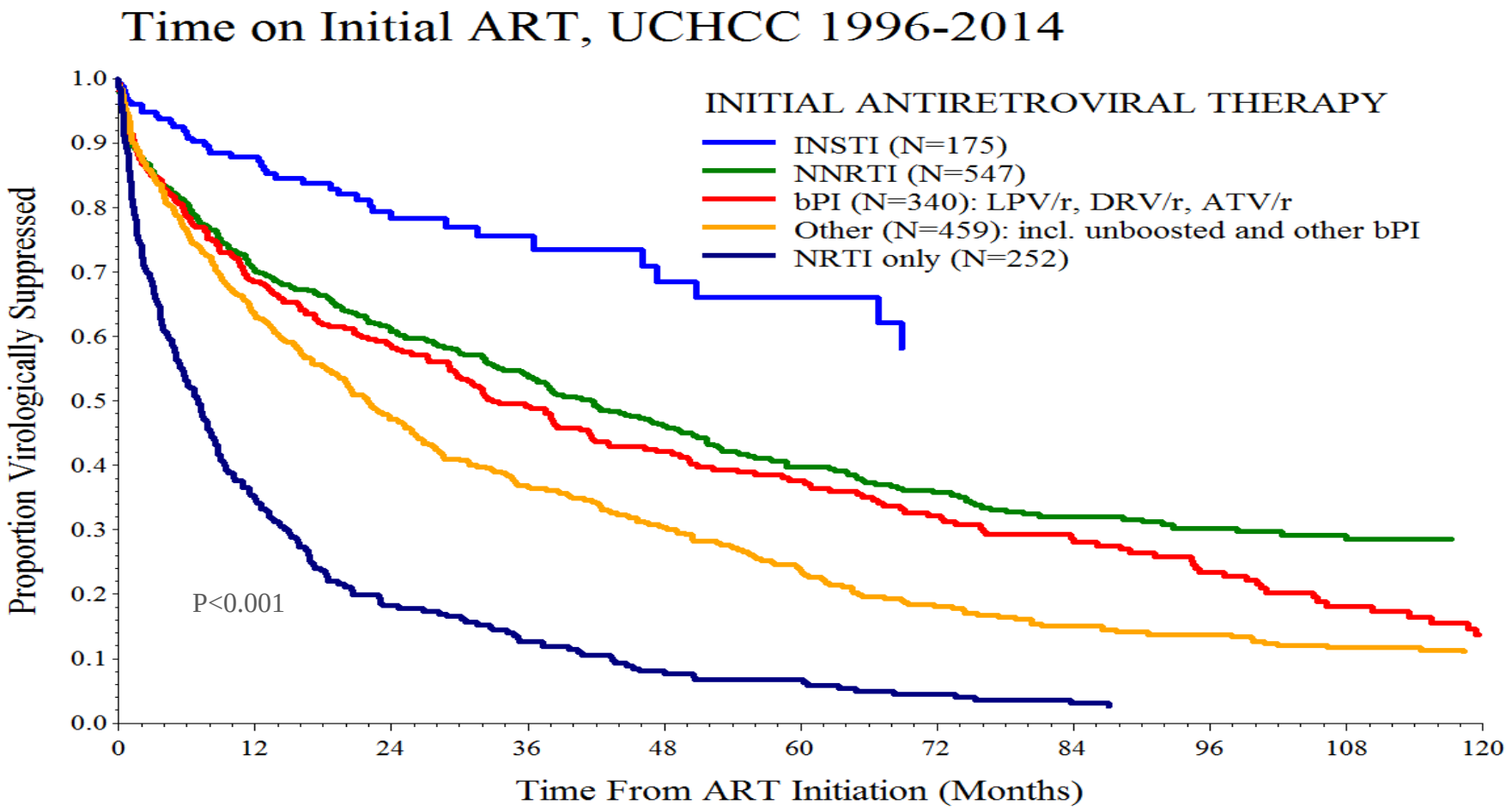


1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

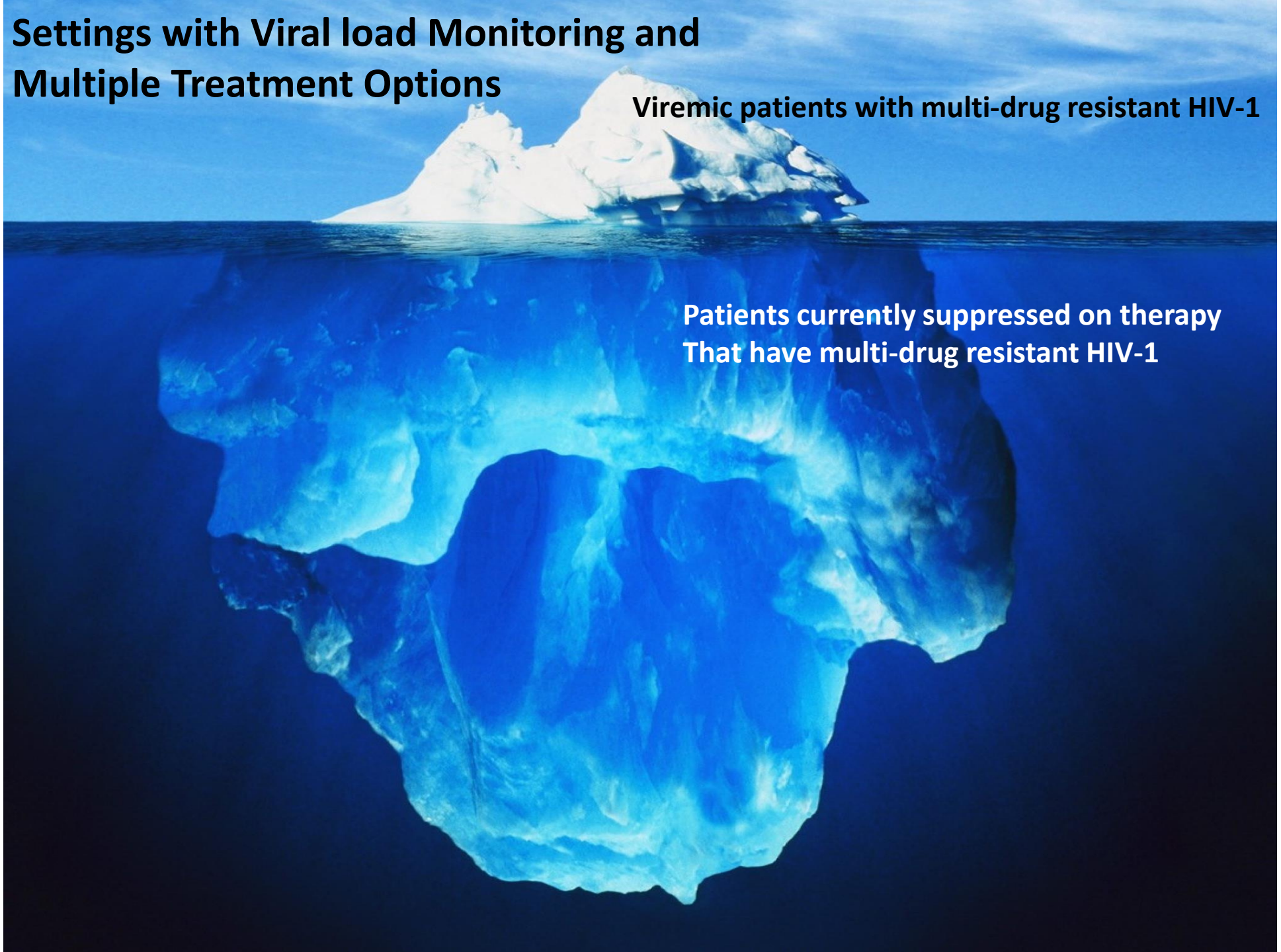
bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Persistence of Initial ART

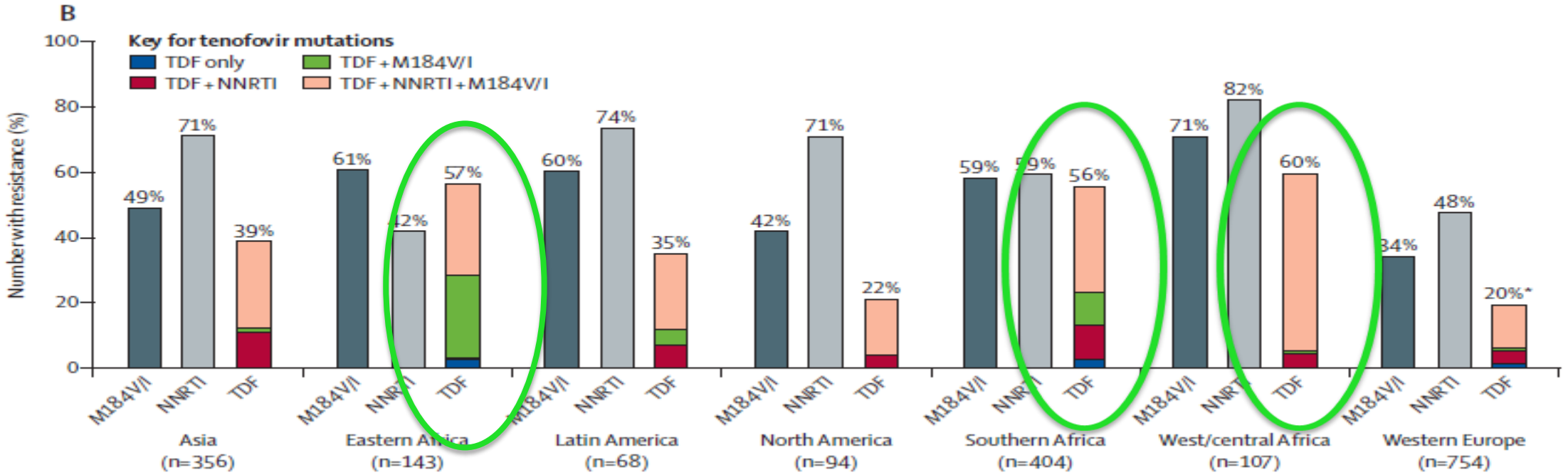


- In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression
- in multivariate analysis see poster 1034 Simoni et al


Settings with Viral load Monitoring and
Multiple Treatment Options
Viremic patients with multi-drug resistant HIV-1
Patients currently suppressed on therapy
That have multi-drug resistant HIV-1

