Optimizing the use of Integrase inhibitors in practice

Ghassan Wali , MD

Infectious Disease Consultant - HIV / AIDS
King Faisal Specialist Hospital And Research Center Jeddah
University of British Columbia

Objectives

- Review the use of INSTIs for one of our HIV naïve patients.
- How to fit the INSTI into a patient's regimen when switching a virologically suppressed patient.
- Managing the potential toxicities of the current INSTIs.
- Two vs. three drugs: promising new options
- Options for the treatment experienced patients

Clinical vignette

- 40 years MSM presents with fever and sore throat and generalized body rash for 1 week. Recent new sexual partner.
- No other medical conditions. Exam normal.
- HIV Ab/Ag positive; HIV differentiation Ab positive
- HIV RNA 500k copies/ml
- CD4 cell count 180
- Creatinine 60
- genotype pending; HLA-B5701 pending.

Case#1

- He says he’s willing to start treatment. What do you start?

A. Dolutegravir + lamivudine
B. Elvitegravir/cobi + FTC/tenofovir AF
C. Dolutegravir + TAF/FTC
D. Darunavir/cobi /+ FTC/tenofovir AF
E. Dolutegravir + abacavir/lamuvidine

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART in Most Patients With HIV Infection

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/(TAF or TDF) ▪ RAL + FTC/(TAF or TDF)	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/TAF

Recommendations basis

- baseline HIV-1 RNA, CD4+ cell count
- CrCl, eGFR
- HLA-B*5701 status
- HBsAg status,
- osteoporosis status
- pregnancy status
- No pharmacologic-boosting agent

Summary of the Anti-Retroviral Treatment in HIV positive naïve patients in Saudi Arabia

Regimen	Preferred treatment	Alternative treatment	Notes
Integrase Inhibitors	TAF / FTC / ELV /C ABC / 3TC / DTG TAF / FTC / BIC TAF / FTC + DTG ABC / 3TC + DTG TAF / FTC + RAL TDF / FTC + DTG TDF / FTC + RAL	TAF / FTC ABC / 3TC + RAL	✓ Negative HLA B5701 prior to ABC & ABC containing regimens use ✓ Avoid 3TC use in HIV/HBV coinfection ✓ TDF is preferred over TAF in HIV/ TB on Rifampicin
Boosted Protease Inhibitors	TAF / FTC + DRV / C TDF / FTC + DRV / C	TAF / FTC + DRV / R TDF / FTC + DRV / R ABC / 3TC + DRV / C TAF / FTC + ATV / R	Not recommended in HIV/TB coinfection on Rifampicin
NNRTI		TAF / FTC / RPV TDF / FTC / RPV	Not recommended if HIV Viral load is > 100,000 copies/ml and/ or CD4 count < 200 cells/µl

