The Key Role of Protease Inhibitors HIV Management

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Janssen Symposium

22 August 2021, 11.00-11.50

OUTLINE

Darunavir/r 600/100 bid in treatment-experienced patients

Darunavir/r 800/100 od in treatment-experienced patients

Darunavir/c 800/150 od in treatment-naïve and -experienced patients

Current Role of Darunavir/r in Thailand

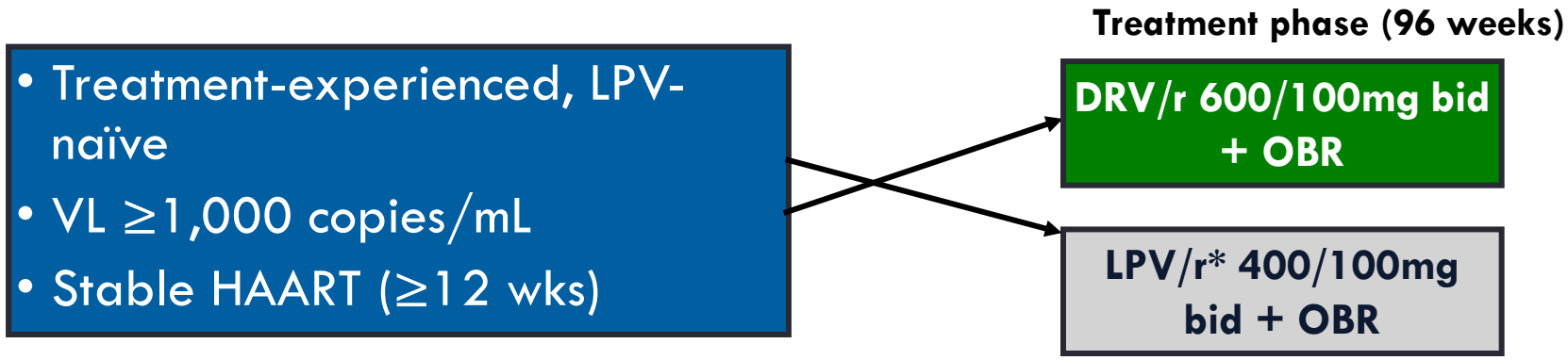
Thai National Guideline on HIV/AIDs Treatment 2020/2021		
1st line regimen	Resistance- associated mutation	2nd line regimen
DTG + NRTIs	NRTIs RAMs	• **Boosted PI** + DTG • 2 active NRTIs + **boosted PI**
NNRTI + NRTIs	NRTIs RAMs	• NRTIs + **boosted PI**
	NNRTIs RAMs + M184V/I	• 2 active NRTIs + **boosted PI**
	NNRTIs RAMs + NRTIs RAMs	• **Boosted PI** + DTG
Boosted PI + NRTIs	NRTIs RAMs + PIs RAMs	• 2 active NRTIs + **boosted PI** (genotypic resistance test)
Other conditions	HIV PEP[1]	DRV/r 800/100 OD
	Pregnancy[2]	DRV/r 600/100 BID

DRV/r or DRV/c

1. Thailand National Guidelines on HIV/AIDs Diagnosis, Treatment and Prevention 2020/2021. Available from: http://thaiaidssociety.org/images/PDF/thai_aids_guidelines_2020_2021.pdf 2. The EACS Guidelines 2019 version 10.0 Available from: http://https://www.eacsociety.org/media/guidelines-10.1_30032021_1.pdf

TITAN: Study Design

- Phase III randomised, controlled trial
- 785 screened, 595 patients randomised and treated
- 1^{ry} objective: non-inferiority in confirmed VL <400 copies/mL with DRV/r vs LPV/r at Week 48



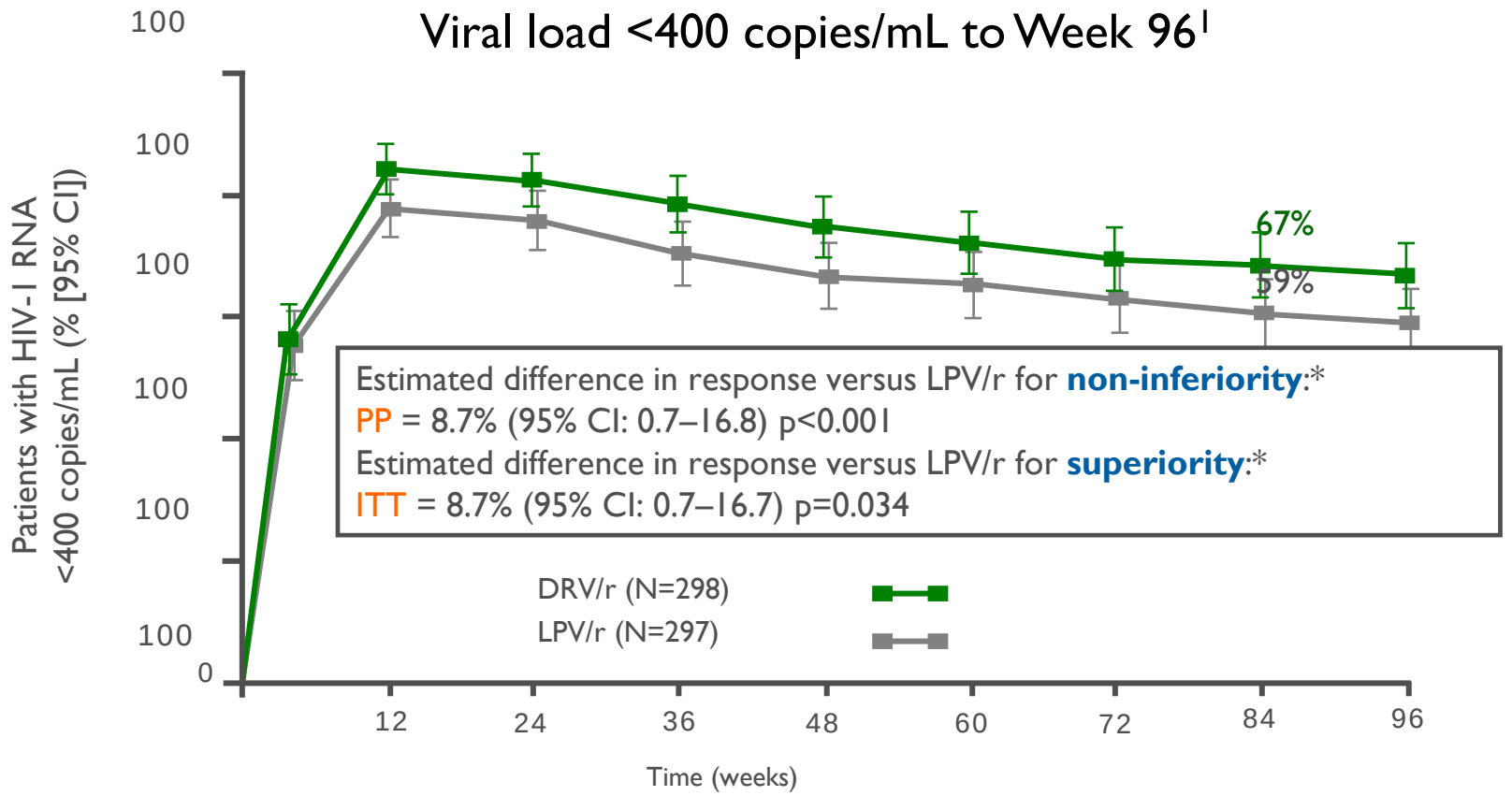
- All patients received optimised background therapy
  - at least two or three ARVs from approved NRTI and/or NNRTI classes; enfuvirtide disallowed

*LPV/r patients were allowed to switch to new formulation upon its approval by the regulatory authorities;
VL = viral load; DRV/r = darunavir with low-dose ritonavir, LPV/r = lopinavir with low-dose ritonavirtw