Resistance in Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples



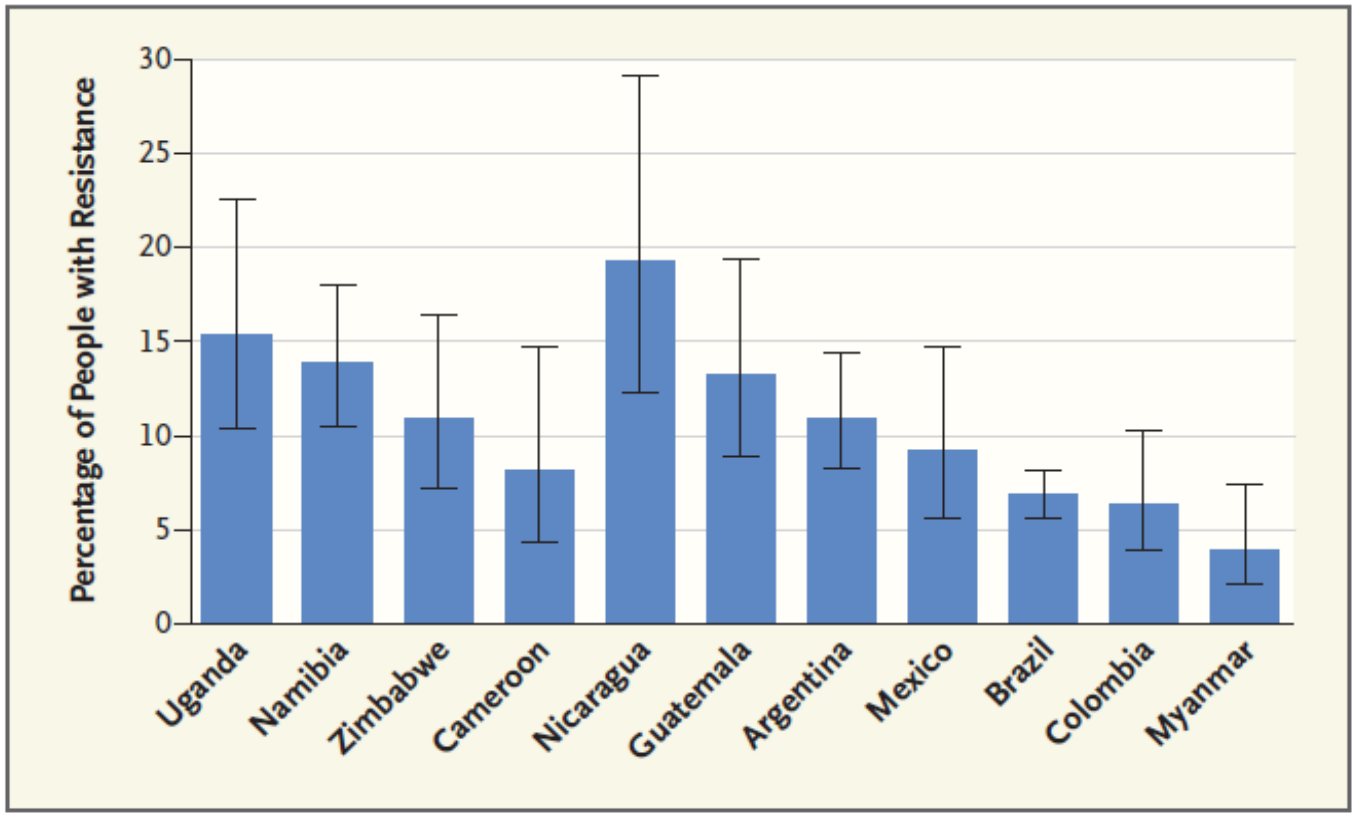
Boyd, M et al *Lancet* 2013; 381: 2091–99

The TenoRes Study Group ***Lancet Infect Dis*** **2016**
Published **Online** January 28, 2015 – **Abstract 503**

Perspective
OCTOBER 26, 2017

HIV Drug Resistance — An Emerging Threat to Epidemic Control

Chris Beyrer, M.D., M.P.H., and Anton Pozniak, M.D.



Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

Drug resistance is one of the markers of failure of HIV programs.

Goals of Antiretroviral Therapy

- Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication
- Minimize or eliminate short and long-term adverse effects of the therapy
- Have therapies that are accessible to all PLWHIV
- Prevent transmission of HIV-1 to others via any route of exposure

GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

Tabla 3. Combinaciones de TAR de inicio recomendadas†

3er Fármaco	Pauta†	Comentarios‡
Preferentes. *Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.*		
INI	DTG/ABC/3TC	- ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	RAL+FTC/TAF	- RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas*.

The opportunity

MAJOR BENEFITS:

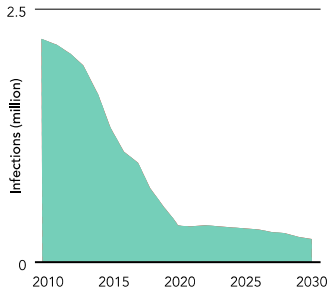
21 MILLION
AIDS-related deaths averted by 2030

28 MILLION
HIV infections averted by 2030

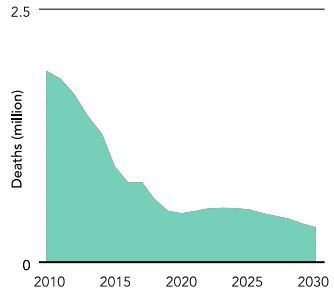
5.9 MILLION
infections among children averted by 2030

17-FOLD
return on HIV investments

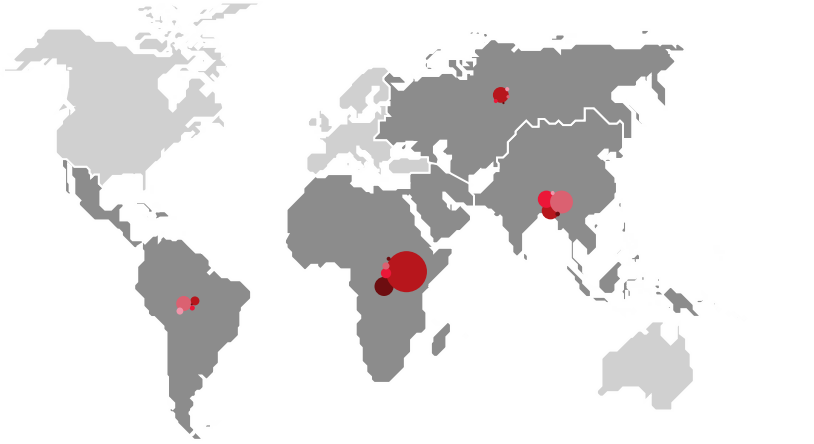
New HIV infections in low- and middle-income countries (million)



AIDS-related deaths in low- and middle-income countries (million)



New HIV infections in different population groups, 2030



The challenge

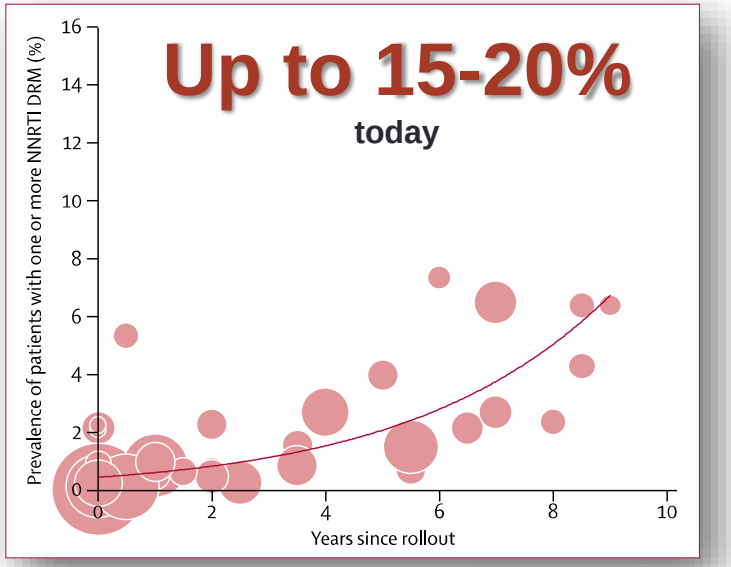


Figure 4: Prevalence of major drug-resistance mutations that confer resistance to non-nucleoside reverse transcriptase inhibitors, by time since antiretroviral rollout in east Africa

Gupta R Lancet ID 2012

No DTG resistance after 1st-line DTG VF in RCTs

Study	Summary efficacy	PDVF in DTG arm	INSTI resistance
FLAMINGO	DTG > DRV/r	2 / 242	0
ARIA	DTG > ATV/r	1/ 248	0
SINGLE	DTG > EFV	18 / 422	0
SPRING-2	DTG = RAL	16 / 411	0
GS-1489	DTG/ABC/3TC=BIC/TAF/FTC	3/315	0
GS-1490	DTG=BIC	0/325	0

- No INSTI resistance emergence in **ideal** conditions
  - ART-naive
  - WT virus → Active backbone
  - Early ART switch after PDFV

Walmsley et al. *J Acquir Immune Defic Syndr* 2015;70:515–19;
Molina et al. *Lancet HIV* 2015;2:e127–36;
Orrell et al. *Lancet* 2017 [Epub ahead of print]
Raffi et al. *Lancet Infect Dis* 2013;13:927–35;
Sax et al. *Lancet* 2017 [Epub ahead of print];
Gallant et al. *Lancet* 2017 [Epub ahead of print

WHAT MAKES DOLUTEGRAVIR ONE OF THE KIND?

