Two Versus Three Drugs - Relevance for the Asian Settings

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2-Drug *vs* 3-Drug ART regimen Implementing Consideration

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Disclosures

Receipt of honoraria or consultation fees and/or participation in a company sponsored speaker's bureau from:

- ViiV, Merck, Jensen-Cilag, Mylan, and Gilead

Future Trends ?

Reduction number of drugs

From 3 to 2 drug-regimen

Reduction in dose frequency

LA injectable ARVs

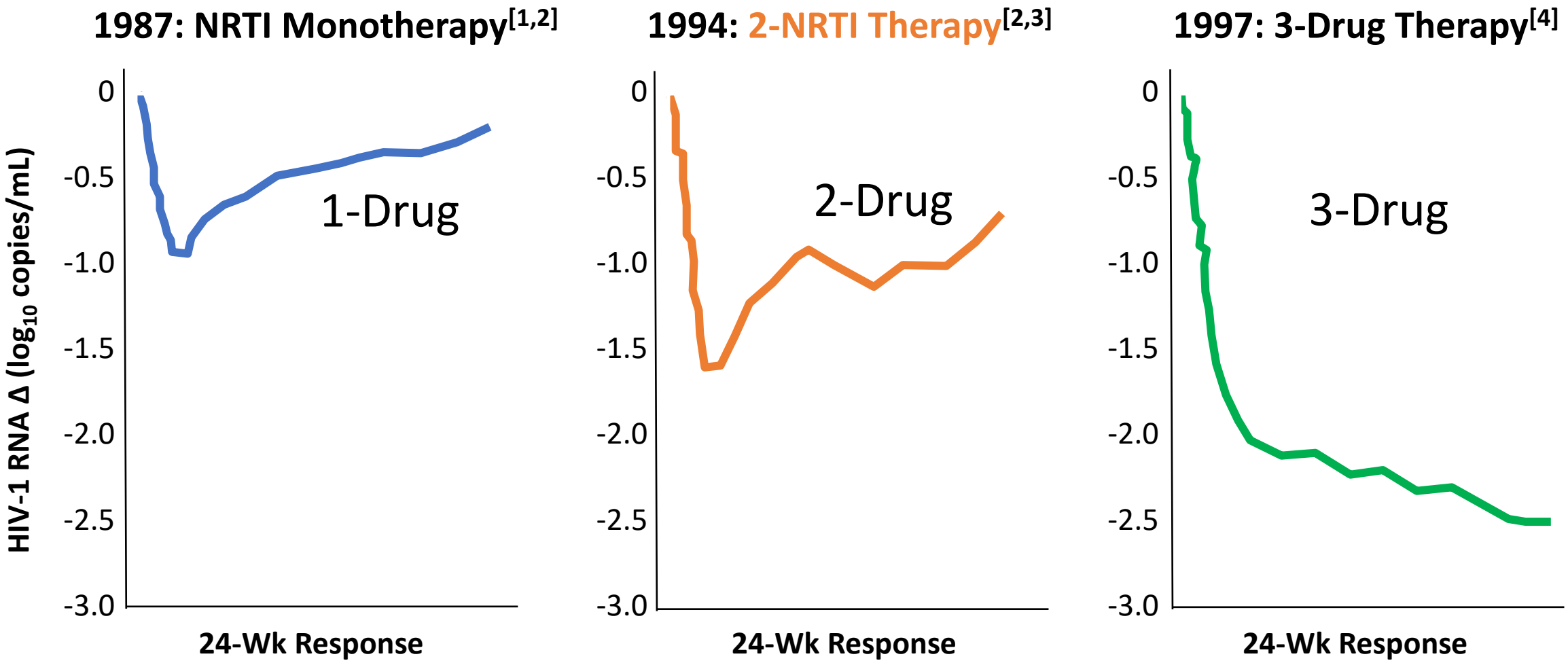
LA implantable ARVs

Why **Dual ART** ?

- **Potential to reduce side effects**
- **Reserve future options**
- ***Cost saving****!*
  - Assuming DTG + 3TC yields >90% efficacy:
- 50% uptake of maintenance or initial ART - savings of **$550 & $800 million**, respectively, over 5 years
- If 25% of currently suppressed persons switch to DTG + 3TC maintenance - savings **>$3 billion**

Modified from Brian Wood, AECT presentation; Source: Girourard et al. CID, March 2016.