Choosing Among Integrase Inhibitors for First-line Therapy

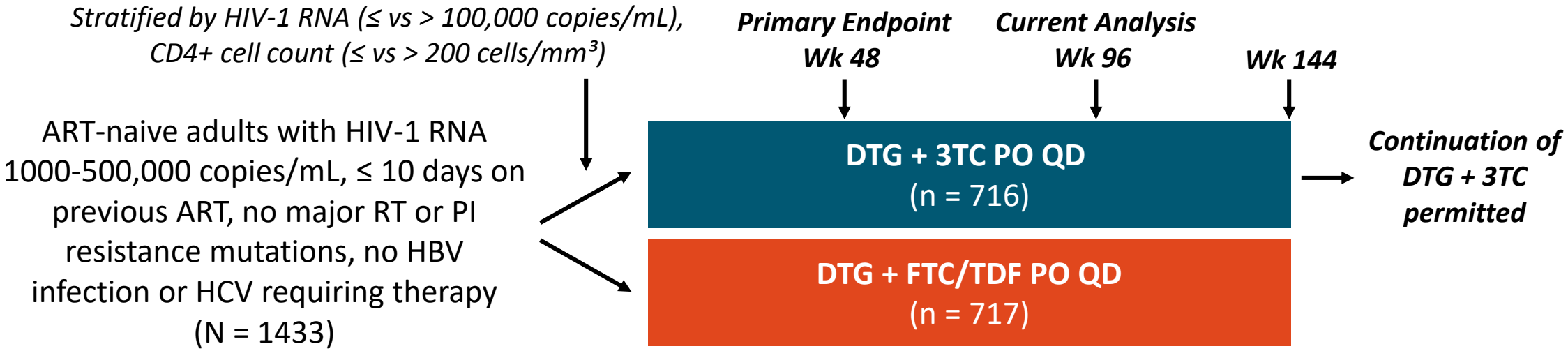
Agent	Advantages	Disadvantages
Bictegravir	▪ STR once daily with FTC/TAF ▪ Few drug or food interactions ▪ High barrier to resistance	▪ Least amount of data ▪ Only available as an STR ▪ No safety data in pregnancy
Dolutegravir	▪ Single agent (eg, with FTC/TAF or FTC/TDF) ▪ STR once daily with 3TC or ABC/3TC ▪ Few drug or food interactions ▪ High barrier to resistance ▪ A preferred option in pregnancy guidelines during second and third trimester	▪ Increases metformin levels ▪ Recent concerns regarding conception/ early pregnancy safety
Elvitegravir	▪ STR once daily with COBI plus FTC/TAF	▪ Numerous drug–drug interactions ▪ Do not use during pregnancy
Raltegravir	▪ Longest experience ▪ Few drug or food interactions ▪ A preferred option in pregnancy guidelines	▪ Multiple pills ▪ No STR ▪ Limited safety data at conception

Studies of Recommended INSTIs as First-line ART Regimens

Trial	INSTI Regimen	Comparator	Wks	Outcome vs Comparator
GS-1489[1]	**BIC**/FTC/TAF	DTG/ABC/3TC	96	Noninferior
GS-1490[2]	**BIC**/FTC/TAF	DTG + FTC/TAF	96	Noninferior
SINGLE[3]	**DTG** + ABC/3TC	EFV/FTC/TDF	144	Favors INSTI
FLAMINGO[4]	**DTG** + 2 NRTIs	DRV + RTV + 2 NRTIs	96	Favors INSTI
SPRING-2[5]	**DTG** + 2 NRTIs	RAL + 2 NRTIs	96	Noninferior
ARIA[6]	**DTG**/ABC/3TC	ATV + RTV + FTC/TDF	48	Favors INSTI
ACTG A5257[7]	**RAL** + FTC/TDF	ATV or DRV + RTV + FTC/TDF	96	Favors INSTI*
STARTMRK[8]	**RAL** + FTC/TDF	EFV + FTC/TDF	240	Favors INSTI

GEMINI-1 and -2: DTG + 3TC in ART-Naive Adults

- Parallel, international, randomized, double-blind phase III noninferiority studies