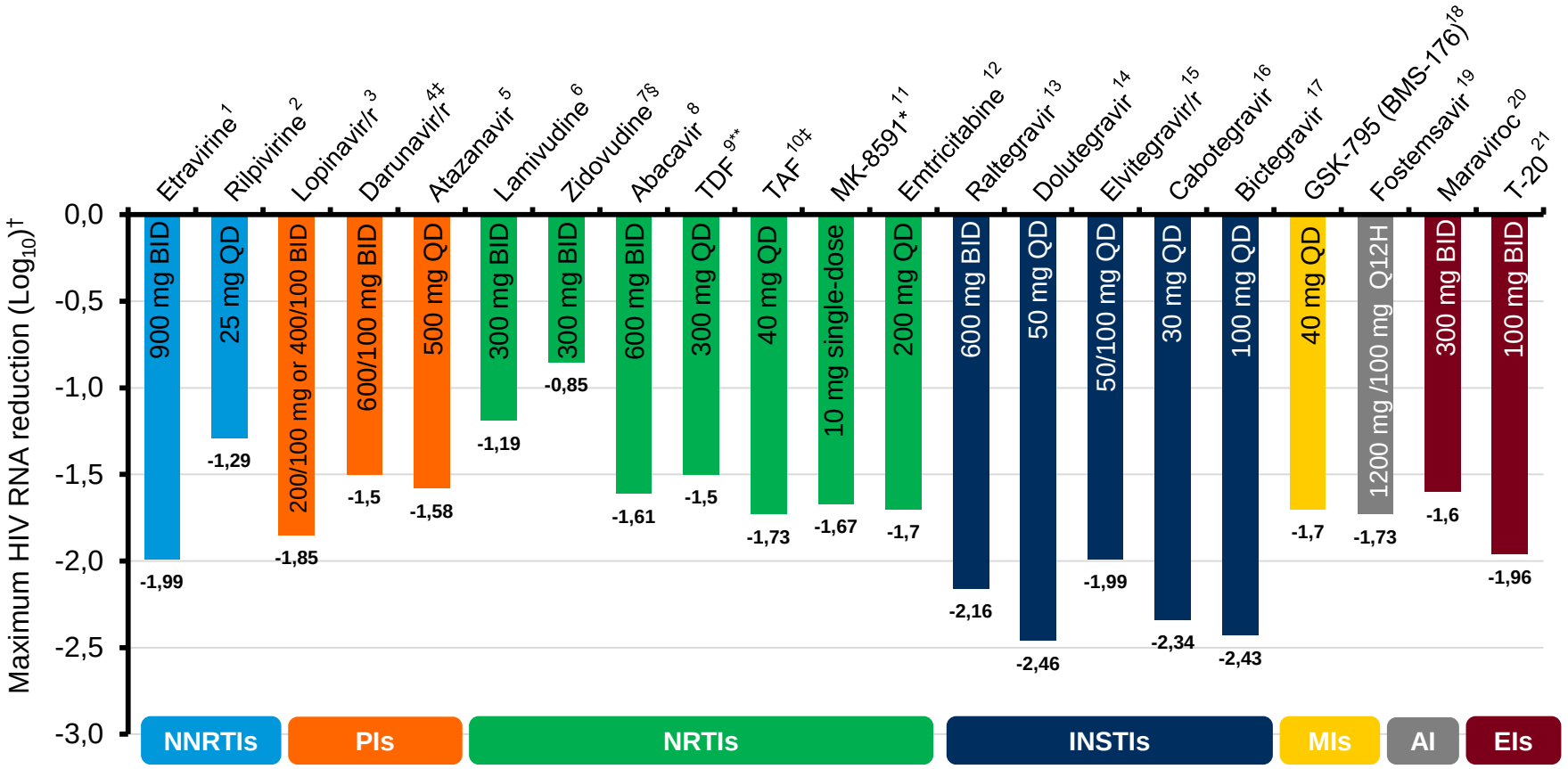
Potent, Relatively simple, flexible

Favorable PK

Well tolerated

INSTIs Exhibit Similar or Higher Antiviral Activity vs Other Drug Classes

PoC ART monotherapy: maximum change in HIV RNA (log_{10}) over 7–14 days



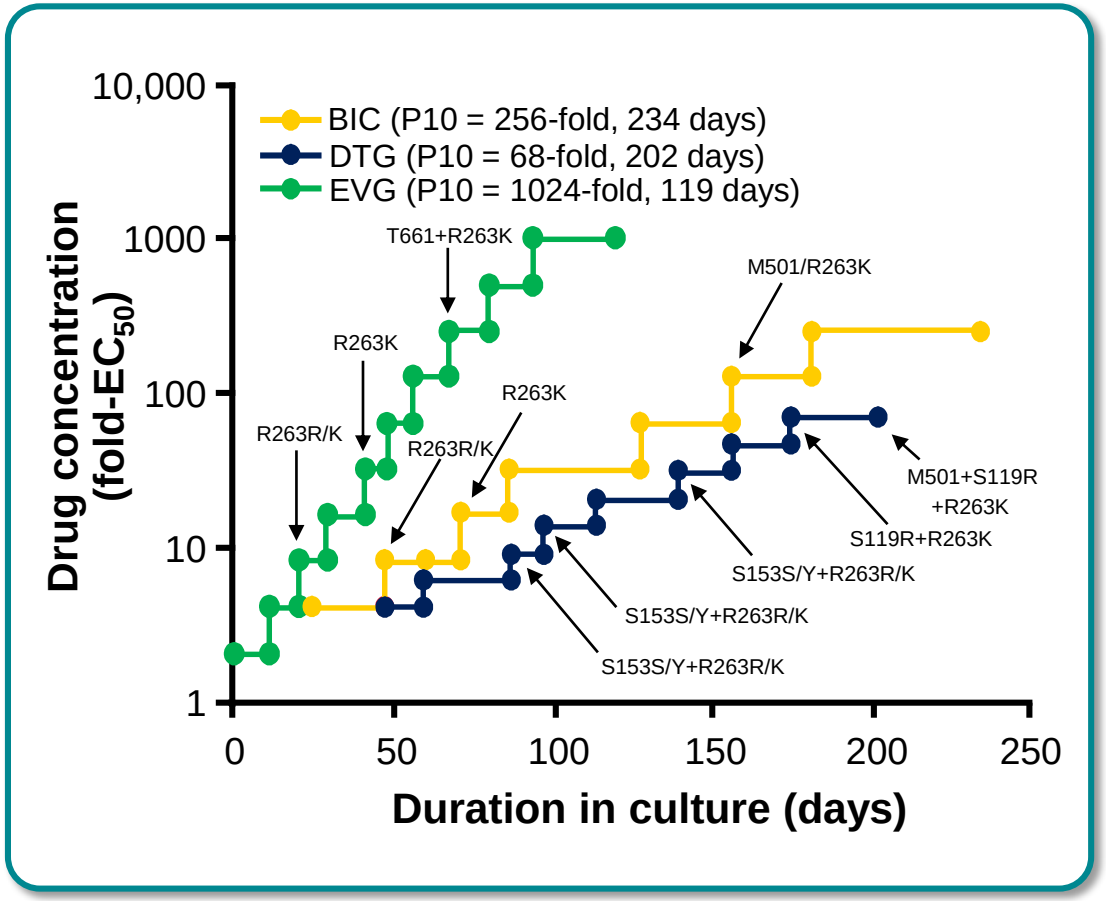
*Single dose. †Mean / median value as available. ‡Day 21. §Week 24. **Day 28.
AI = attachment inhibitor; ART = antiretroviral therapy; BID = twice daily; EI = entry inhibitor;
INSTI = integrase strand transfer inhibitor; MI = maturation inhibitor;
NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor;
PI = protease inhibitor; PoC = proof of concept; QD = once daily; TAF = tenofovir alafenamide fumarate;
TDF = tenofovir disoproxil fumarate.

See slide notes for references.

Selection of Resistance-Associated Mutations *In Vitro* Indicate BIC and DTG Have a Higher Barrier to Resistance Than EVG

Progress of BIC, DTG and EVG resistance selection with HIV-1 IIIb

- Dose-escalation selection was conducted in parallel for BIC, DTG and EVG
  - Resistance selections progressed at a faster rate with EVG compared with BIC and DTG
  - A higher fold change in EC_{50} was reported with EVG vs with BIC and DTG
  - BIC and DTG have a higher barrier to resistance emergence than EVG



BIC = bictegravir; DTG = dolutegravir;
EC_{50} = concentration required to inhibit viral replication by 50%;
EVG = elvitegravir.

Tsiang et al. *Antimicrob Agents Chemother* 2016;60:7086–97.

DTG and BIC Have Improved Activity Against INSTI-Resistant HIV-1 Mutants Compared With RAL and EVG

- The antiviral activity of INSTIs was assessed against a panel of known INSTI-resistant mutants[1]
  - DTG and BIC displayed increased activity against INSTI-resistant mutants vs RAL and EVG[1]
    - Note: the FC cut-offs shown below are arbitrary and are based on *in vitro* data only

Activity of integrase inhibitors against INSTI-resistant HIV-1 mutants[1]

Mutant	Mean FC, IC_{50}			
	DTG	BIC	RAL	EVG
E92Q	1.8	2.0	38	85
Y143R	1.9	1.8	418	14.4
Q148R	1.0	1.0	427	363
N155H	2.4	1.6	188	112
R263K	2.5	2.9	10.4	10.5
E138K/Q148K	13.7	13.7	1533	3581
G140S/Q148R	6.5	3.1	2461	868
E92Q/N155H	2.8	2.0	624	768
N155H/Q148R	4.7	7.1	2181	2169

0 to ≤2 | >2 to ≤10 | >10 to ≤ 50 | >50 to ≤ 100 | >100 to ≤ 500 | >500

BIC = bictegravir; DTG = dolutegravir; EVG = elvitegravir; FC = fold change;
IC_{50} = half maximal inhibitory concentration; INSTI = integrase strand transfer inhibitor;
RAL = raltegravir.

1. Tsiang et al. *Antimicrob Agents Chemother* 2016;60:7086–97.

Response by Baseline DTG FC at Weeks 24 and 48

DTG 50 mg BID (ITT-E, Snapshot Algorithm)

DTG FC Group		Week 24 <50 c/mL	Week 48 <50 c/mL
	N*	N (%)	N (%)
All	213	140 (66%)	128 (60%)
<3	138	104 (75%)	94 (68%)
3 to <10	47	23 (49%)	21 (45%)
≥10	20	5 (25%)	5 (25%)

*Note: 8/213 had missing DTG FC at baseline

Vavro et al. CROI 2015; Seattle, WA. Poster 609.

Response by Derived IN Mutation Groups at Weeks 24 and 48

DTG 50 mg BID (ITT-E, Snapshot Algorithm)

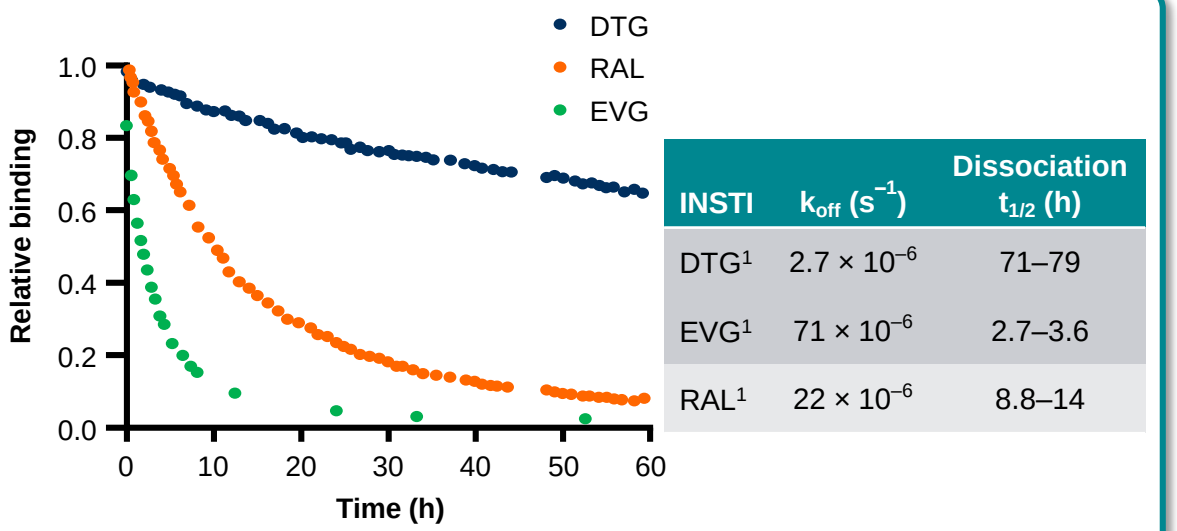
Baseline IN Mutation Group		Week 24 <50 c/mL	Week 48 <50 c/mL
	N	N (%)	N (%)
All	213	140 (66%)	128 (60%)
No Q148	140	109 (78%)	98 (70%)
Q148 + 1*	48	25 (52%)	23 (48%)
Q148 + ≥2*	25	6 (24%)	7 (28%)

*L74I, E138A/K/T, G140A/C/S

Vavro et al. CROI 2015; Seattle, WA. Poster 609.

¿Cómo se explica la barrera a resistencia de DTG?

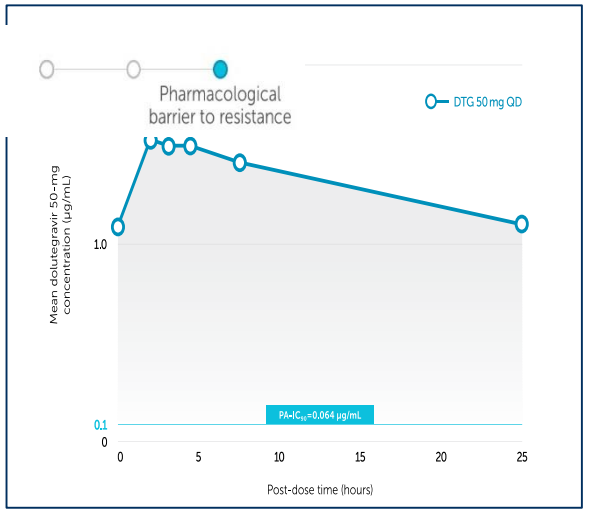
- Compared with RAL and EVG, DTG dissociate more slowly from a WT IN-DNA complex at 37°C[1,2]
  - The structural and electronic characteristics of the metal-binding scaffold may contribute to the slower dissociation kinetics
  - The clinical relevance of these kinetics is yet to be determined



INSTI	k_{off} (s^{-1})	Dissociation $t_{1/2}$ (h)
DTG[1]	2.7×10^{-6}	71–79
EVG[1]	71×10^{-6}	2.7–3.6
RAL[1]	22×10^{-6}	8.8–14

DTG = dolutegravir; EVG = elvitegravir; IN = integrase; INSTI = integrase strand transfer inhibitor; k_{off} = dissociation rate; NA = not available; RAL = raltegravir; $t_{1/2}$ = half life; WT = wild-type.