Evolution of ART: 1987-1997

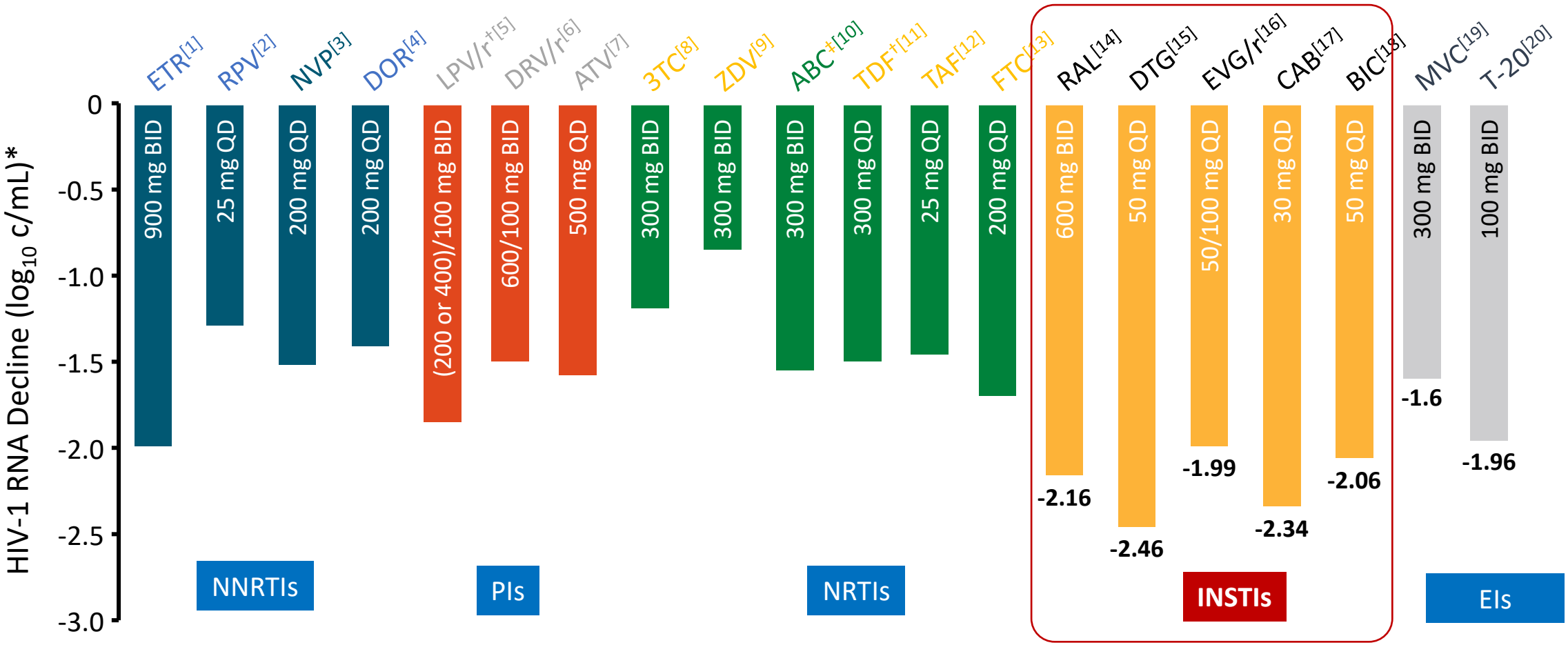


1. Fischl. NEJM. 1987;317:185. 2. Harrigan. J Acquir Immune Defic Syndr Hum Retrovirol. 1995;10 Suppl 1:S34.
3. Eron. NEJM. 1995;333:1662. 4. Gulick. NEJM. 1997;337:734.

Slide credit: clinicaloptions.com

Current ART : INSTIs is the most potent drug class

Antiviral Activity After 7-14 Days of Monotherapy



*Mean reported for most ARVs; median reported for RPV, DRV/r, ABC, TAF, and T-20.

2007 : RAL, 2012 : EVG/c
2013: DTG, 2018: BIC

1. Gruzdev. AIDS. 2003;17:2487. 2. Goebel. AIDS. 2006;20:1721. 3. de Jong. J Infect Dis. 1997;175:966. 4. Schürmann. AIDS. 2016;30:57. 5. Murphy. AIDS. 2001;15:F1.
6. Arastéh. AIDS. 2005;19:943. 7. Sanne. JAIDS. 2003;32:18. 8. Eron. NEJM. 1995;333:1662. 9. Ruane. Pharmacotherapy. 2004;24:307. 10. Staszewski. AIDS. 1998;12:F197.
11. Louie. AIDS. 2003;17:1151. 12. Ruane. JAIDS. 2013;63:449. 13. Rousseau. J Infect Dis. 2003;188:1652. 14. Markowitz. JAIDS. 2006;43:509. 15. Min. AIDS. 2011;25:1737.
16. DeJesus. JAIDS. 2006;43:1. 17. Spreen. HIV Clin Trials. 2013;14:192. 18. Gallant. JAIDS. 2017;75:61. 19. Fätkenheuer. Nat Med. 2005;11:1170. 20. Kilby. Nat Med. 1998;4:1302.