D. Bánhegyi Current HIV Research, 2012; 10: 171-181

TITAN: Darunavir/r 600/100 bid in Tx-experienced Patients

TITAN: Superiority of DRV/r vs. LPV/r

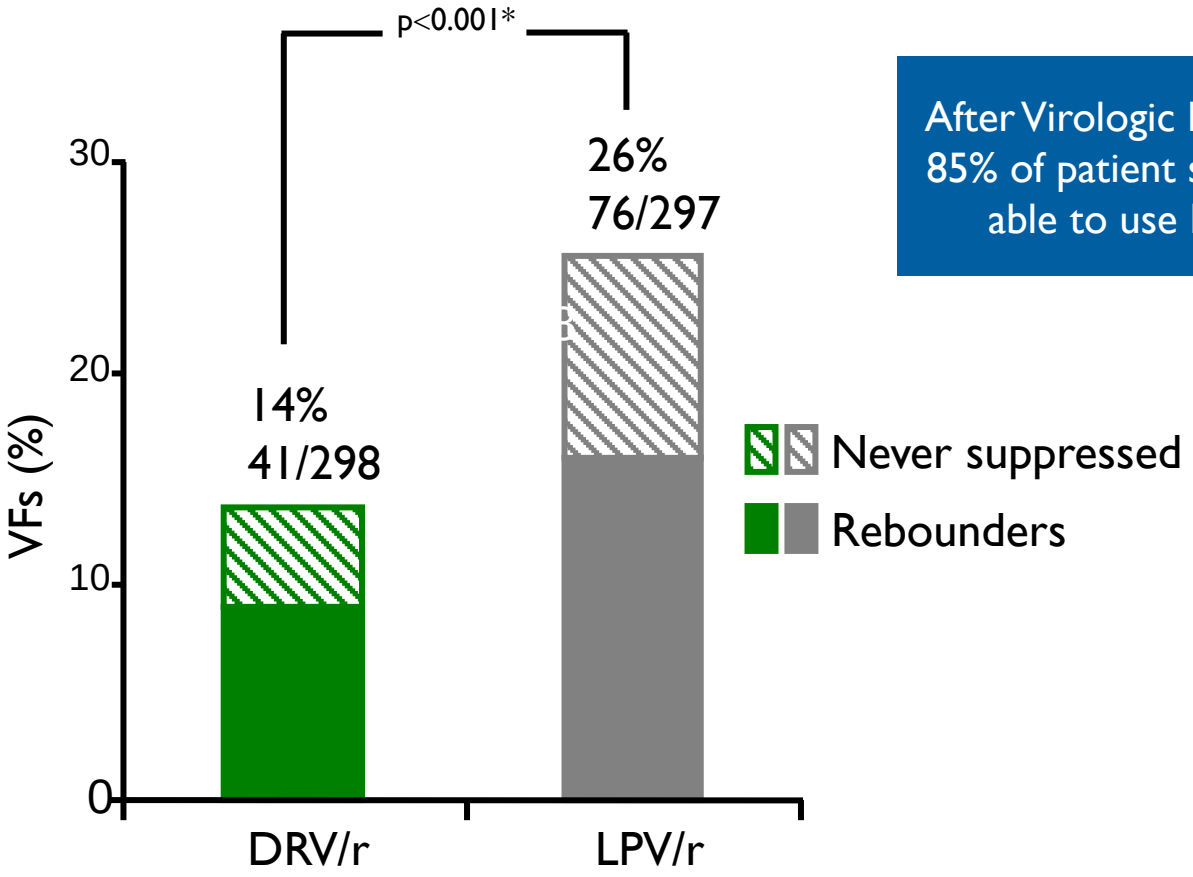


*Derived from a logistic regression model including use of an NNRTI in the OBR as factor and baseline $\log_{10}$ plasma viral load as covariate

D. Bánhegyi Current HIV Research, 2012; 10: 171-181

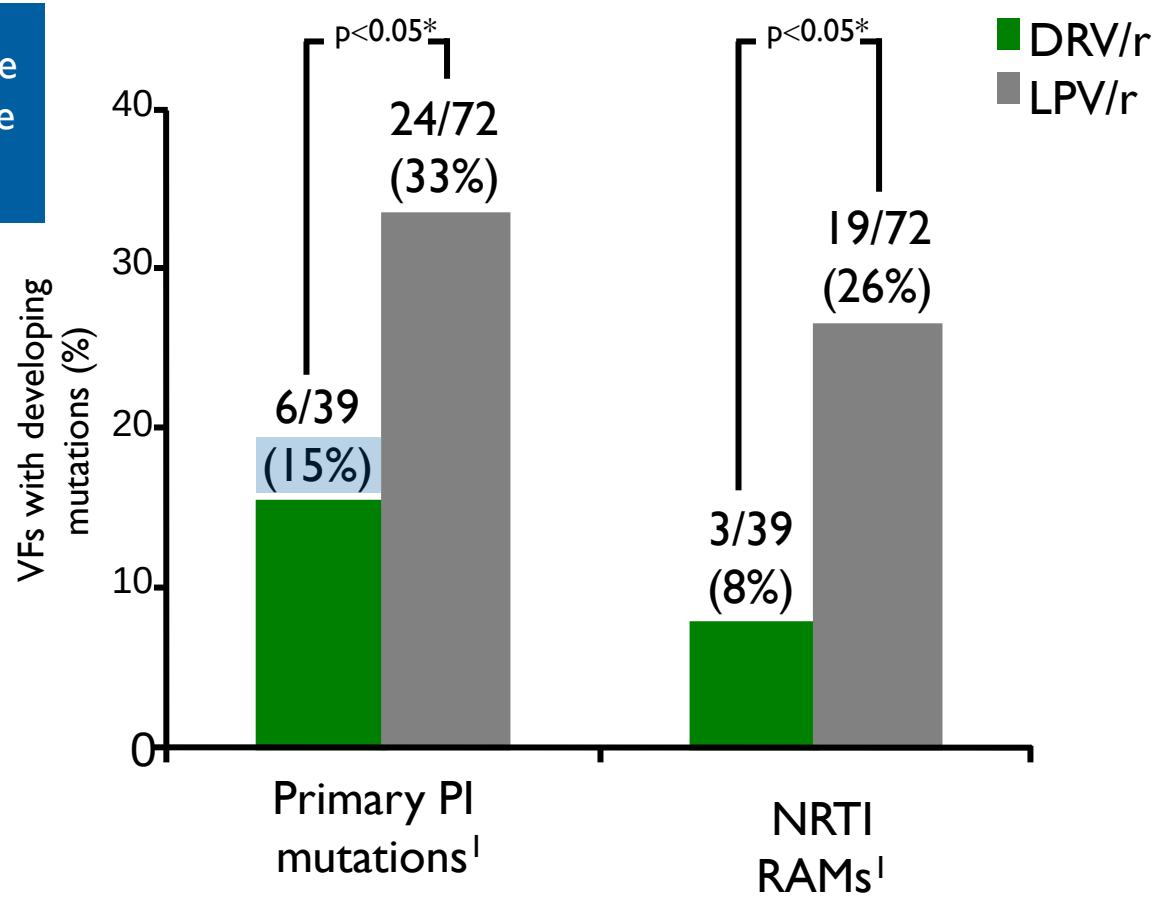
TITAN: Darunavir/r 600/100 bid in Tx-experienced Patients

Fewer VFs in DRV/r arm at Week 96



After Virologic Failure 85% of patient still be able to use PIs

Less VFs on DRV/r developed mutations



Ps. At Week 48 analysis: 31 VFs in the DRV/r arm and 65 VFs in the LPV/r arm

D. Bánhegyi Current HIV Research, 2012; 10: 171-181

TITAN: Conclusion

In treatment-experienced, LPV-naïve population:

- DRV/r was not only non-inferior, but **virologically superior to LPV/r**
- DRV/r was **better than LPV/r in preventing the development of resistance** upon VF
  - VF rate in DRV/r arm was half of VF rate in LPV/r arm
  - DRV/r **provided better protection of NRTI and the PI classes upon failure** versus LPV/r
  - **cross-resistance with other PIs was less** frequent with DRV than with LPV upon VF

1. D. Bánhegyi Current HIV Research, 2012; 10: 171-181 2. Madruga J.V. et al. Lancet. 2007 ;(370): 49-58

OUTLINE

Darunavir/r 600/100 bid in treatment-experienced patients

Darunavir/r 800/100 od in treatment-experienced patients

Darunavir/c 800/150 od in treatment-naïve and -experienced patients

Aims of HIV treatment : Darunavir/r 800/100 od

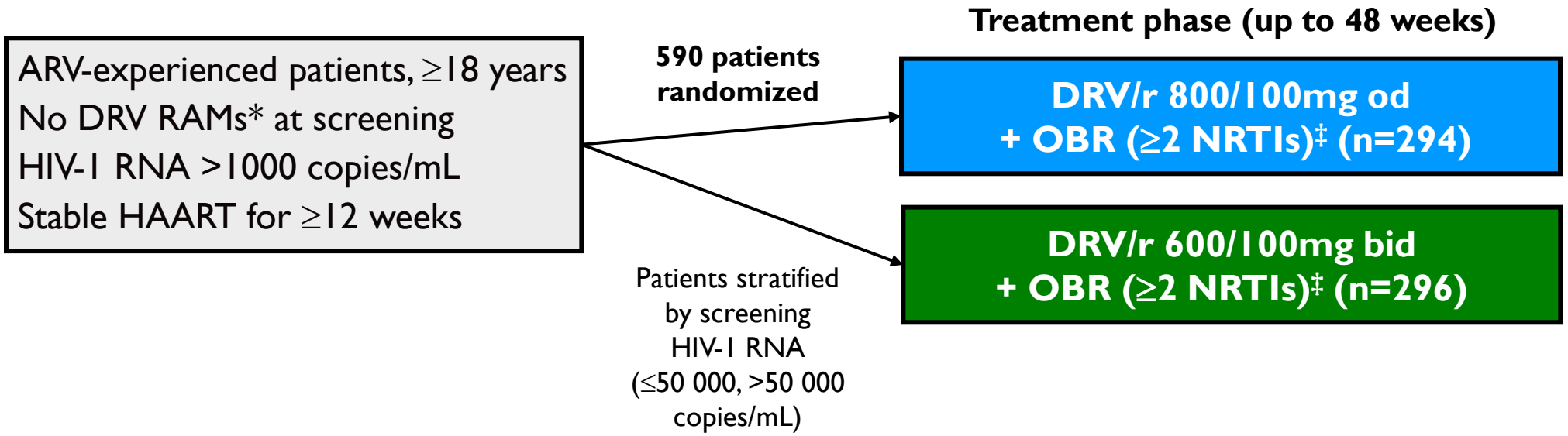
In addition to **achieving an undetectable VL**, HIV treatment also aims to:

- Reduce ART-related toxicity and prevent long-term toxicity
- Maintain and improve quality of life

1. The EACS Guidelines 2019 version 10.0 Available from: http://https://www.eacsociety.org/media/guidelines-10.1_30032021_1.pdf

ODIN: Study Design

- A Phase III, randomized, open-label study to assess efficacy, safety and tolerability of "once-daily DRV/r" versus "twice-daily DRV/r" in ARV-experienced patients with no DRV RAMs[1,2] at screening

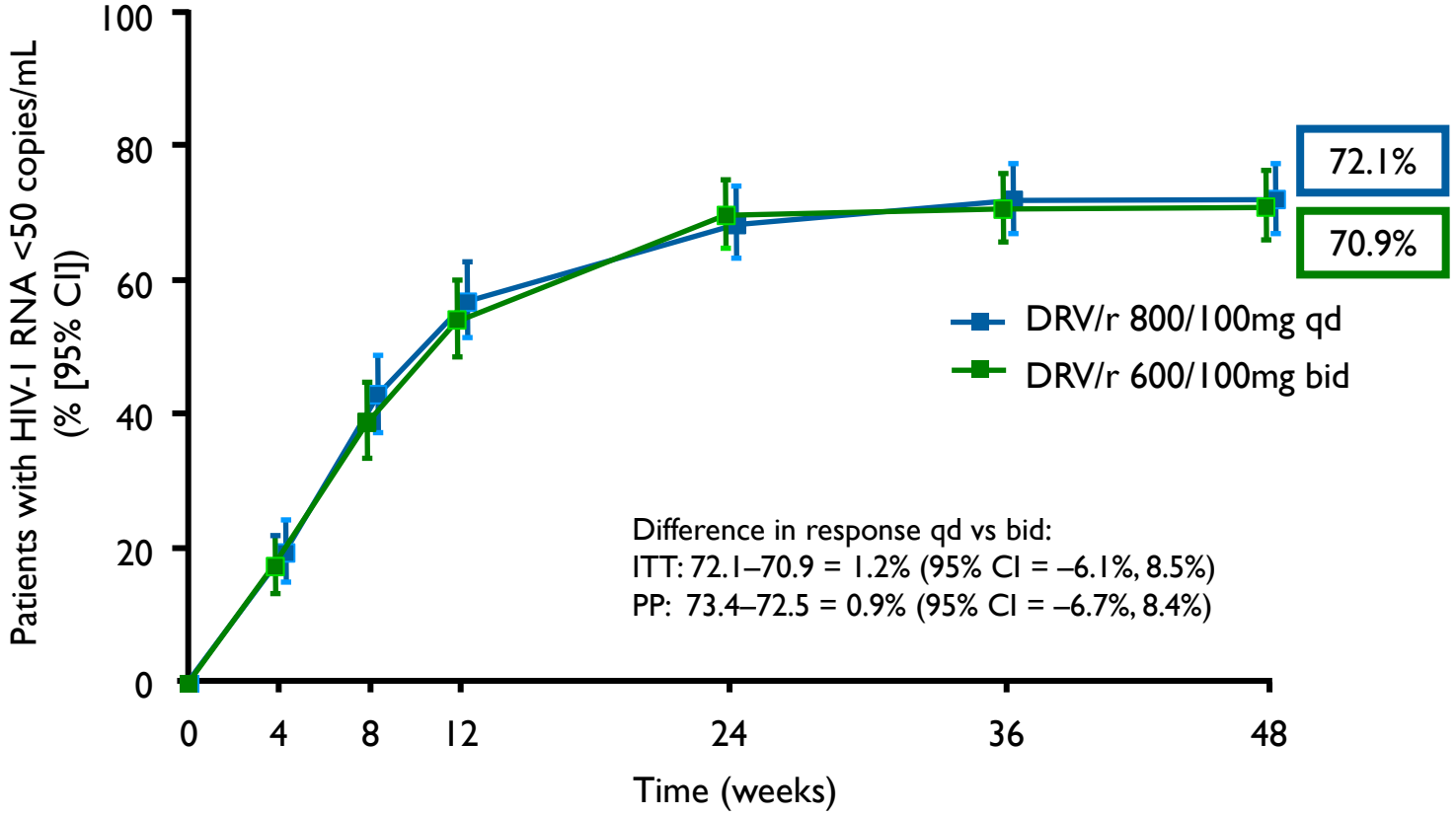


*V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V
‡Investigator-selected OBR based on ARV history and resistance testing

1. Johnson VA, et al. Top HIV Med 2009;17:138–45 2. De Meyer S, et al. 6th EHDRW 2008. Abstract 54

ODIN: Darunavir/r 800/100 od in Tx-experienced Patients

ODIN[1]: No Difference in VL<50 copies/mL to Week 48 (ITT-TLOVR)