1. Hightower et al. *Antimicrob Agents Chemother* 2011;5:4552–9;



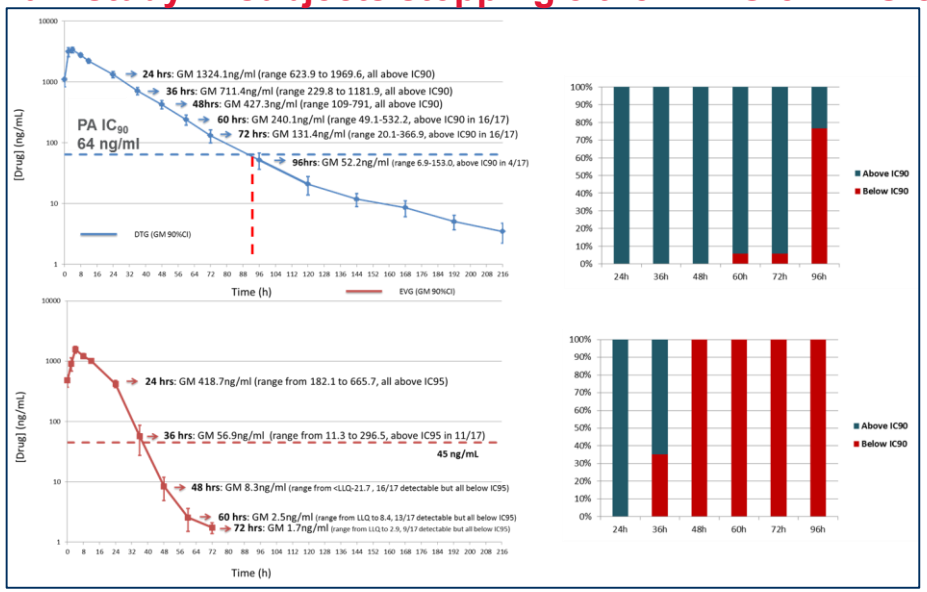
With 50 mg of dolutegravir the peak drug level is 3.40 µg/mL —an inhibitory quotient

19x greater than PA-IC_{90}

which may also contribute to a high barrier to resistance.

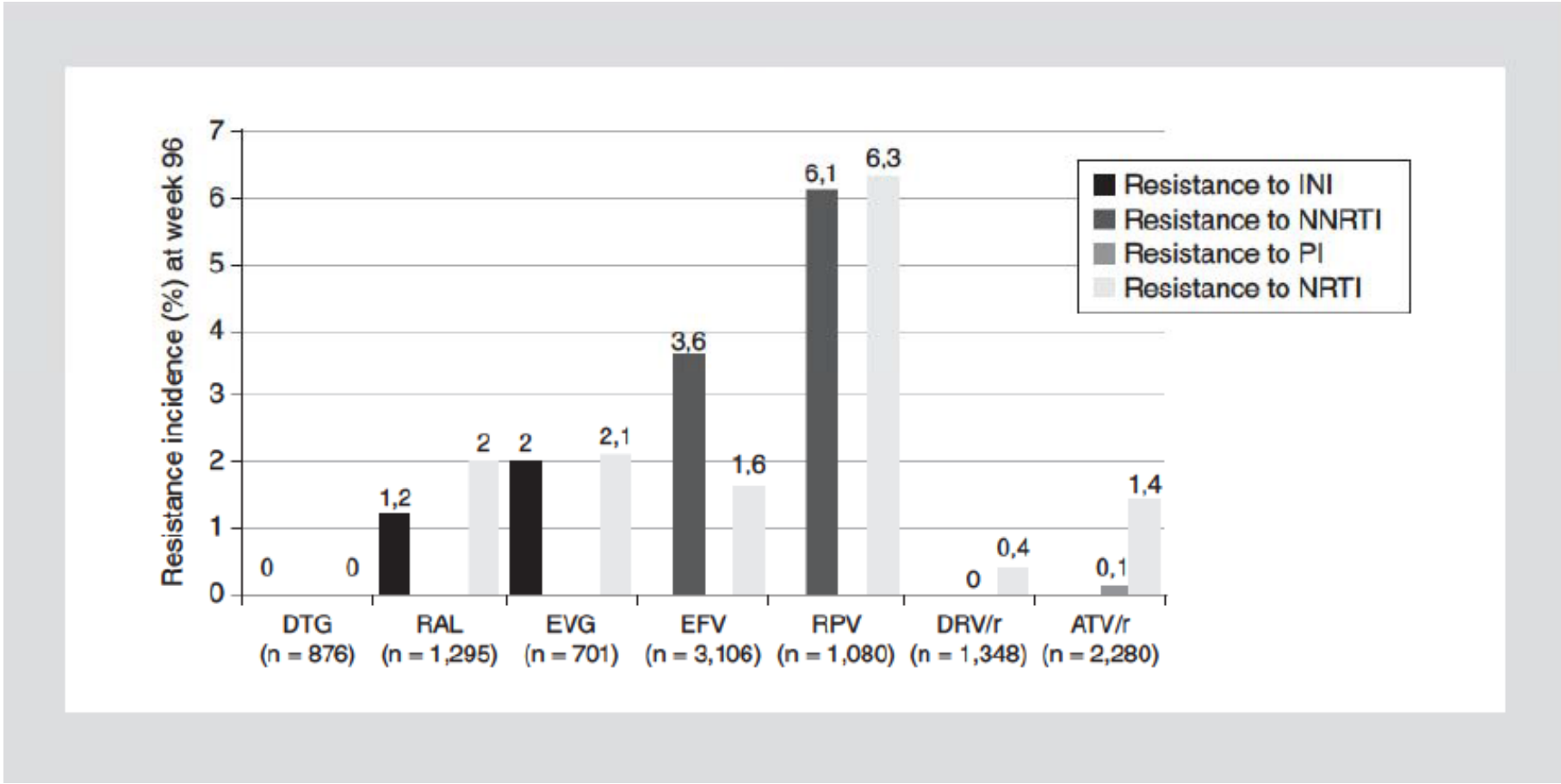
van Lunzen. Lancet Infect Dis. 2012 Feb;12(2):111-8.

'Tail' study in subjects stopping either DTG or EVG/cobi



Adaptado de Elliot,et al J Antimicrob Chemother (2015) 71 (4): 1031-1036.

DATOS CLÍNICOS DE RESISTENCIAS DE INIs. Naïve



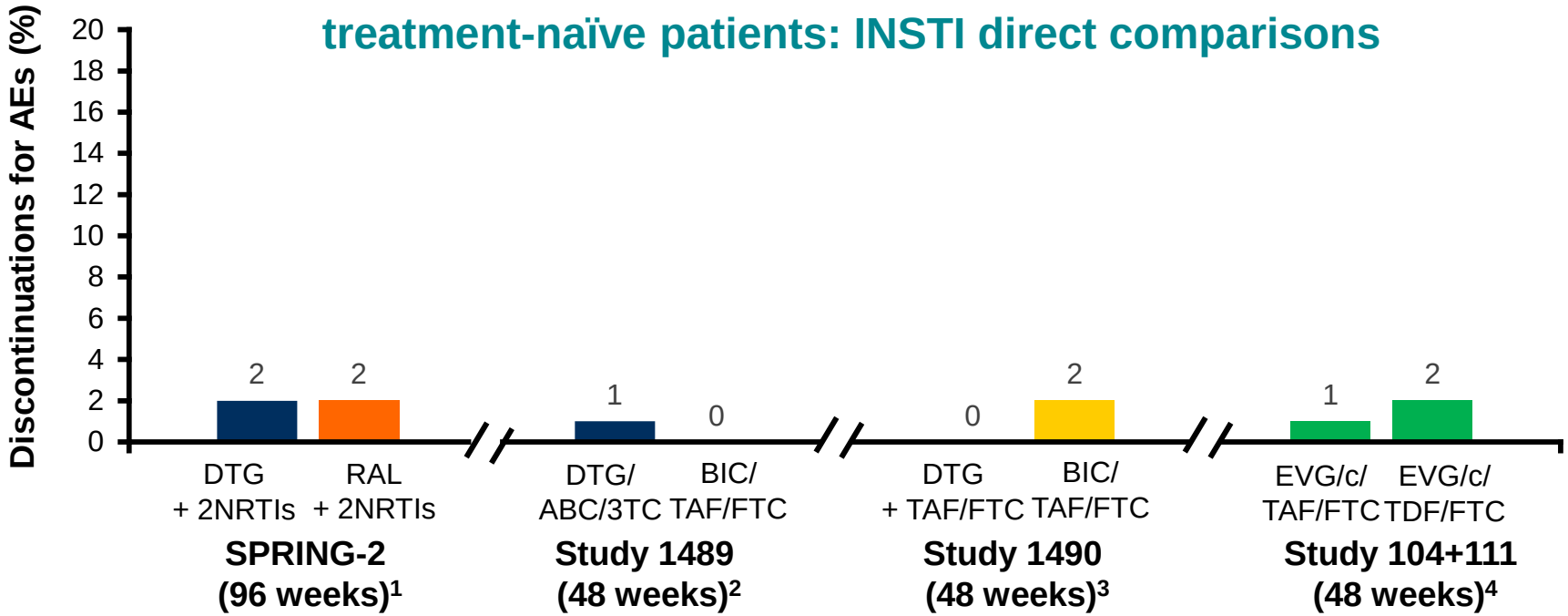
Incidence of resistance at week 96 in pivotal clinical trials of antiretroviral therapy in naïve patients

Libre et al. AIDS rev. 2015

Discontinuations Due to AEs Were Few in Treatment-Naïve Studies Directly Comparing INSTIs

- In Phase 3 studies in treatment-naïve patients, discontinuations due to AEs are few with all INSTIs
- Although there are direct comparisons for DTG with RAL and BIC with DTG, there is no direct comparator study of DTG with EVG, and no head-to-head studies of EVG/c/TAF/FTC with any other INSTI

Discontinuations from Phase 3 studies of treatment-naïve patients: INSTI direct comparisons



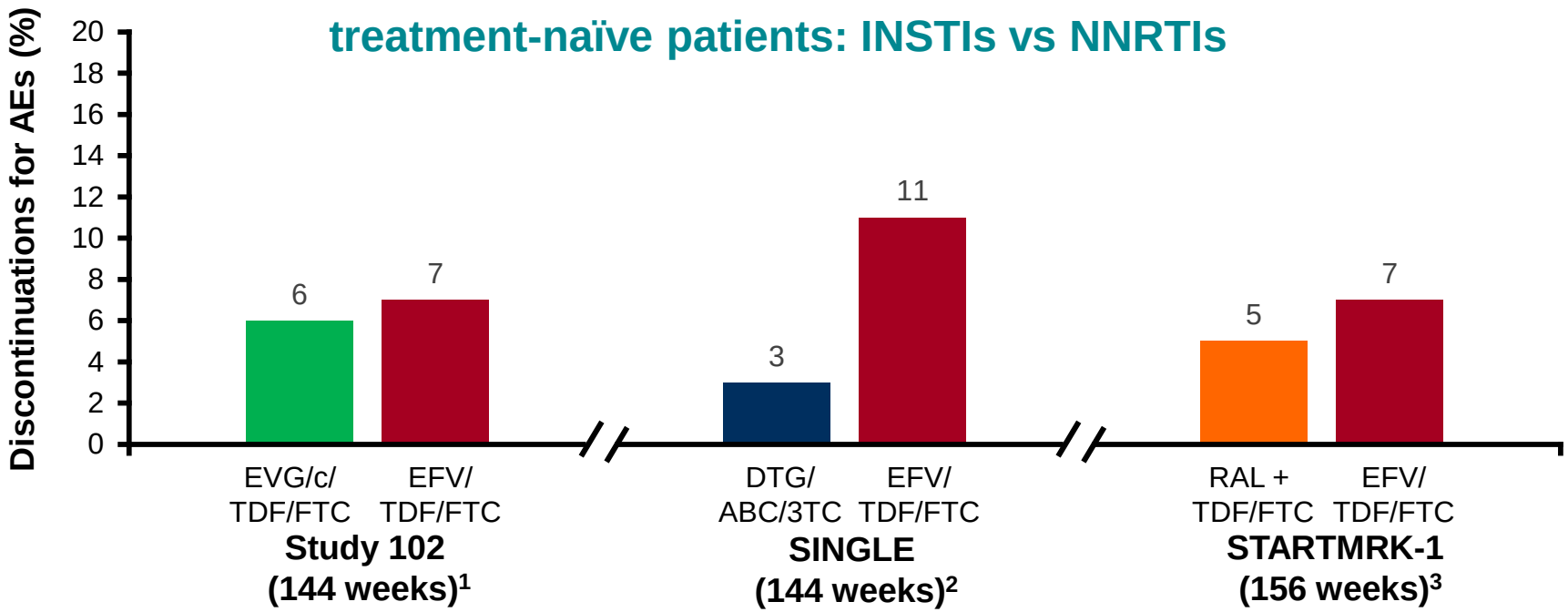
3TC = lamivudine; ABC = abacavir; AE = adverse event; BIC = bictegravir; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

1. Raffi et al. *Lancet Infect Dis* 2013;13:927–35;
2. Gallant et al. *Lancet* 2017 [Epub ahead of print];
3. Sax et al. *Lancet* 2017 [Epub ahead of print];
4. Sax et al. *Lancet* 2015;385:2606–15.