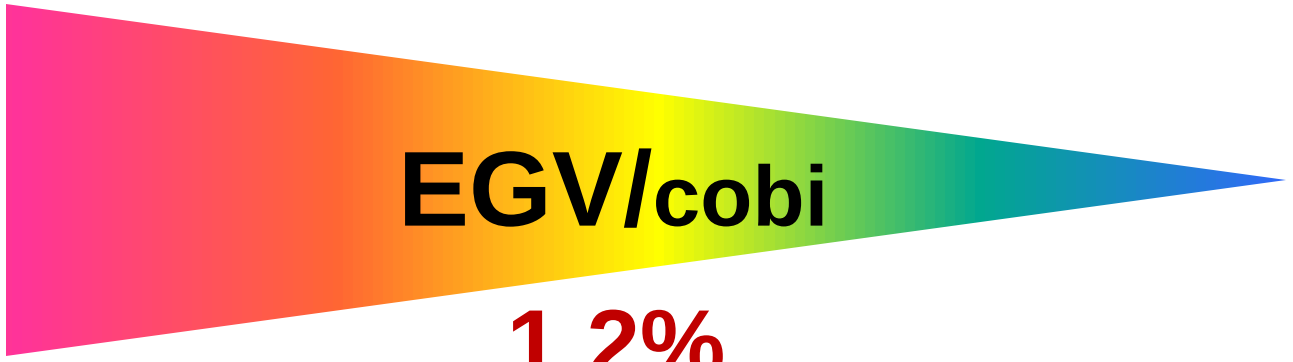
HIV Integrase Inhibitors

Chance to develop drug resistance

Subgroup meta-analysis from clinical trials

You, PLoS One. 2016;11:e0160087

High *Chance to develop drug resistance* **Low**



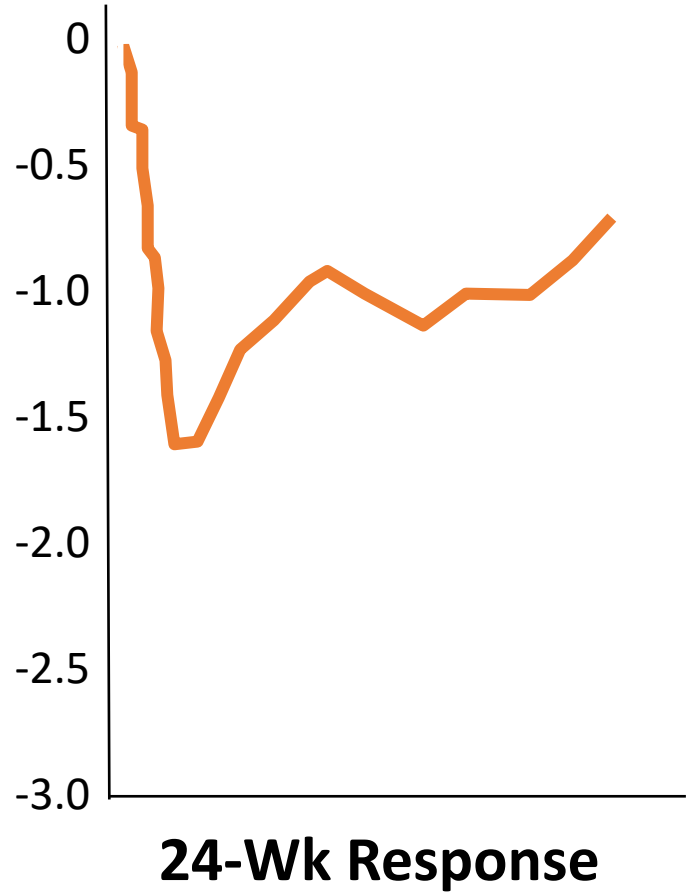
RAL vs DTG – DR rate 3.9% vs 0.1% (40-fold higher)
RAL, EVG/c: 10 major integrase mutations (N155H, Y143C/R, Q148H/R, Y143Y/H, L74L/M, E92Q, E138E/A, Y143C, Q148Q and Y143S)
DTG 13 mutations (T97T/A, E138E/D, V151V/I, N155H, Q148, Y143C/H/R, T66A and E92Q).