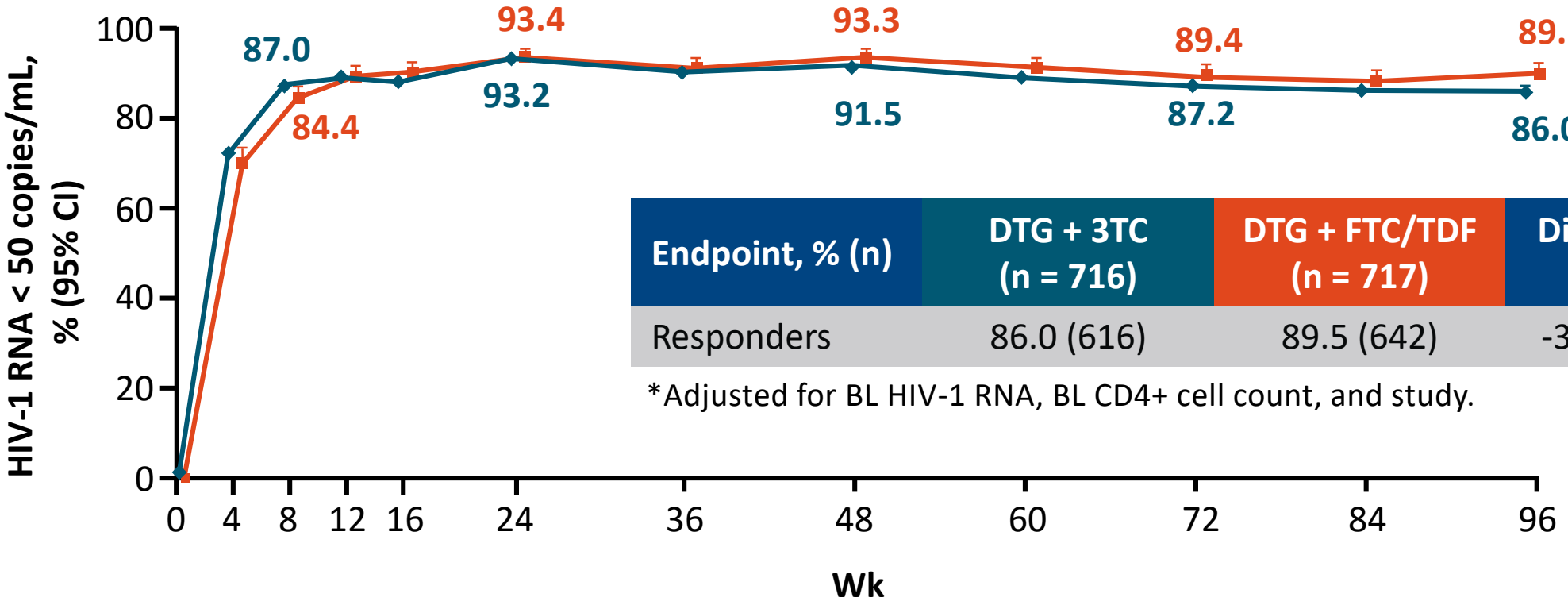
Screening within 28 days of study start; studies double-blinded until Wk 96, open-label until Wk 144.

- Secondary endpoints at Wk 96: HIV-1 RNA < 50 copies/mL (FDA Snapshot and TRDF analyses); AEs; resistance; changes from BL in bone, renal, and lipid parameters

Cahn. IAS 2019. Abstr WEAB0404LB. NCT02831673. NCT02831764.

GEMINI-1 and -2: Virologic Response

- 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.

Do we still have to use Boosted Pis?

Pros

- before availability of resistance data
- Patients with poor adherence

Cons

- Drug–drug interactions
- GI intolerance
- Hyperlipidemia
- CV risk with some PIs

1. DHHS ART Guidelines. October 2018. 2. ATV PI. 3. DRV/COBI/FTC/TAF PI. 4. Worm. J Infect Dis. 2010;201:318.

Do we still have to use NNRTIs?

Pros

- Adverse events of INSTIs
- In women desiring pregnancy
- If pt experiencing weight gain with INSTIs

Cons

- Low barrier to resistance at VF with EFV, RPV
- Neuropsychiatric AEs with EFV
- Higher rates of VF in RPV patients with HIV-1 RNA > 100,000 copies/mL and CD4+ cell counts < 200 cells/mm3
- RPV must be taken with a meal
- Fixed-dose combination with DOR includes TDF not TAF
- Lipid increases with EFV