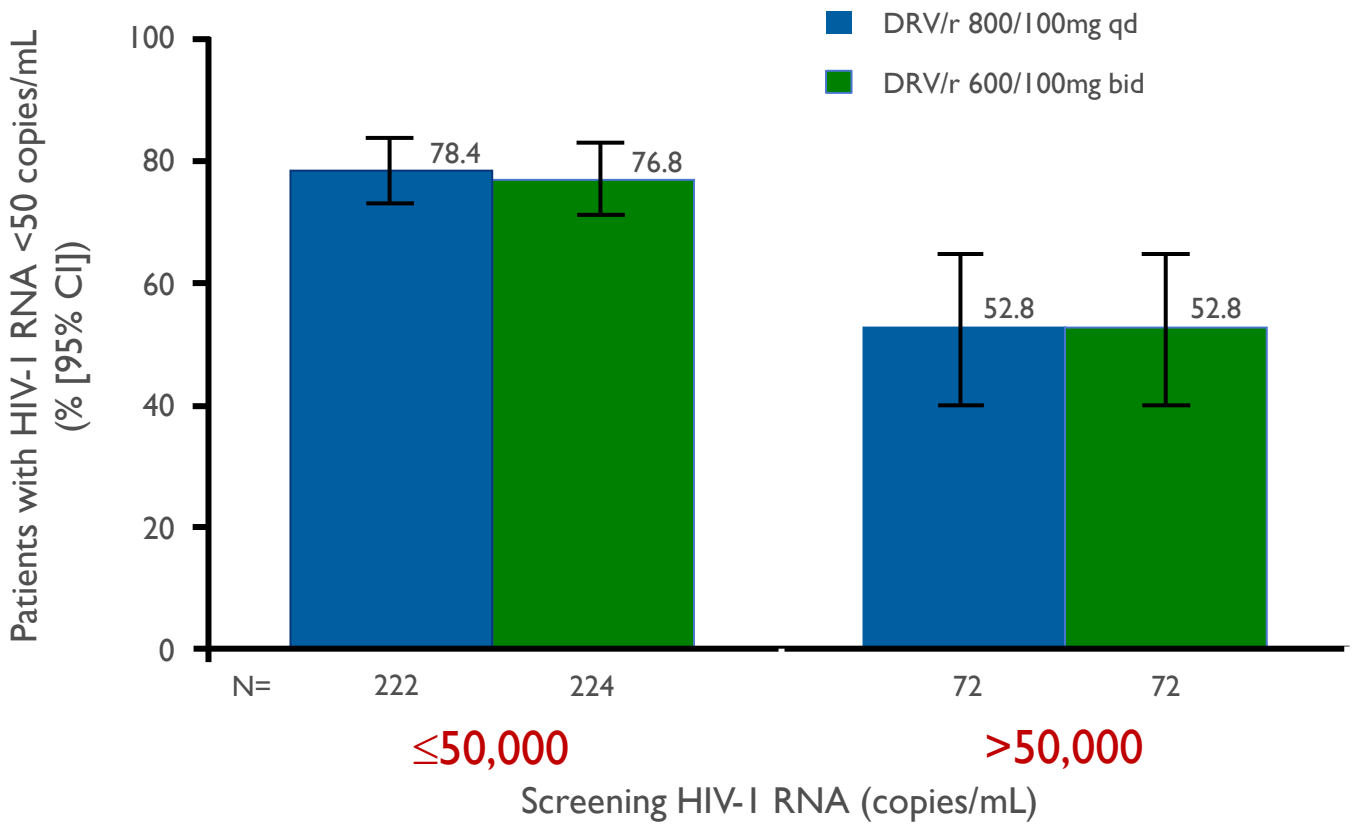


- No difference in median change in CD4 count:
  - +100 cells/mm^3 (DRV/r 800/100 mg qd) vs. 94 cells/mm^3 (DRV/r 600/100 mg bid)

Cahn P et al. AIDS 2011 Apr 24;25(7):929-39.

ODIN: Darunavir/r 800/100 od in Tx-experienced Patients

ODIN: Confirmed Virologic Response by VL at Screening



Cahn P et al. AIDS 2011 Apr 24;25(7):929-39.

ODIN: Darunavir/r 800/100 od in Tx-experienced Patients

Significantly Less Lipid Abnormalities in DRV/r qd Arm

Treatment-emergent grade 2–4 lipid and liver-related laboratory abnormalities (≥2% incidence), n (%)*	Once-daily DRV/r 800/100mg (N=294)	Twice-daily DRV/r 600/100mg (N=296)	P value
Triglycerides	15 (5.2)	31 (11.0)	<0.014
Total cholesterol*	29 (10.1)	58 (20.6)	<0.0007
LDLc cholesterol*	28 (9.8)	47 (16.7)	<0.019
ALT	5 (1.7)	10 (3.5)	0.20
AST	6 (2.1)	10 (3.5)	0.32
Non-graded lipid-related laboratory abnormalities, n (%)			
HDL below the lower normal limit	57 (19.9)	52 (18.4)	0.67

*Based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events 2004, which does not have a grade 1 classification for triglycerides and grade 4 for total cholesterol and LDL

- Median fasting lipid concentrations in both arms remained below the thresholds defined by NCEP (National Cholesterol Education program)

Cahn P et al. AIDS 2011 Apr 24;25(7):929-39.