* Acosta RK. AAC. 2019

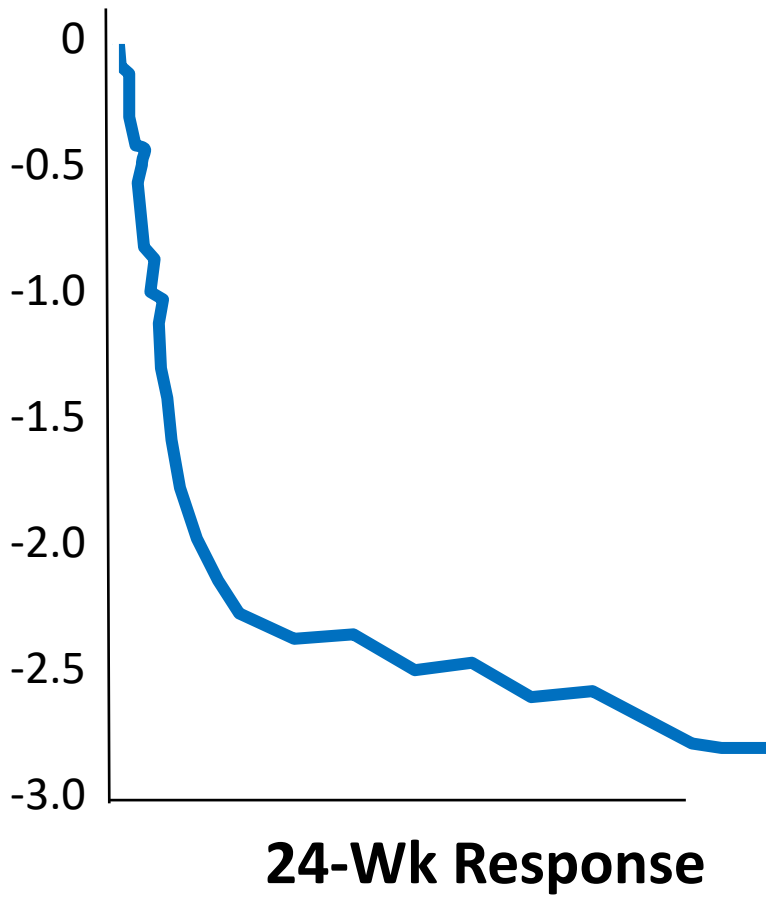
DTG, BIC : Options for patients who plan to start ART before having resistance test results

The **Past** 2-drug ≠ **Current** 2-drug regimen

1994: 2-NRTI Therapy



>2017: 2-ARVs: DTG/3TC, DTG/RPV



Dual ART

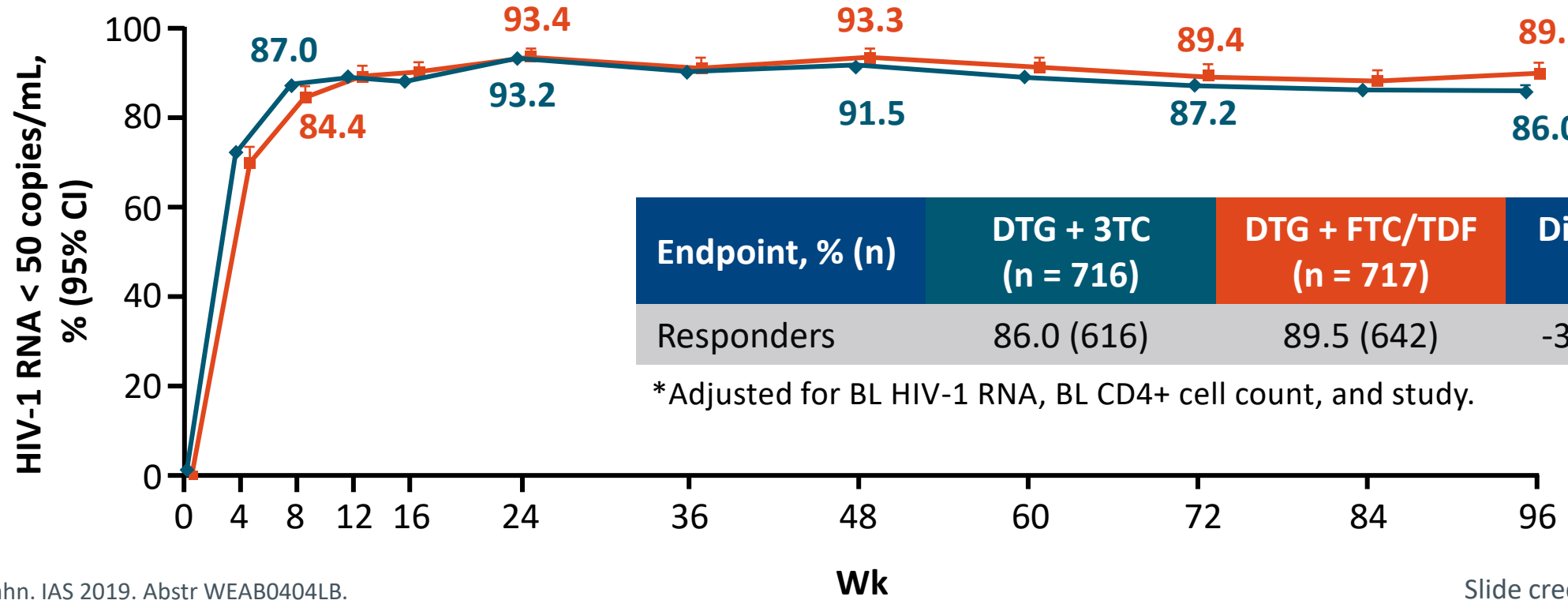
- **DTG+3TC** (Oral): FDA Approved
- **DTG/RPV** (Oral): FDA Approved
- **CAB+RPV** (LA injectable) : Approval is pending (Oral lead-in is needed)