INSTI-Containing Regimens Were Associated With Fewer Discontinuations Due to AEs Than EFV/TDF/FTC in Treatment-Naïve Patients

- DTG-, EVG- and RAL-containing regimens were all associated with fewer discontinuations due to AEs than EFV/TDF/FTC over the long term
- Data comparing BIC with EFV or RPV are not available

Discontinuations from Phase 3 studies of treatment-naïve patients: INSTIs vs NNRTIs



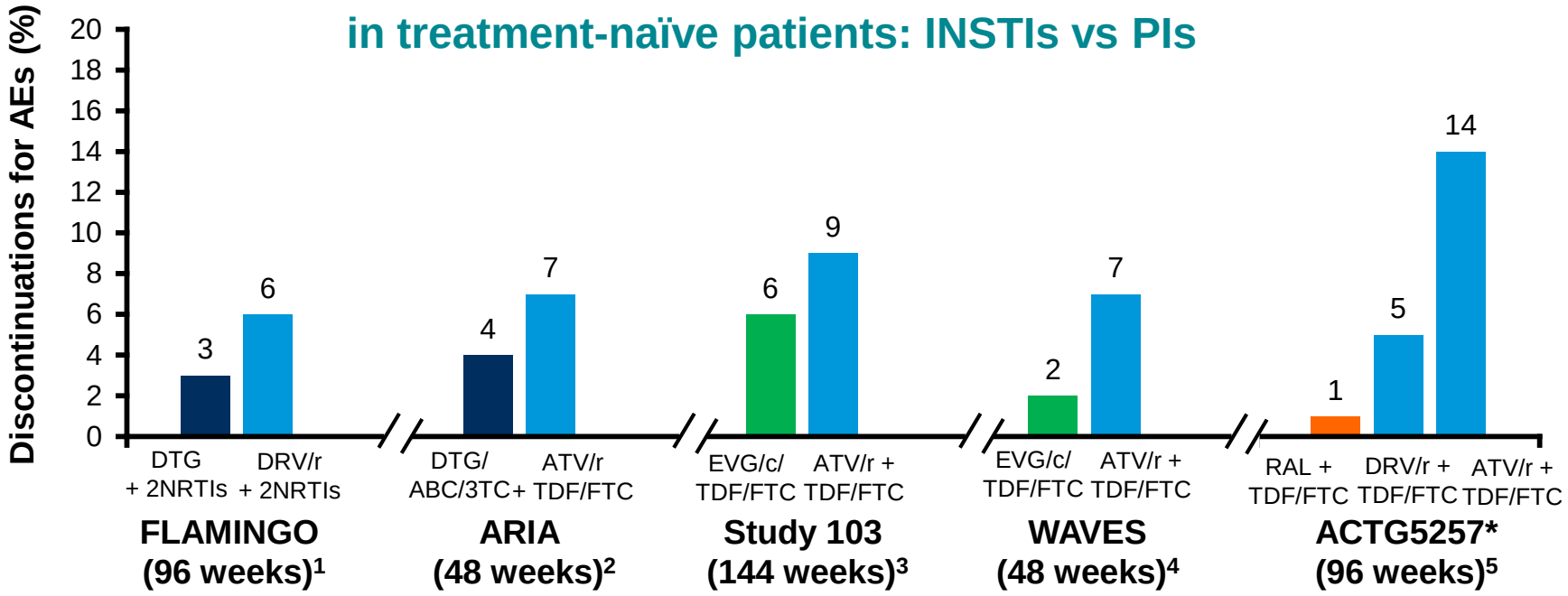
3TC = lamivudine; ABC = abacavir; AE = adverse event; BIC = bictegravir;
DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat;
FTC = emtricitabine; INSTI = integrase strand transfer inhibitor;
NNRTI = non-nucleoside reverse transcriptase inhibitor;
RAL= raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate.

1. Wohl et al. *J Acquir Immune Defic Syndr* 2014;65:e118–20;
2. Walmsley et al. *J Acquir Immune Defic Syndr* 2015;70:515–9;
3. Rockstroh et al. *Clin Infect Dis* 2011;53:807–16.

Discontinuations Due to AEs Were Lower With INSTI-Based Regimens vs With Boosted PI-Based Regimens in Treatment-Naïve Patients

- INSTIs have been associated with fewer discontinuations due to AEs than boosted DRV and ATV in treatment-naïve patients
- Data comparing BIC with any of the PIs are not available

Discontinuations from Phase 3 studies in treatment-naïve patients: INSTIs vs PIs



*Rates reflect the % of patients with toxicity-associated discontinuations.
3TC = lamivudine; ABC = abacavir; AE = adverse event; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumarate.

1. Molina et al. *Lancet HIV* 2015; 2:e127–36;
2. Orrell et al. Lancet 2017 [Epub ahead of print];
3. Clumeck et al. *J Acquir Immune Defic Syndr* 2014;65:e121–4;
4. Squires et al. *Lancet HIV* 2016;3:e410–20;
5. Lennox et al. *Ann Intern Med* 2014;161:461–71.

Different Metabolic Pathways Can Lead to Differences in the Potential for DDIs (1)

DDIs between INSTIs and miscellaneous therapeutics

		DTG[1–4]	RAL[1]	EVG/c[1]	BIC[5]
Gastrointestinal agent	Antacids	■	■	■	■
Steroid	Beclometasone inhaler	◆	◆	◆	?
	Budesonide inhaler	◆	◆	■	?
	Fluticasone inhaler	◆	◆	■	?
Analgesic	Buprenorphine	◆	◆	◆	?
	Methadone	◆	◆	◆	?
Antimigraine agent	Ergotamine	◆	◆	●	?
Contraceptive	Ethinylestradiol	◆	◆	■	◆
Bronchodilator	Salmeterol inhaler	◆	◆	■	?
Erectile dysfunction agent	Sildenafil	◆	◆	■	?
Supplement	St John's wort	●	◆	●	?
Antihyperglycaemic	Metformin	■	◆	■	■
Other	Varenicline	◆	◆	◆	?
Stimulants	Amyl nitrate	◆	◆	◆	?
	Cocaine	◆	◆	■	?
	Ecstasy (MDMA)	◆	◆	■	?
	Mephedrone	◆	◆	■	?
	Methamphetamine	◆	◆	■	?

Key to symbols

- ● These drugs should not be co-administered
- ■ Potential interaction: may require close monitoring, alteration of drug dosage or timing of administration
- ◆ No clinically significant interactions expected

- DTG, RAL and EVG have a well-characterised DDI profile[1–4]
  - Data on the BIC metabolic pathway are limited; DDI data cannot be extrapolated from DTG[5]

This table is not exhaustive; for additional DDI data and dosage adjustments, see www.hiv-druginteractions.org (University of Liverpool).
BIC = bictegravir; DDI = drug–drug interaction; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; INSTI = integrase strand transfer inhibitor; MDMA = 3,4-methylenedioxymethamphetamine; RAL = raltegravir.

1. University of Liverpool. Drug interactions chart; www.hiv-druginteractions.org. Accessed August 2017;
2. Tivicay SPC. August 2017; 3. Song et al. *J Aquir Immune Defic Syndr* 2016;72:400–7;
4. Song et al. *Ann Pharmacother* 2015;49:784–9;
5. Zhang et al. CROI 2017. Abstract 40.

Different Metabolic Pathways Can Lead to Differences in the Potential for DDIs (2)

DDIs between INSTIs and miscellaneous therapeutics

		DTG[1,2]	RAL[1]	EVG/c[1]	BIC[3]
Depressants	Alcohol	◆	◆	◆	?
	Alprazolam	◆	◆	■	?
	Codeine	◆	◆	■	?
	Diazepam	◆	◆	■	?
	GHB (gamma hydroxybutyrate)	◆	◆	■	?
	Heroin (diamorphone)	◆	◆	■	?
	Hydrocodone	◆	◆	■	?
	Hydromorphone	◆	◆	◆	?
	Ketamine	◆	◆	■	?
	Pethidine (meperidine)	◆	◆	■	?
	Methadone	◆	◆	◆	?
	Midazolam (oral)	◆	◆	●	◆
	Morphine	◆	◆	■	?
	Oxycodone	◆	◆	■	?
	Temazepam	◆	◆	◆	?
	Triazolam	◆	◆	●	?
Hallucinogens	Cannabis	◆	◆	◆	?
	Lysergic acid diethylamide (LSD)	◆	◆	■	?
	Phencyclidine (PCP, angel dust)	◆	◆	■	?

Key to symbols

- ● These drugs should not be co-administered
- ■ Potential interaction: may require close monitoring, alteration of drug dosage or timing of administration
- ◆ No clinically significant interactions expected

- DTG, RAL and EVG have a well-characterised DDI profile[1–4]
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1. University of Liverpool. Drug interactions chart; www.hiv-druginteractions.org. Accessed August 2017;
2. Tivicay SPC. August 2017;
3. Zhang et al. CROI 2017. Abstract 40.

Under Pressure

UN Member States committed: ambitious targets by 2030

90 90 90: THE UNAIDS STRATEGY TO FURTHER CURB THE HIV EPIDEMIC

based on expanded access to treatment and on the "treatment as prevention" concept

90% of all people living with HIV will know their HIV status

90% of all people diagnosed with HIV will receive sustained antiretroviral therapy.

90% of all people receiving antiretroviral therapy will have durable suppression.

Challenge is keeping patients on ART virologically suppressed

Resistance

Serious barrier to achieving the last "90" target

The one way to ensure zero resistance is to not treat anyone - not an option.

Focus on minimizing resistance to reduce impact on health and cost.