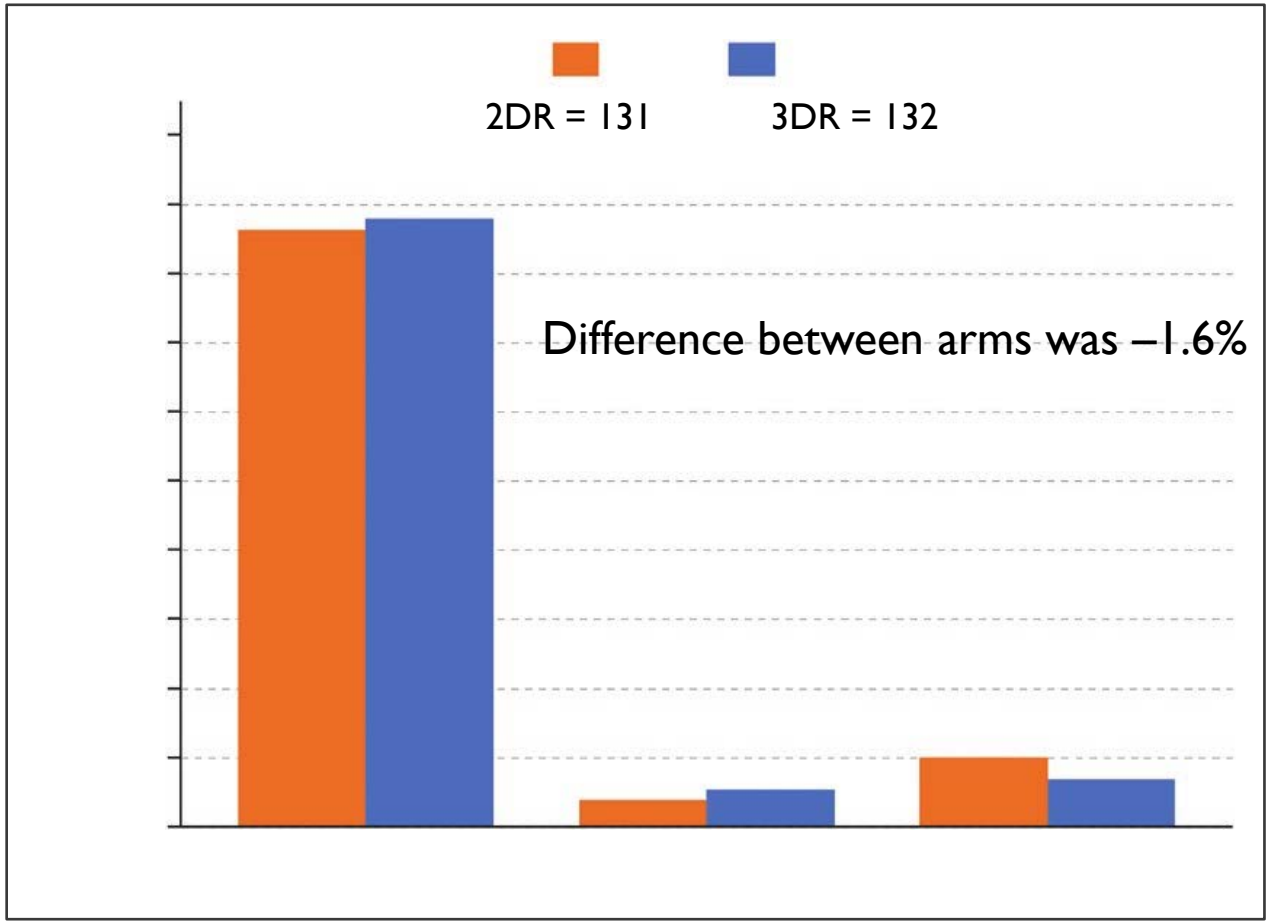
ODIN: Conclusions

- **Once-daily DRV/r 800/100 mg was effective and non-inferior** to DRV/r 600/100 bid in **treatment-experienced** HIV-1-infected patients **with no DRV RAMs**
- Virologic failure was low and rarely resulted in resistance
  - only one patient developed primary PI RAMs and DRV RAMs following virologic failure
- DRV/r was generally well tolerated
  - there were few discontinuations due to AEs
  - the low incidence of diarrhea was consistent with previous data
  - the **incidence of grade 2–4 lipid elevations with once-daily DRV/r 800/100mg was approximately half** that of DRV/r 600/100mg bid
- These findings suggest that once-daily DRV/r could be considered an option for patients failing previous treatments with no DRV RAMs

Cahn P et al. AIDS 2011 Apr 24;25(7):929-39.

DUALIS: Switching to DTG + DRV/b in Virologically Suppressed Patients

- Randomized, open-label, noninferiority trial
- PWH with HIV RNA <50 copies/ mL taking 2NRTI + bDRV (3DR) for ≥24 weeks were randomized
- To compared "switch to DTG + bDRV (2DR)} vs. continuation of 2NRTI + bDRV (3DR)
- 1ry end point = proportion of HIV RNA <50 copies/mL at week 48
- Noninferiority margin was ≤ -10.0%.
- 263 subjects were randomized (2DR n = 131, 3DR n = 132)



Spinner C, et al. Open Forum Infectious Diseases DOI: 10.1093/ofid/ofaa356

OUTLINE

Darunavir/r 600/100 bid in treatment-experienced patients

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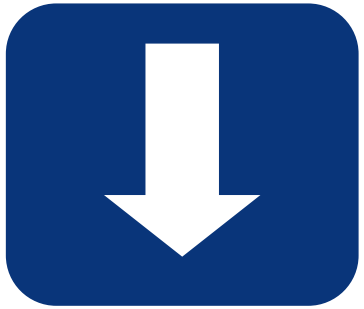
Darunavir/c 800/150 od in treatment-naïve and -experienced patients

Further Increased Adherence and Improving Quality of Life

- As HIV is now a chronic disease, long-term good health is essential for PLHIV[1]
- Treatment decisions for PLHIV should be aimed at:[2]



Eliminating or improving adverse events

Preventing long-term ART-related toxicity

Facilitating treatment of co-morbid conditions

Avoiding drug–drug interactions

Minimising pill burden and adjusting food restrictions

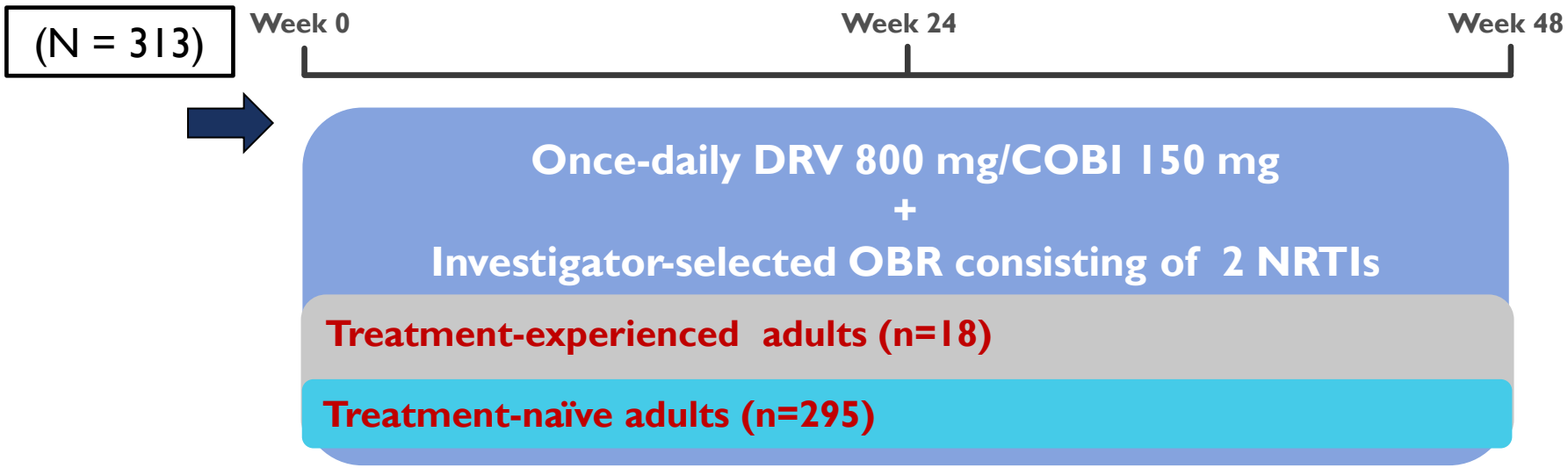
Improving quality of life

FDC (fixed-dose combination)

- Combinations of ARVs where the individual doses are fixed/set
- Offers simplified regimen options to PLHIV

1. Lazarus V et al. BMC Medicine 2016;14:94. 2. The EACS Guidelines 2019 version 10.0 Available from: http://https://www.eacsociety.org/media/guidelines-10.1_30032021_1.pdf

GS-US-216-0130: Open-label Single-arm Trial



- Key entry criteria:
  - Plasma HIV-1 RNA ≥1,000 c/mL
  - Screening genotype: fully-sensitive to DRV (0 DRV RAMs) and 2 nucs (if M184V/I, may add 3TC or FTC)
  - eGFR CG ≥ 80 mL/min

Primary endpoint: Any treatment-emergent grade 3 (severe) or grade 4 (life-threatening) AEs occurring through Week 24

OBR, optimized background regimen; DRV, darunavir; COBI; cobicistat; NRTI, nucleoside reverse transcriptase inhibitors
*DRV RAMs, darunavir resistance-associated mutations V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V
eGFR CG, estimated glomerular filtration by Cockroft-Gault

Tashima K, et al. *AIDS Res Ther.* 2014;11:39.