2-Drug Regimens and Approval Status

Two Drug Regimen	Trade name	U.S. FDA Approval	Indication
Dolutegravir and lamivudine (**DTG / 3TC**) - STR	Dovato	Apr 8, 2019	First-line, and Switch regimen
Dolutegravir and rilpivirine (**DTG / RPV**) - STR	Juluca	Nov 21, 2017	Switch in VL suppressed >6 mo
LA Cabotegravir and rilpivirine (**CAB/RPV-LA**) injectable	Cabenuva	Pending (Resubmitted Aug 2020) (**Health Canada**, Mar 20, 2020)	Switch option in VL suppressed patients, and after an oral lead-in with CAB+RPV

GEMINI-1 and -2: Virologic Response Through Wk 96

- In ART-naive adults, **DTG + 3TC** met criteria for **noninferior efficacy** vs **DTG + FTC/TDF** at Wk 96
- No treatment-emergent resistance observed in patients with CVW



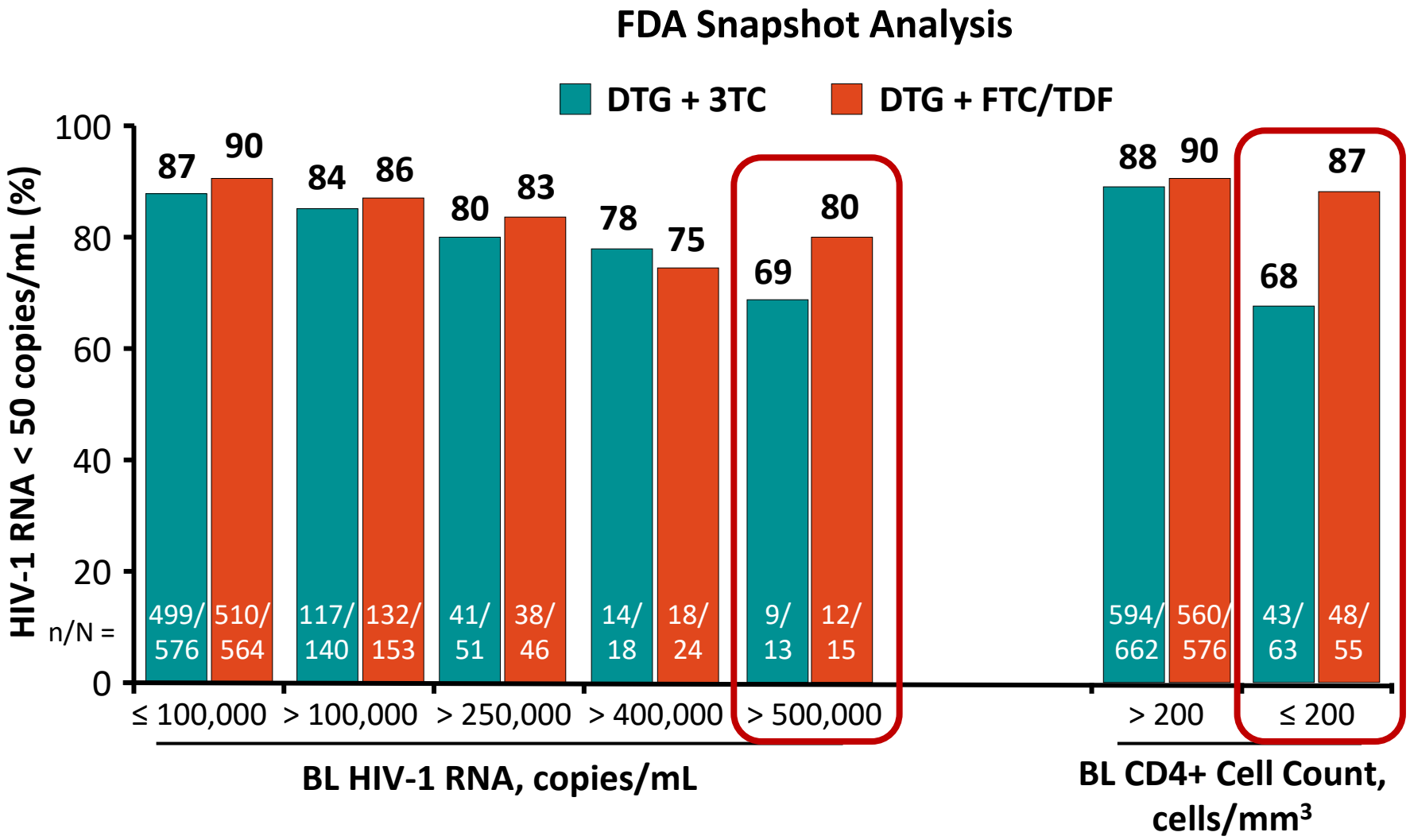
Endpoint, % (n)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	Difference,* % (95% CI)
Responders	86.0 (616)	89.5 (642)	-3.4 (-6.7 to 0)

*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

Cahn. IAS 2019. Abstr WEAB0404LB.