Outcomes according to policy where **> 15%** of all ART initiators have NNRTI resistance in year 0 (2018): Mean **death rate on ART** 2018-2038

0 No change

1 For all ART initiators: - Change the standard first line regimen to a dolutegravir based regimen

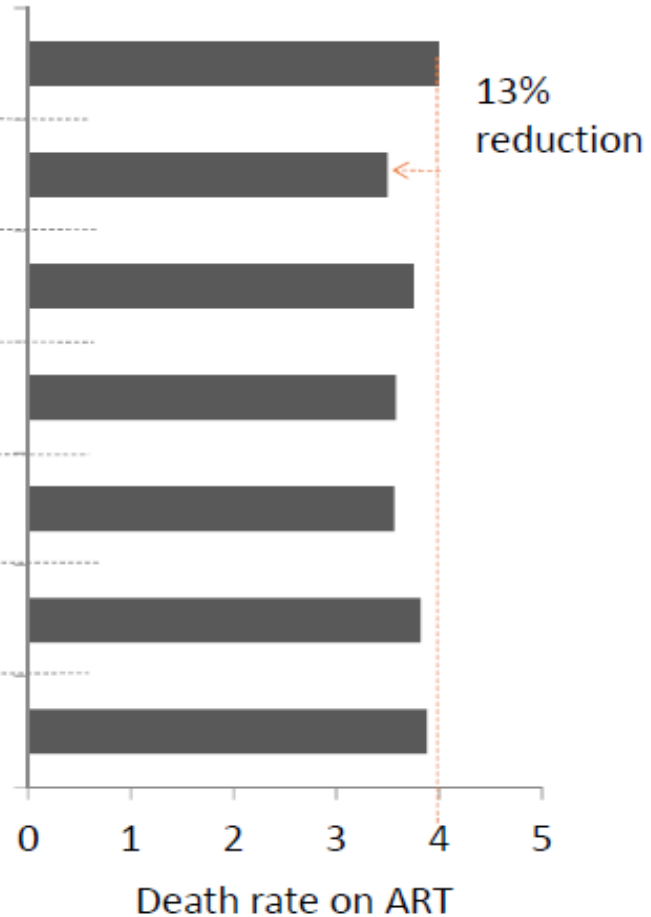
2 For all ART initiators: - Resistance test at 6m if viral load > 1000 - use atazanavir if NNRTI resistance is detected.

3 For all on ART: - Increase the rate of switching to second line in people with viral load failure

4 For all on ART: - Resistance testing to confirm failure – high probability of switch if resistance detected

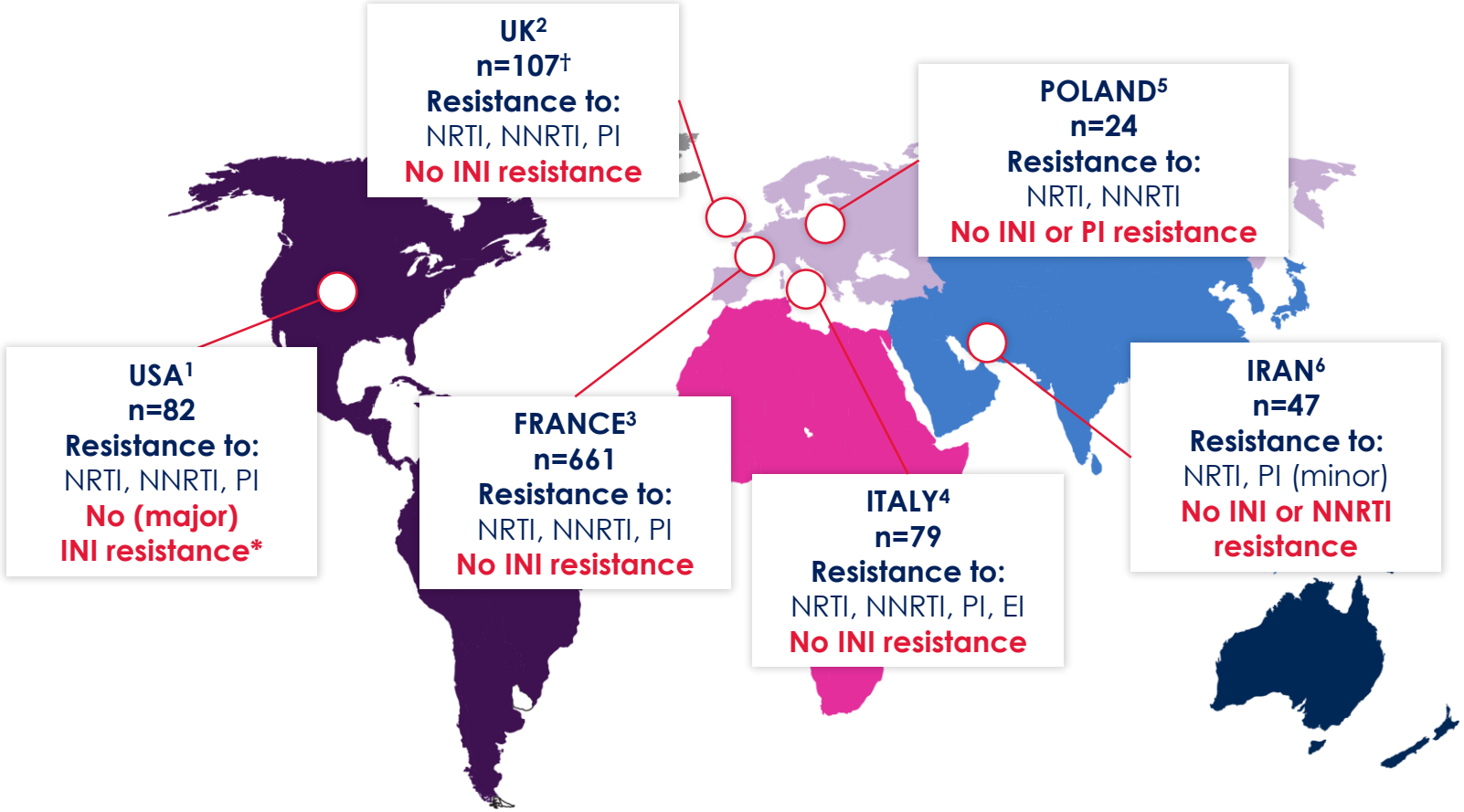
5 For ART initiators with prior ARV exposure: - Change the standard first line regimen to dolutegravir based regimen

6 For ART initiators with prior ARV exposure: - Resistance test at 6m if viral load > 1000 - use atazanavir if NNRTI resistance is detected.



Phillips et al Lancet HIV (in press)

NO MAJOR TRANSMITTED INI DRUG RESISTANCE WAS OBSERVED IN OBSERVATIONAL COHORTS IN SIX COUNTRIES



*One patient had an L74M mutation, which confers potential low-level resistance to RAL and EVG and has been found in association with major INI resistance and as a natural polymorphism; †INI resistance-associated mutations were investigated in 57 patients

EVG, elvitegravir; RAL, raltegravir

1. Stekler JD *et al. Antivir Ther* 2015;20:77–80; 2. Garcia-Diaz A *et al. J Int AIDS Soc* 2014:2;17:19752; 3. Descamps D *et al. J Antimicrob Chemother* 2013;68:2626–2631; 4. Cossarini F *et al. J Acquir Immune Defic Syndr* 2011;56:e51–e54; 5. Parczewski M *et al. PLoS One* 2012;7:e31674; 6. Jahanbakhs F *et al. PLoS One* 2013;8:e61864

Time to consider Dolutegravir for treatment in Uganda: HIV drug resistance profiles of virologic failures on first-,second-, or third line/Raltegravir containing combined antiretroviral treatments

Emmanuel Ndashimye[1], Art P[1], Avino M[1], Gibson R[1,], Quinones-Mateu[2], Kyeyune F[3], Nankya I[3], Mugyenyi P[3], Kityo C[3], and Arts E[1]

[1]Department of Microbiology and Immunology, Schulich School of Medicine & Dentistry University of Western Ontario, London, Ontario, Canada
[2]Case western Reserve University, Cleveland, Ohio, USA
[3]Joint Clinical Research Centre, Kampala, Uganda,

HIV-1 infected patients failing on RAL-based regimen with primary and/or secondary (compensatory) INSTI mutations

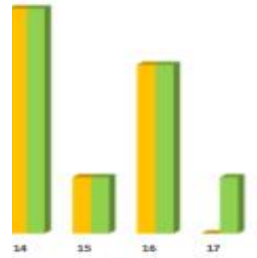
Primary/secondary mutations	n (%)	DTG	RAL	EVG
M50I/L/MR				
M50I,L74I				
T97A				
T97A,G163R,L74M				
N155H				
N155H,T97A				
N155H,T97AT				
N155H,T97A,E157Q,L74I				
N155H,E157Q,G163R,M50L,L7				
Y143R,T97A				
Y143R,T97AT,G163R	1(3.0)	P	H	I
Y143R,T97A,M50I,L74LM	1(3.0)	P	H	I
E138A,T97A,V151A	1(3.0)	P	I	I
E138K,G140A,S147G,Q148K	1(3.0)	H	H	H
T66A,T97A,G163R,L74M	1(3.0)	S	I	H

In all 400 patients; Y143R (0.75%), Q148K (0.25%), N155H (1.5%), E138A/K (0.5%), G140A (0.25%), S147G (0.25%). Accessory mutations; T97A (8.75%), M50I 6.5%), L74M/I (3%), E157Q (1.25%), V151I/A (2%), G163R (1.5%). In bold are major DRMs.

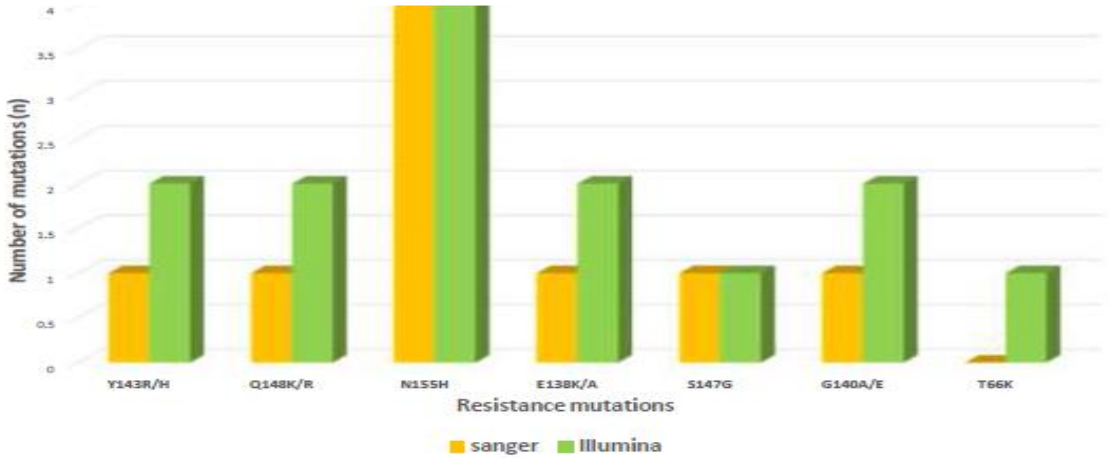
INSTIs DRMs detected by Population and Illumina in RAL failures

Conclusion

- No primary DTG DRMs were found in 366 INSTIs naïve patients, and only one patient was found to have DTG resistance genotype in RAL failures.