GS-US-216-0130: Safety of Darunavir/c 800/150 od

- Week 24, onset of any grade 3 or grade 4 AEs regardless of causality was low; 6% in overall population[1]
- 16 patients experienced gr 3 (5%) and 2 patients experienced grade 4 (0.6%) AEs[1]
- 3 serious AEs, all occurring in treatment-naïve patients, were felt be related to study drug[1]
    - 1 patient each reported IRIS and maculo-papular rash
- Changes in serum Cr are consistent with cobicistat inhibition of creatinine secretion

Most frequent ADRs at least grade 2 (GS-US-216-0130)	GS-US-216-0130 24 and 48 Weeks (n=313)† 24 weeks	48 weeks	ARTEMIS 192 Weeks TDF/FTC (n=343) +	ODIN 48 Weeks (n=294)
Drug exposure (weeks)	31.4‡	58.4‡	162.5§	44.8§
Abdominal pain	1.3%	1.3%	6%	3.1%
Diarrhea	5.1%	5.4%	9%	5.8%
Flatulence	1%	1%	—	0.7%
Nausea	3.2%	3.5%	4%	4.8%
Vomiting	1.6%	1.9%	2%	3.4%
Fatigue	—	—	<1%	0.3%
(Drug) Hypersensitivity	1.6%	1.9%	—	—
Anorexia	—	—	2%	0.3%
Headache	1.6%	2.9%	7%	3.4%
Rash	5.8%	5.4%	6%	2.0%
Discontinuation due to ADRs	3.8%	3.8%	2.3%	3.4%

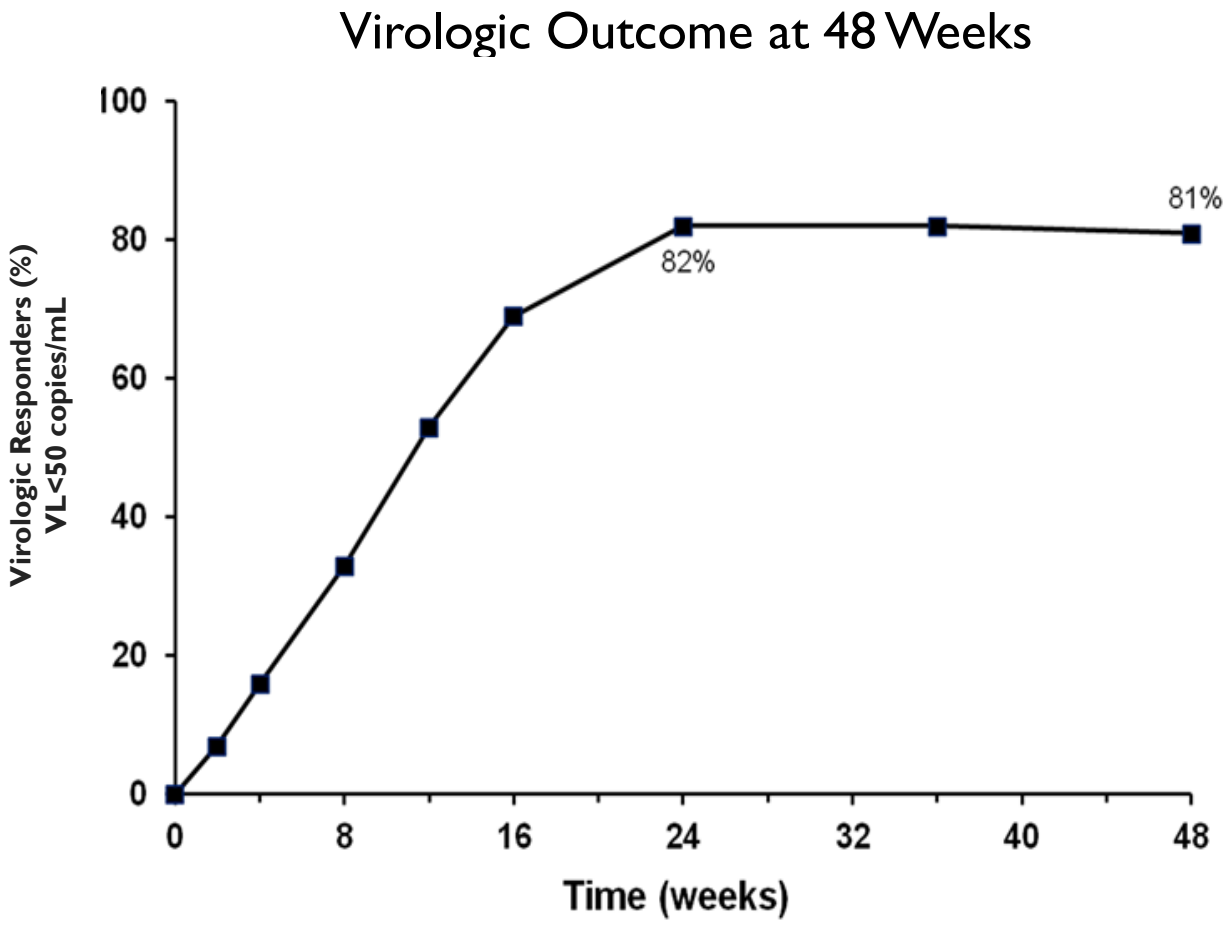
*Excluding laboratory abnormalities as ADRs. †DRV and COBI were administered as single agents in this clinical trial. ‡Median exposure. §Mean exposure ADR, adverse drug reaction; COBI, cobicistat; DRV, darunavir; OBR, optimized background regimen; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

Direct comparisons should not be made between data from separate clinical trials

Tashima K, et al. *AIDS Res Ther.* 2014;11:39.

GS-US-216-0130: Virologic Outcome at 48 Weeks

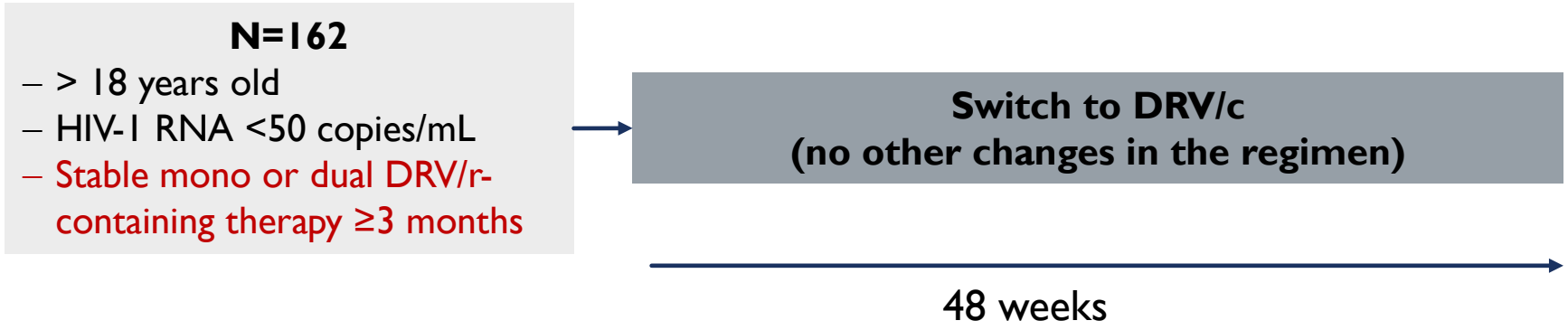
Cobicistat-boosted darunavir in HIV-1 infected: week 48 results of a Phase IIIb, open-label, single-arm trial[1]



- ITT subjects = 313 patients
  - Treatment-naïve: 295 (94%)
  - Treatment-experienced with no DRV RAMS: 18 (6%)
- Virologic response defined as VL <50 copies/mL and evaluated by **FDA snapshot analysis**
  - Week 24: rate was 82% (258/313; 95% CI : 78 – 87%)
  - Week 48: rate was 81% (253/313; 95% CI : 76 – 85%)
- Virologic responses with DRV/c 800/150mg qd is consistent with previous data for DRV/r 800/100mg qd for ARTEMIS(68.8%) and ODIN(72.1%)

Tashima K, et al. AIDS Res Ther. 2014;11:39.