Slide credit: clinicaloptions.com

GEMINI-1/2: Virologic Response at Wk 96 by Baseline HIV-1 RNA Level and CD4+ Cell Count



van Wyk. IDWeek 2019. Abstr 2842.

Slide credit: clinicaloptions.com

Adult HIV Treatment Guidelines on First-line ART

DHHS[1]	IAS-USA[2]	EACS[3]	WHO[4]
▪ **BIC**/FTC/TAF ▪ **DTG**/3TC/ABC ▪ **DTG** + FTC/(TAF or TDF) ▪ **RAL** + FTC/(TAF or TDF) ▪ **DTG/3TC**	▪ **BIC**/FTC/TAF ▪ **DTG**/3TC/ABC ▪ **DTG** + FTC/TAF	▪ **BIC**/FTC/TAF ▪ DTG/3TC/ABC ▪ **DTG** + FTC/(TAF or TDF) ▪ RAL + FTC/(TAF or TDF) ▪ **RPV**/FTC/(TAF or TDF) ▪ **DOR**/XTC/(TAF or TDF) ▪ **DRV**(COBI or RTV) + FTC/(TAF or TDF) ▪ **DTG/3TC**	▪ **DTG** + (3TC or FTC)/TDF

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, bone mineral density, and pregnancy status or intent

1. DHHS ART. Guidelines. 2019. 2. Saag. JAMA. 2018;320:379. 3. EACS. 2019. 4. WHO ART. December 2019.

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DHHS Guidelines
18 December 2019

DTG/3TC

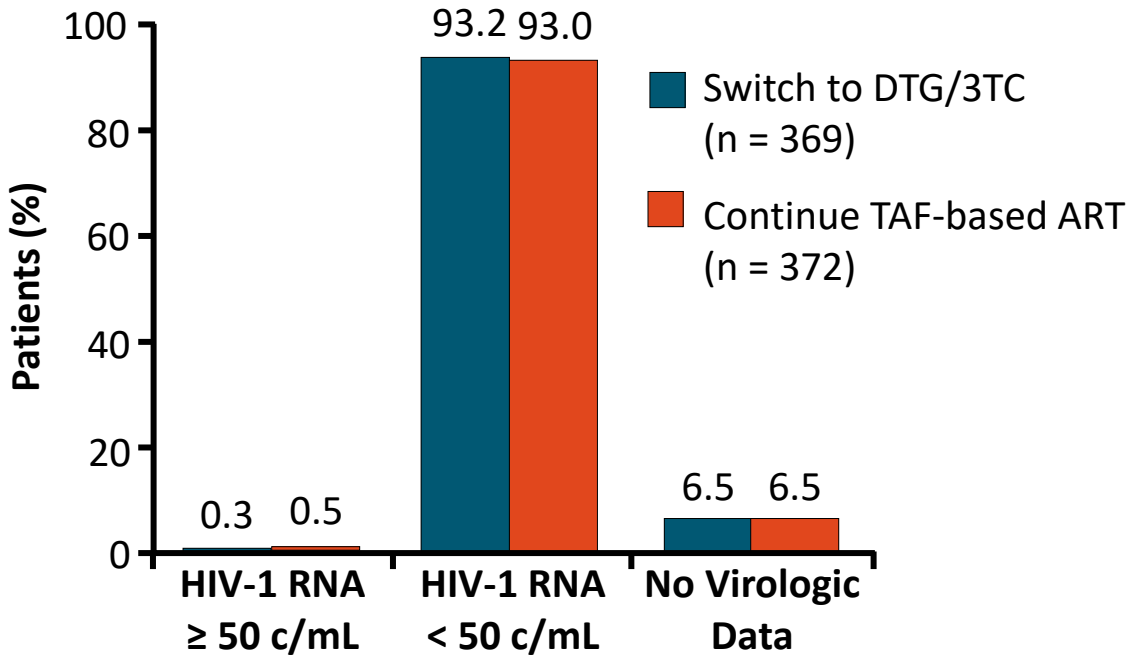
Dolutegravir/lamivudine – **is not recommended in**

1. individuals with HIV RNA **>500,000** copies/mL,
2. **HBV** co-infection, or
3. in whom **Rapid ART** is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