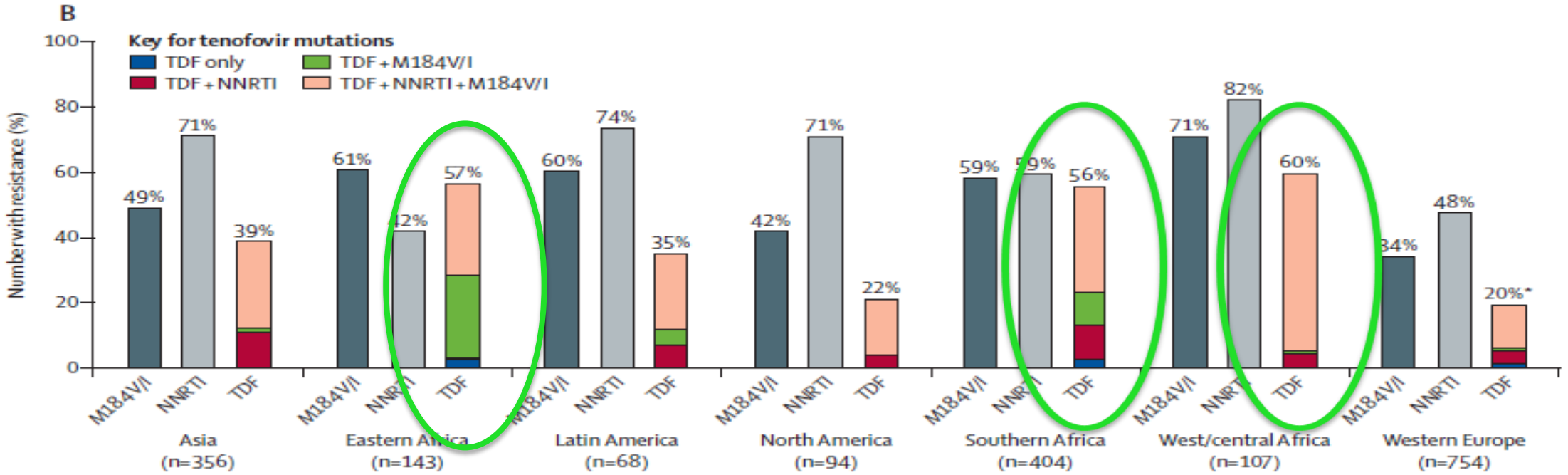


d Illumina



Resistance in Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples

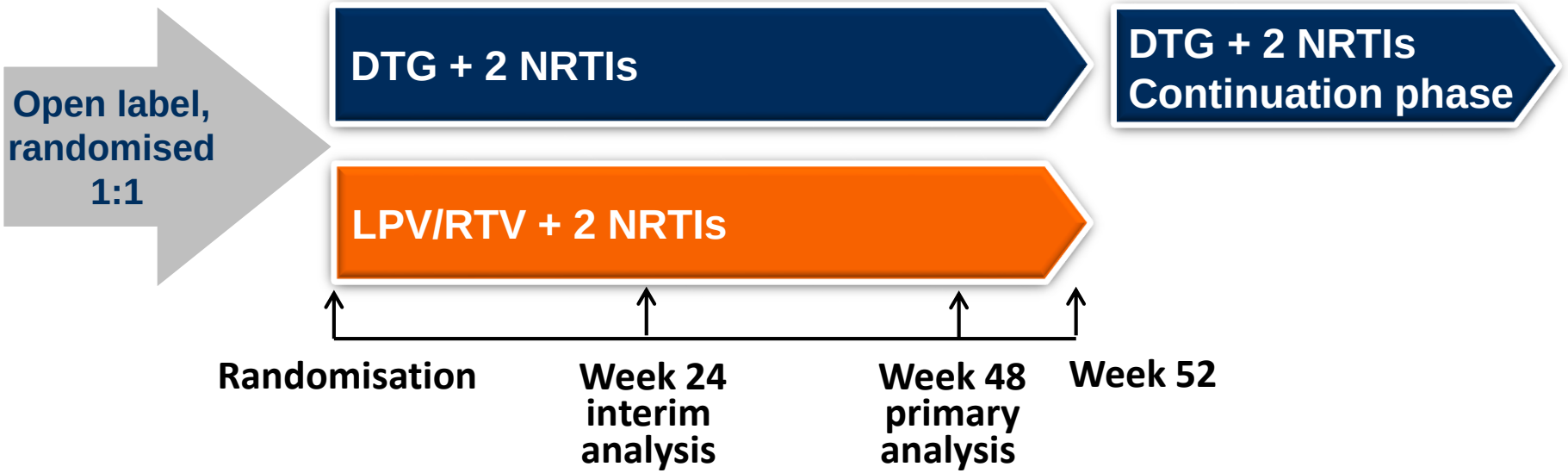


Boyd, M et al *Lancet* 2013; 381: 2091–99

The TenoRes Study Group ***Lancet Infect Dis*** **2016**
Published **Online** January 28, 2015 – **Abstract 503**

DAWNING Study

Open-label randomised noninferiority phase IIIb study



- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs. Investigator-selected NRTIs had to include at least one fully active NRTI based on viral resistance testing at Screening
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)
- **Primary endpoint:** proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

FDA, US Food and Drug Administration; INSTI, integrase strand transfer inhibitor.

Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

Baseline Resistance Profile and NRTI Background Regimen Post Randomisation

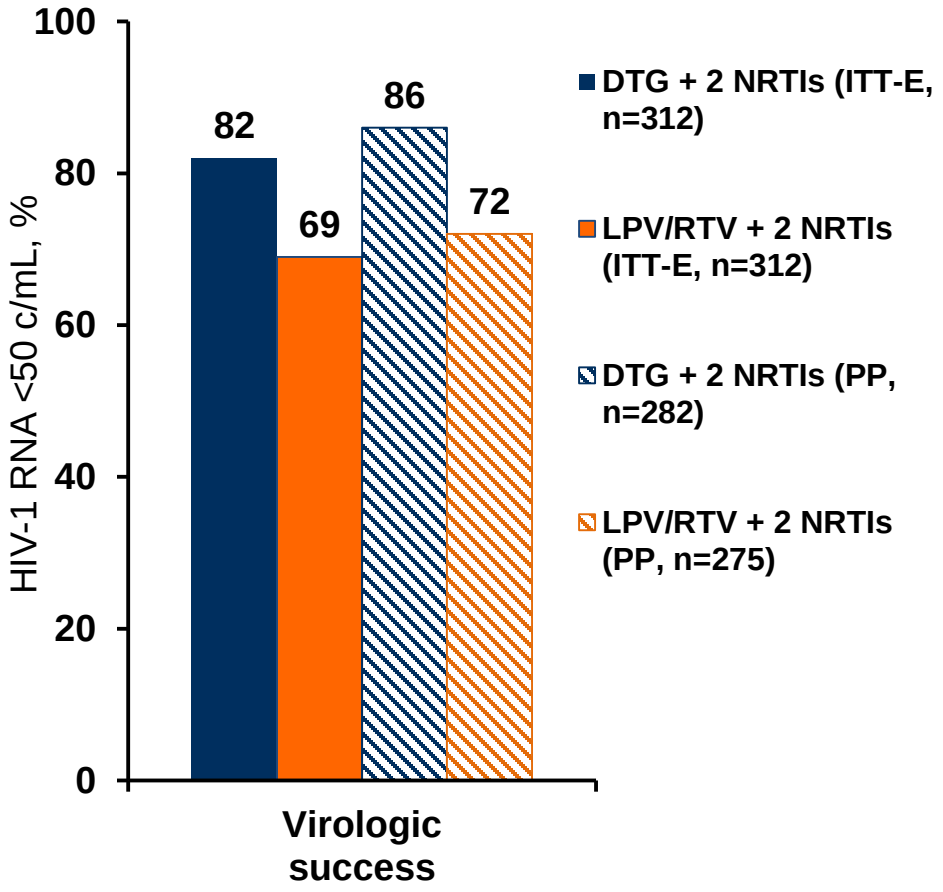
n (%)	DTG + 2 NRTIs (n=312)	LPV/RTV + 2 NRTIs (n=312)
Resistance profile		
Any NRTI, n (%)	**282 (90%)**	**279 (89%)**
M184V/I only	77 (25%)	85 (27%)
M184V + 1 or more additional NRTI RAMs	184 (59%)	167 (54%)
K65R	95 (30%)	91 (29%)
K70E	33 (11%)	37 (12%)
1 TAM	54 (17%)	63 (20%)
2 or more TAMS	17 (6%)	18 (6%)
Any NNRTI, n (%)	**298 (96%)**	**295 (95%)**
1 major NNRTI RAMs	68 (22%)	61 (20%)
2 or more major NNRTI RAMs	230 (74%)	234 (75%)
NRTI background regimen, n (%)		
AZT + 3TC	131 (42)	121 (39)
TDF + 3TC or FTC	128 (41)	134 (43)
TDF + AZT	36 (12)	40 (13)
ABC + 3TC	7 (2)	7 (2)
Other	10 (3)	10 (3)

RAMs, Resistance Associated Mutations;

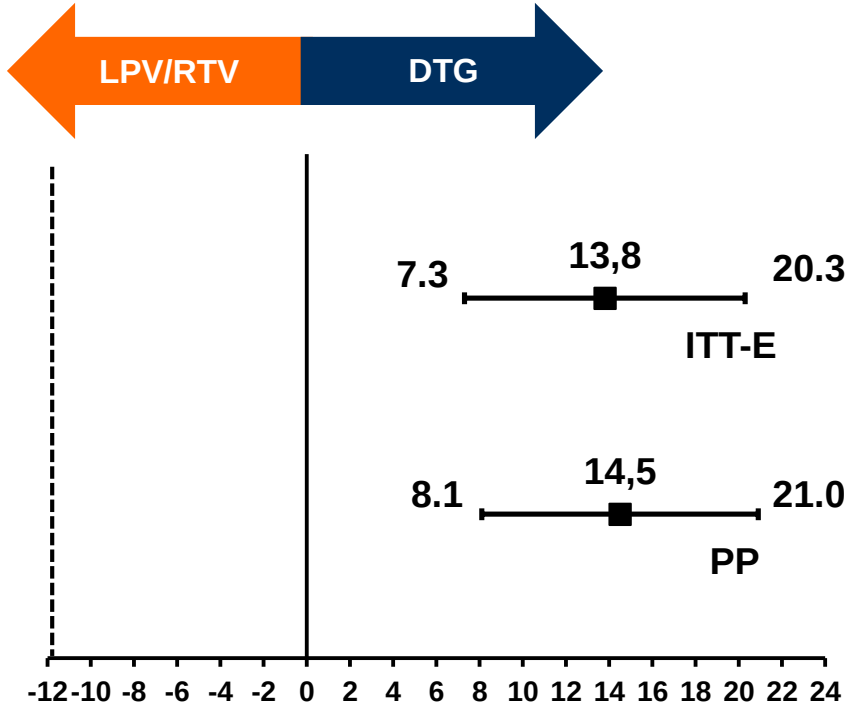
Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

Snapshot Outcomes at Week 24: ITT-E and PP Populations

Virologic outcomes



Treatment differences (95% CI)