Observational Prospective Cohort in 3 Spanish Centers



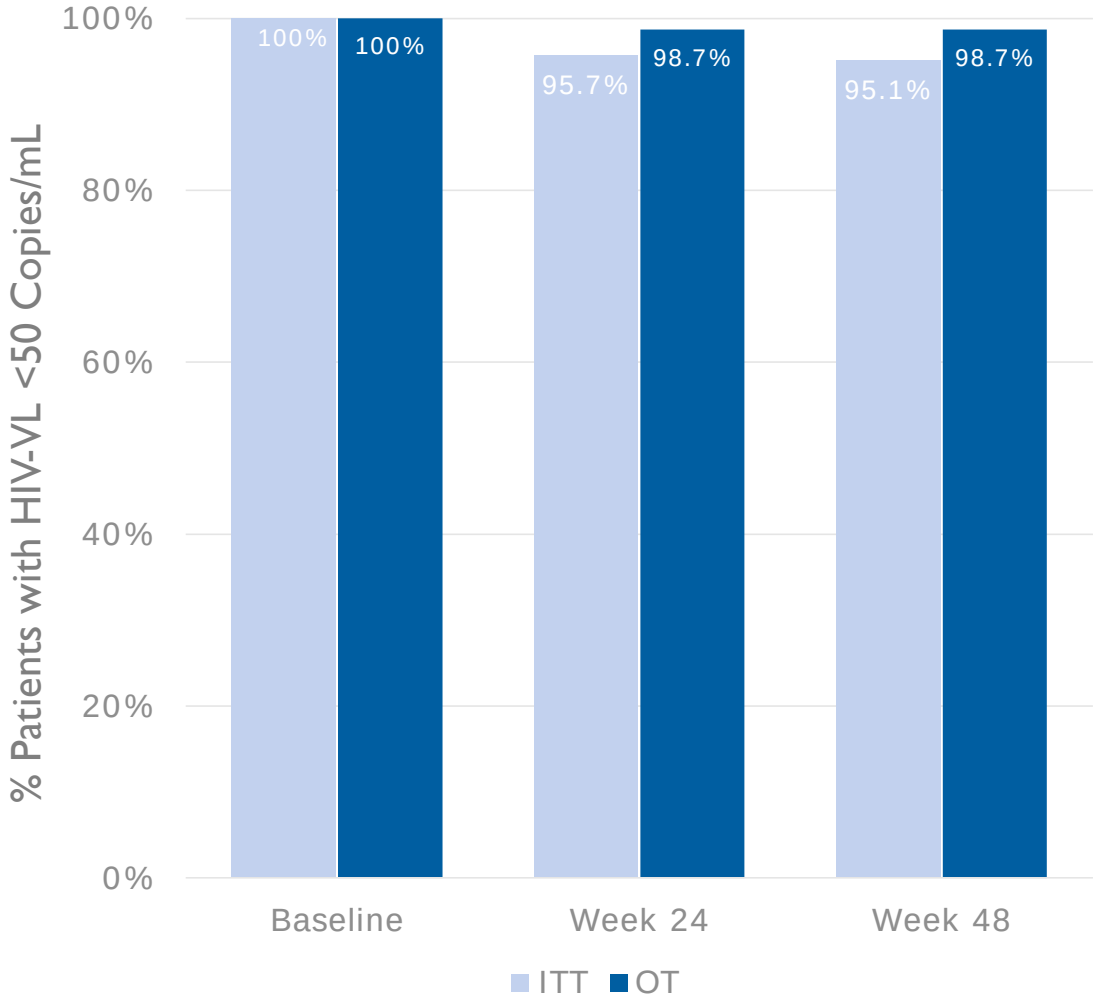
- **Primary Endpoint:** % patients without VF at week 48 (ITT; incomplete/missing data=failure)

- **Secondary Endpoints:** Efficacy in an on-treatment analysis (OT), changes in CD4 cell count, fasting lipids and creatinine concentrations

Mena A et al. HIV Clinical Trials 2018;19(5):197-201

Observational Prospective Cohort in 3 Spanish Centers

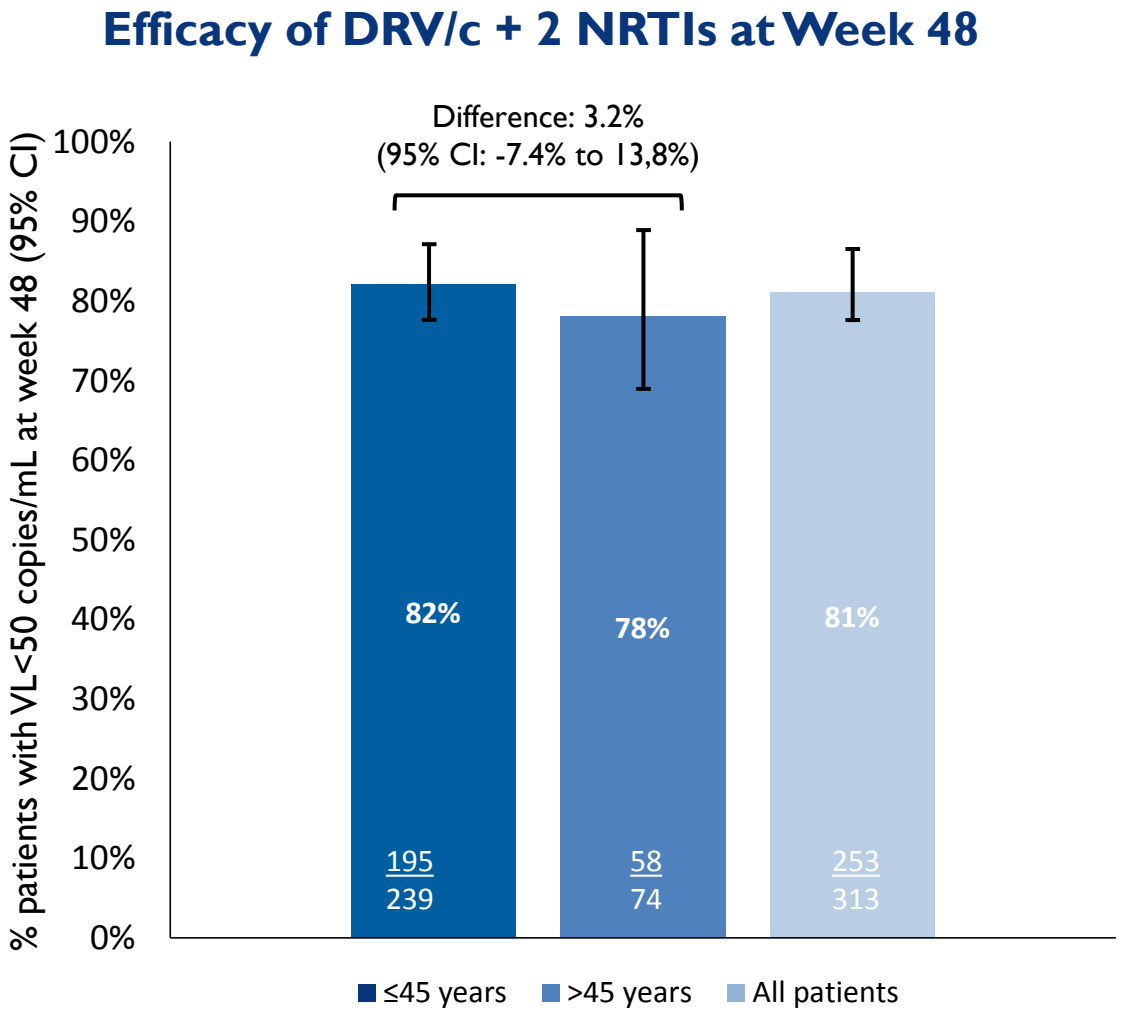
DRV/c maintains effectiveness of DRV/r in HIV-infected patients under mono or dual therapy[1]



- Switch to DRV/c (no other changes in the regimen) in 162 patients with stable mono or dual DRV/r-containing therapy ≥3 months
- CD4 counts remained stable:
  - Baseline: 688±301 cells/mm^3
  - Week 48: 702±304 cells/mm^3
- Adherence >90%:
  - Baseline: in 93.8% of patients
  - Week 24: in 94.3%
  - Week 48: in 92.4%
- Switching from DRV/r to DRV/c in patients receiving mono or dual therapy was safe and effective