TANGO: Virologic Outcomes by FDA Snapshot at Wk 48

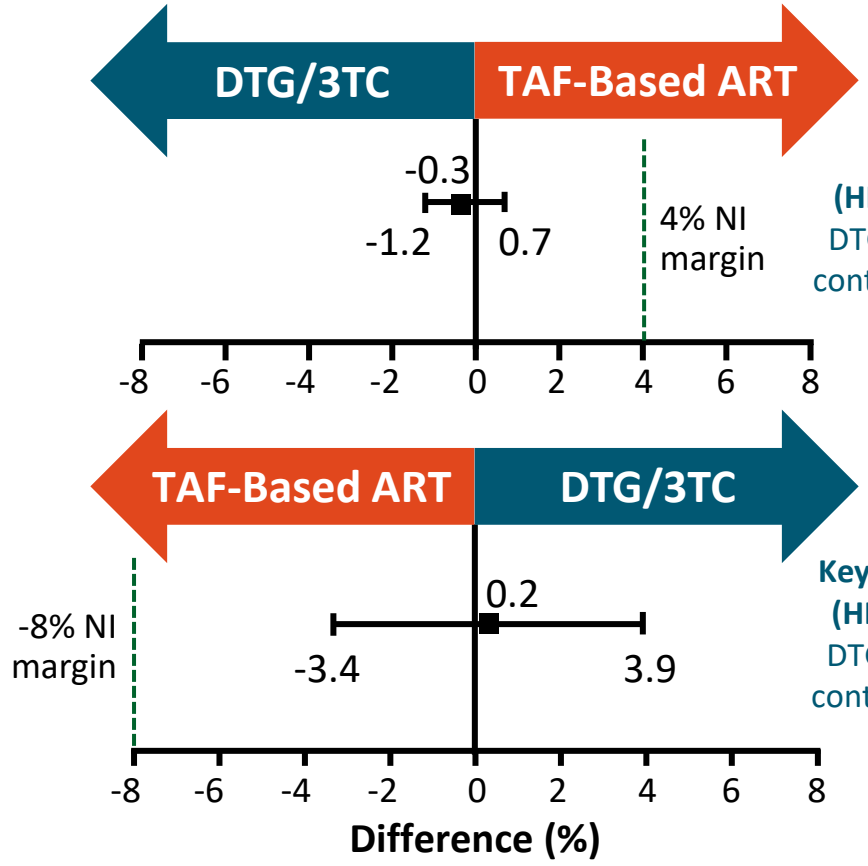
DTG/3TC Switching Study

Virologic Outcomes (ITT-E)



- No CVW in DTG/3TC arm, CVW in 1 (< 1%) patient in TAF-based ART arm; no resistance detected at failure
- All 7 patients (4 in DTG/3TC group, 3 in TAF-based ART group) with proviral M184V/I mutation at baseline maintained HIV-1 RNA < 50 c/mL at Wk 48

Adjusted Treatment Difference (95% CI)*



Primary Endpoint (HIV-1 RNA ≥ 50 c/mL)
DTG/3TC noninferior to continued TAF-based ART

Key Secondary Endpoint (HIV-1 RNA < 50 c/mL)
DTG/3TC noninferior to continued TAF-based ART

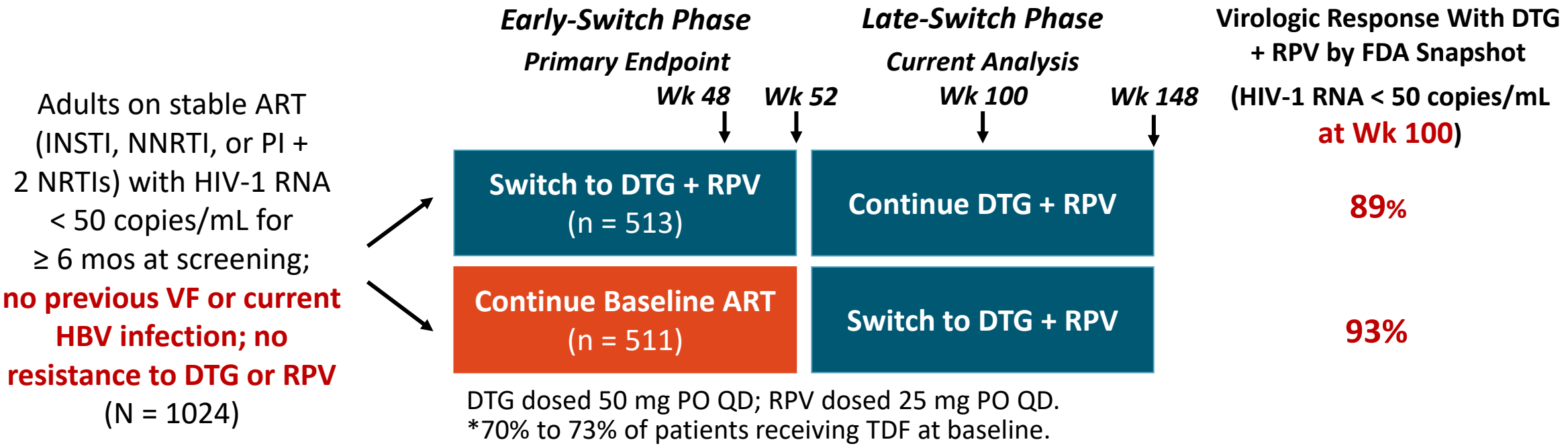
*Adjusted for baseline third agent class.