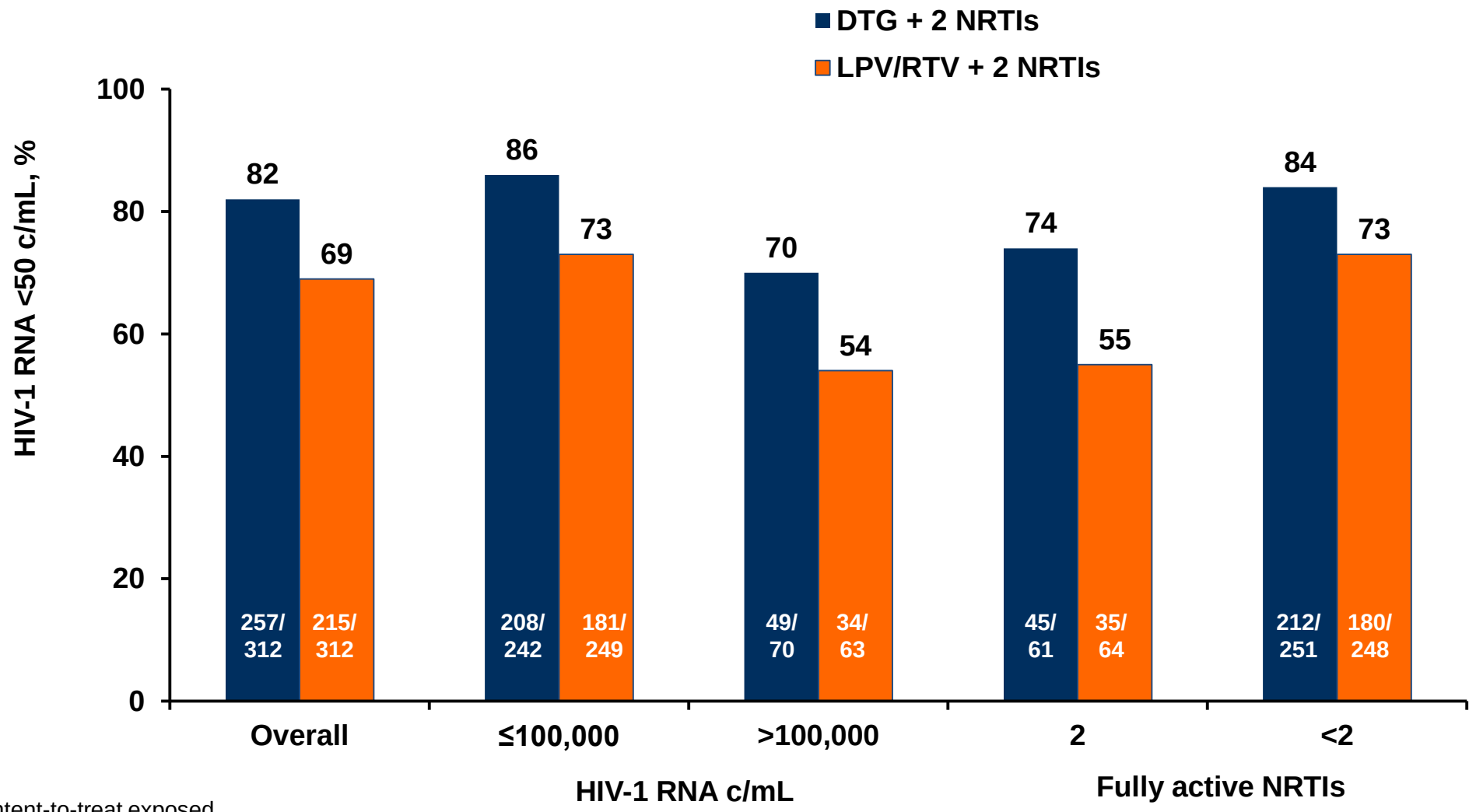


- DTG + 2 NRTIs is **superior** to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (<50 c/mL) at Week 24, ***P*<0.001**

CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

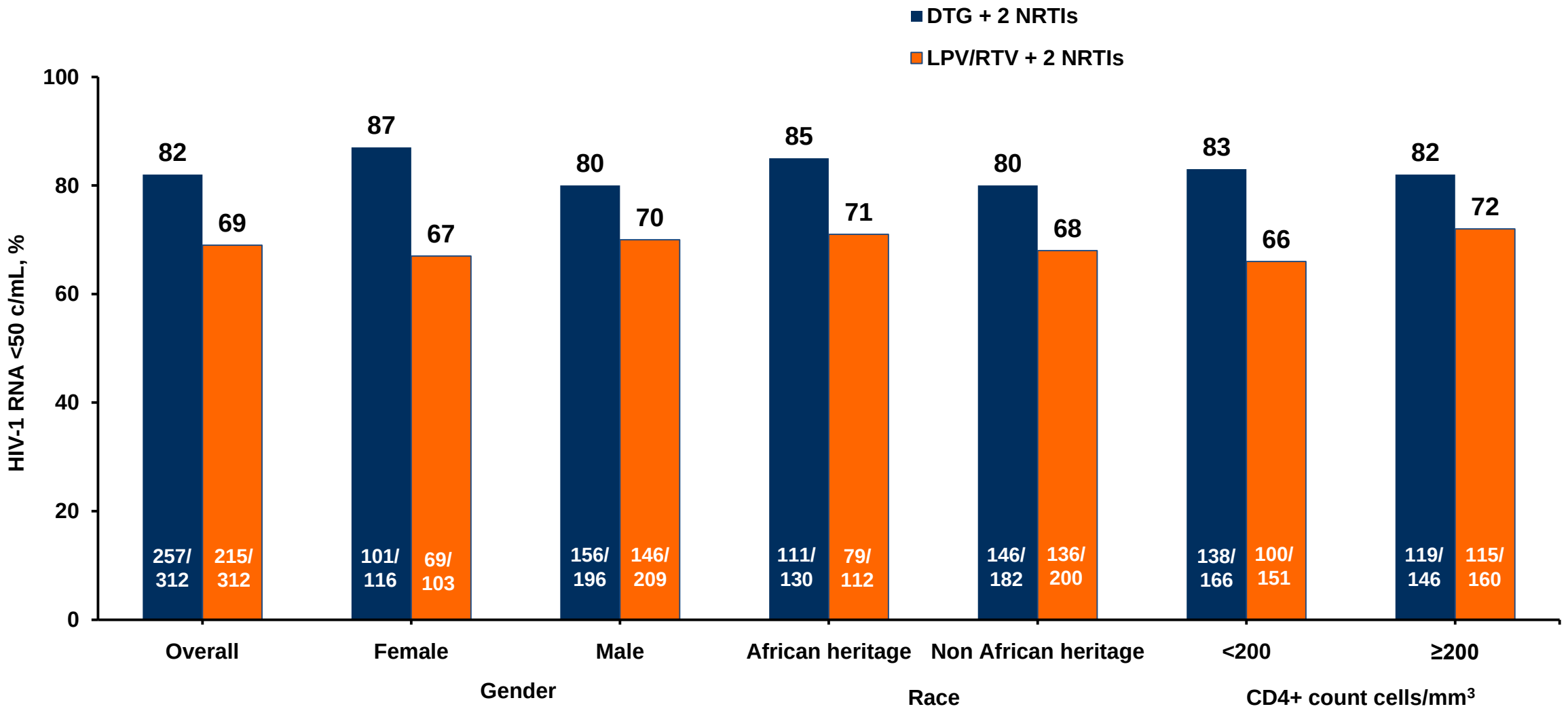
Snapshot Outcomes by baseline viral load and no. active NRTIs at Week 24: ITT-E



ITT-E, intent-to-treat exposed.

Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

Snapshot Outcomes by Key Baseline Subgroups at Week 24: ITT-E



ITT-E, intent-to-treat exposed.

Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

Treatment-Emergent Mutations in Patients With Confirmed Virologic Withdrawal (CVW)

- 10 (3%) of patients in the DTG arm and 28 (9%) of patients in the LPV/r arm met the criteria for CVW in the randomized phase
- The resistance analysis was performed on subjects meeting CVW criteria

Resistance analysis	DTG + 2 NRTIs (n=8)	LPV/RTV + 2 NRTIs (n=24)
INSTI	**0**	**0**
NRTI	**0**	**3***
K70R	0	2
M184V	0	1
K219Q	0	1
K219E	0	1
PI	**0**	**0**

* Both K70R and M184V developed in one subject, K70R and K219E in another.

- No subject receiving DTG + 2 NRTIs developed INSTI or NRTI resistance-associated mutations.

Criteria for CVW: HIV-1 RNA decrease <1 $\log_{10}$ c/mL by Week 16, HIV-1 RNA rebound to ≥400 c/mL after prior confirmed suppression, confirmed ≥400 c/mL on or after Week 24; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Brown et al. ICASA 2017; Abidjan, Côte d'Ivoire. THAB1501.

Razones por las cuales es necesario analizar los datos de investigacion clínica y básica …

Antiretroviral Therapy: The Future

HIV-1 discovered

1983

ZDV monotherapy

1987

ZDV/3TC

1995

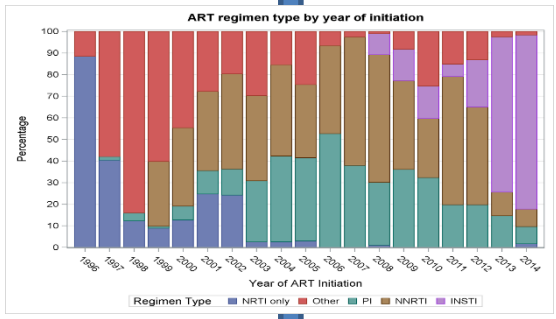
Triple Drug Therapy

1996

Single Tablet Regimens

2006

The Integrase Era



2012-13

Long Acting Injectable?

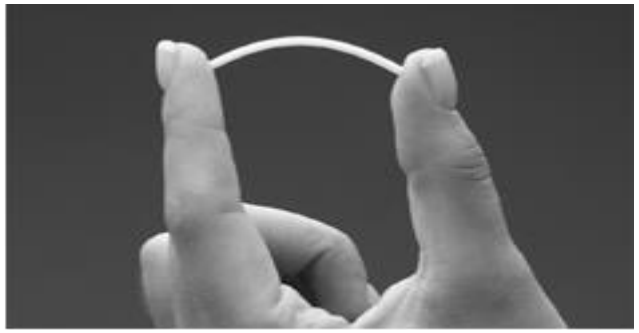
2017

?????

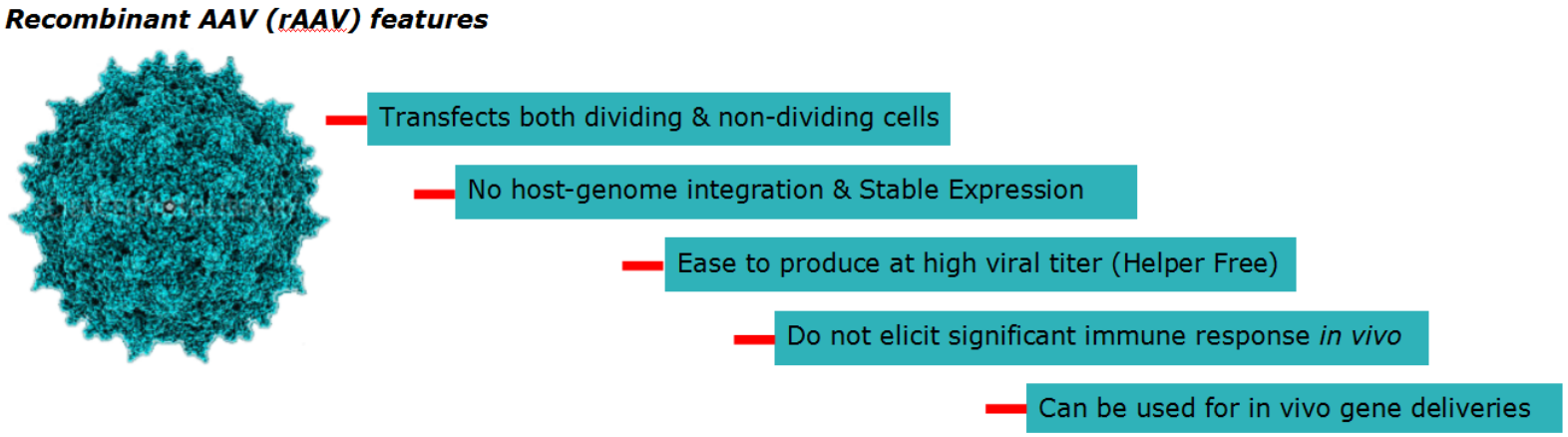
2020

Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals



- Vectored delivery of combinations of antibody-based therapy or protein based therapy



Razones por las cuales es necesario analizar los datos de investigacion clínica y básica

- *Buen entendimiento e interpretación de datos de investigacion para el optimo manejo clinico*
- *Terapias innovadoras que protejan el futuro de individuos*
- *Tener una vision integradora del individuo y de Salud Publica*
- *EL FUTURO ES HOY*

Gracias !!!