Mena A et al. HIV Clinical Trials 2018;19(5):197-201

Treating Older HIV-1-infected Subjects with Darunavir/c



Post hoc analysis of GS-US-216-0130

- Evaluation of two age groups:
  >45 years and ≤45 years

Mean CD4 increase after 48 weeks:

- ≤45 years: 191 cells/mm^3
- >45 years: 187 cells/mm^3

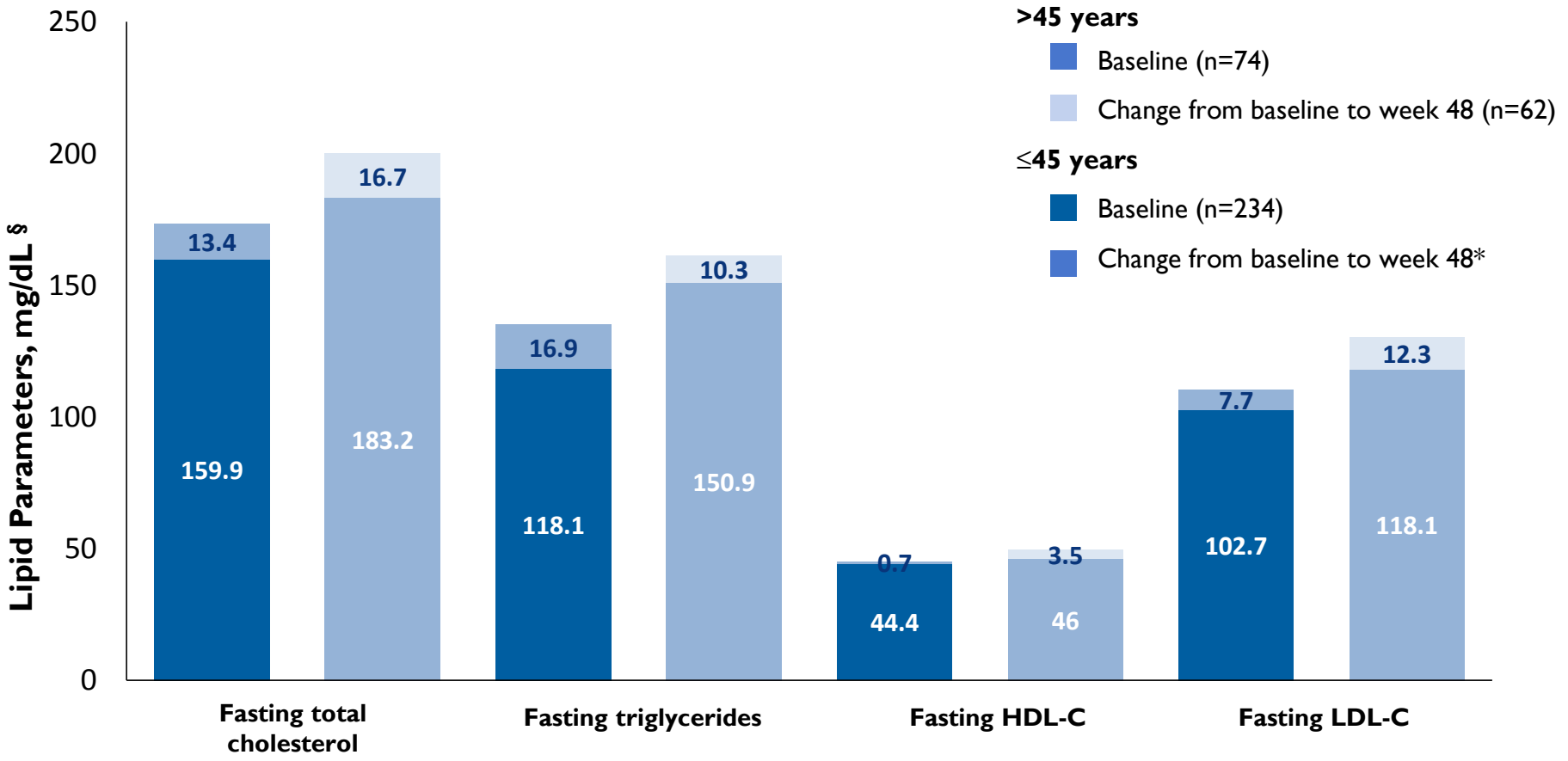
Treatment-emergent RAMs:

- Naïve patient:
  - ≤45 years: M184V (n=1)
- Experienced patients:
  - ≤45 years: I84I/V without phenotypic resistance to DRV (n=1)
  - >45 years: M184V (n=1)

K. Brown, et al. Reviews on Recent Clinical Trials, 2017, 12, 1-8

Treating Older HIV-1-infected Subjects with Darunavir/c

Changes in Lipid Parameters



* Total cholesterol and triglycerides: n=192; HDL-C: n=191; LDL-C: n=194

§ Lipid parameters are reported as mean

1. K. Brown, et al. Reviews on Recent Clinical Trials, 2017, 12, 1-8

Summary Benefits of DRV/c FDC

High Virologic Response and **Low Virologic Failure**

High barrier to **genetic resistance**

General **well tolerated**

Less Lipid abnormality

More convenience & **Increase** adherence

Darunavir/c FDC is potential for improved adherence
for treatment naïve adults, treatment-experienced adults with no-DRV-RAMS

1. Orkin et al. HIV Medicine. 2013;14:49–59. 2. Lathouwers E, et al. Antiviral Therapy. 2013;18:289-300.

Thailand National List of Essential Medicines (NLEM) 2021

ประกาศคณะกรรมการพัฒนาระบบยาแห่งชาติ
เรื่อง บัญชียาหลักแห่งชาติ
พ.ศ. ๒๕๖๔

เพื่อให้บัญชียาหลักแห่งชาติมีการปรับปรุงแก้ไข ตามสภาพของปัญหาสุขภาพ วิทยาการและข้อมูลเกี่ยวกับยาที่เปลี่ยนแปลงไปอย่างต่อเนื่องทันสถานการณ์

อาศัยอำนาจตามความในข้อ ๘ (๔) แห่งระเบียบสำนักนายกรัฐมนตรี ว่าด้วยคณะกรรมการพัฒนาระบบยาแห่งชาติ พ.ศ. ๒๕๕๑ คณะกรรมการพัฒนาระบบยาแห่งชาติ จึงออกประกาศไว้ดังต่อไปนี้

ข้อ ๑ ให้ยกเลิก

๑.๑ ประกาศคณะกรรมการพัฒนาระบบยาแห่งชาติ เรื่อง บัญชียาหลักแห่งชาติ พ.ศ. ๒๕๖๓ ลงวันที่ ๒๘ กันยายน ๒๕๖๓

๑.๒ ประกาศคณะกรรมการพัฒนาระบบยาแห่งชาติ เรื่อง บัญชียาหลักแห่งชาติ (ฉบับที่ ๒) พ.ศ. ๒๕๖๔ ลงวันที่ ๑๑ มกราคม ๒๕๖๔

ข้อ ๒ ให้ใช้รายการยาในบัญชีแนบท้ายประกาศนี้เป็นยาในบัญชียาหลักแห่งชาติ

ข้อ ๓ ประกาศคณะกรรมการพัฒนาระบบยาแห่งชาติฉบับนี้ให้ใช้บังคับเมื่อพ้นกำหนดสามสิบวันนับแต่วันประกาศในราชกิจจานุเบกษาเป็นต้นไป

18.	Darunavir (DRV)	tab (เฉพาะ 300 และ 600 mg as base)	ค

เงื่อนไข

ใช้รักษาโรคติดเชื้อเอชไอวีที่ดื้อต่อยาสูตรพื้นฐาน และสูตรที่สอง โดยเป็นไปตามแนวทางการตรวจวินิจฉัย รักษา และป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2563/2564

OUTLINE

Darunavir/r 600/100 bid in treatment-experienced patients

Darunavir/r 800/100 od in treatment-experienced patients

Darunavir/c 800/150 od in treatment-naïve and -experienced patients

Thank you