van Wyk. IAS 2019. Abstr WEAB0403LB.

Slide credit: clinicaloptions.com

SWORD-1 and -2: Switch to DTG + RPV vs Continuation of Baseline ART in Virologically Suppressed Adults

- Parallel, randomized, open-label, multicenter phase III noninferiority studies[1,2]



DTG dosed 50 mg PO QD; RPV dosed 25 mg PO QD.
*70% to 73% of patients receiving TDF at baseline.

- **Primary endpoint at Wk 48** : HIV-1 RNA < 50 copies/mL maintained in **95% of patients** in **each arm**; adjusted treatment difference: **-0.2% (95% CI: -3.0% to 2.5%)**[2]

1. Aboud. AIDS 2018. Abstr THPEB047. 2. Llibre. Lancet. 2018;391:839.

Slide credit: clinicaloptions.com

Updated European AIDS Clinical Society **(EACS)** guidelines: on Dual ART switch options

Now recommend 5 two-drug switch options for virologically suppressed people:

- Dolutegravir and rilpivirine (*Juluca)* **DTG/RPV**
- Dolutegravir and lamivudine (*Dovato*) **DTG/3TC**
- Boosted darunavir and lamivudine - **bDRV/3TC**
- Boosted atazanavir and lamivudine **– bATV/3TC**
- Boosted darunavir and rilpivirine – **bDRV/RPV**

EACS recommends dual therapy only where

- **viral load has been undetectable for at least six months,**
- **no evidence of lamivudine resistance** and **no chronic hepatitis B infection.**

https://www.aidsmap.com/news/nov-2019/options-two-drug-simplification-expand

2-Drug Regimens and Implementing in **Asia**

Two Drug Regimen	Hig-income countries	LMICs	Indication
Dolutegravir and lamivudine (**DTG / 3TC**) - STR	STR-Dovato	Not available	First-line, and switch option
Dolutegravir and rilpivirine (**DTG / RPV**) - STR	STR-Juluca	Not available	Switch in VL suppressed >6 mo
LA Cabotegravir and rilpivirine (**CAB/RPV-LA**) injectable	Not available	Not available	In VL suppressed patients, and an oral lead-in with CAB+RPV is needed

DTG/3TC and clinical implmentation in Thailand

- **Is an alternative first-line regimen**
- **First-line/switch option** in patients with **poor renal function**
  - Is contraindicated to **TDF**, whereas TAF is not widely available
  - No HBV coinfection, no history/risk of 3TC-DR
- **Not as a STR**, it is a 3-pill regimen (1 DTG tab + 2 3TC tablets)
- **No BL VL/DR testing** in general: may be at risk of having primary 3TC-R in some cases

DTG/RPV clinical implmentation in Thailand

- **Switch treatment option** in patients with poor renal function
  - Whereas TAF is not widely available
  - no history of NNRTI-DR, INSTs-DR
- **Less commonly use** than **DTG/3TC**:
  - Meal-restriction of **RPV**
  - RPV is contraindicated with PPIs, long-interval apart (4 hrs after RPV) when taking with H2-blockers, antacid

Relevant DTG **Drug-Drug** Interaction

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Co-administered Drug	Effect on Concentration	Clinical Comment
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with DTG
Anticonvulsant: Carbamazepine	↓Dolutegravir	An **additional dolutegravir 50-mg dose** should be taken, separated by 12hours from DTG
Antidiabetic: Metformin[a]	↑Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of DOVATO and metformin.
Antimycobacterial: Rifampin	↓Dolutegravir	An **additional 50-mg dose of dolutegravir** should be taken, separated by 12hours from DTG
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer DTG 2 hours before or 6hours after taking medications containing polyvalent cations.

Key questions remain for 2-Drug ART :

- Efficacy of initial dual ART at very high viral loads, low CD4 count ?
- Overall risk/benefit ratio now that we have **TAF**?
- Risk of resistance with suboptimal adherence or DR transmitted virus ? ***3TC- and RPV-DR*** *in particular*
- Activity in CNS, genital shedding?
- Effect on persistent inflammation ?

Thank You