1. EFV PI. 2. RPV PI. 3 Cohen. AIDS. 2014;28:989.

Case#1

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B. Elvitegravir/cobi + FTC/tenofovir AF
C. Dolutegravir + TAF/FTC
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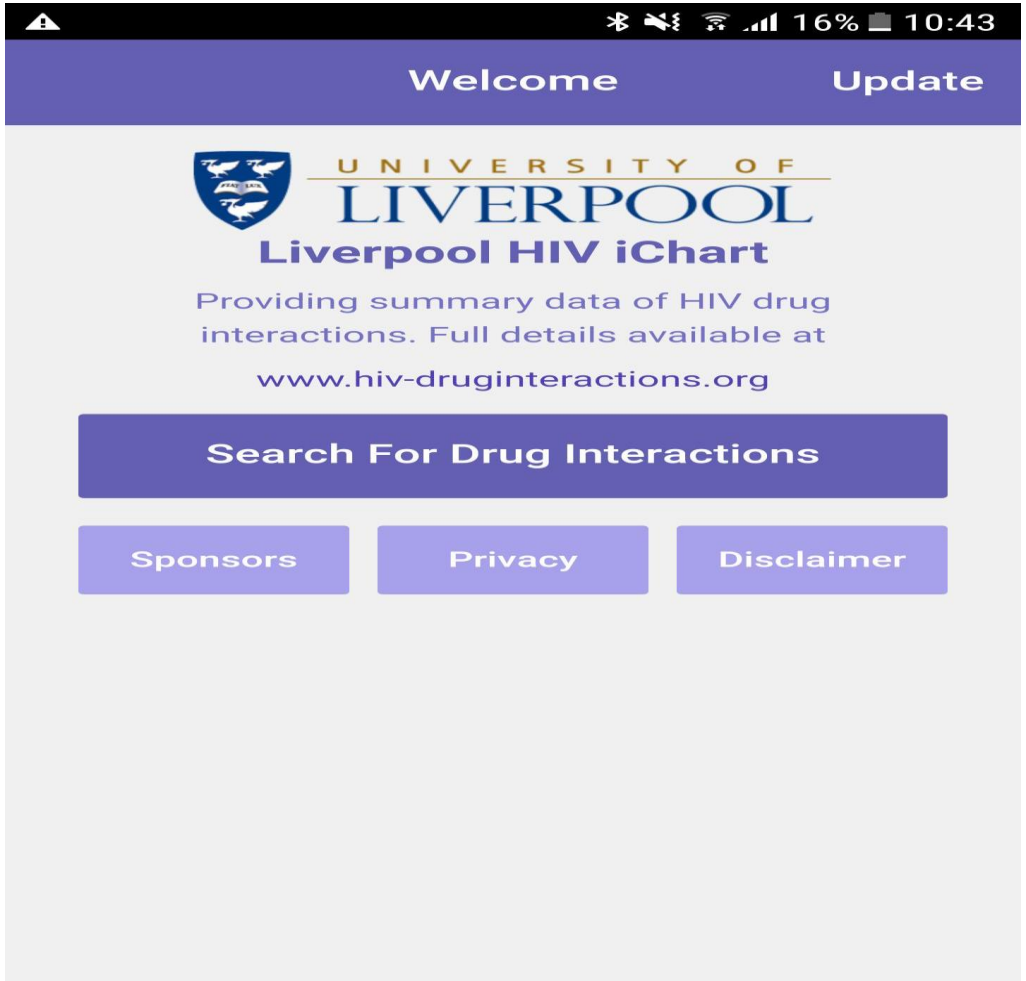
E. Dolutegravir + abacavir/lamuvidine

Case#2: managing INSTI toxicities and potential drug interactions

- 50 year old male with long standing HIV is taking DTG,ABC,3TC.
- He remain virologically suppressed on this regimen for 3 years.
- He is complaining of tremendous weight gain (9 kilos) that's uncontrolled with diet and lifestyle modifications.
- He has vitamin D deficiency, GERD and osteopenia.
- His HBA1C is 8; he gets started on metformin.
- He wants to change his regimen but demands one pill, do you agree?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Welcome
Update
UNIVERSITY OF
LIVERPOOL
Liverpool HIV iChart
Providing summary data of HIV drug interactions. Full details available at
www.hiv-druginteractions.org
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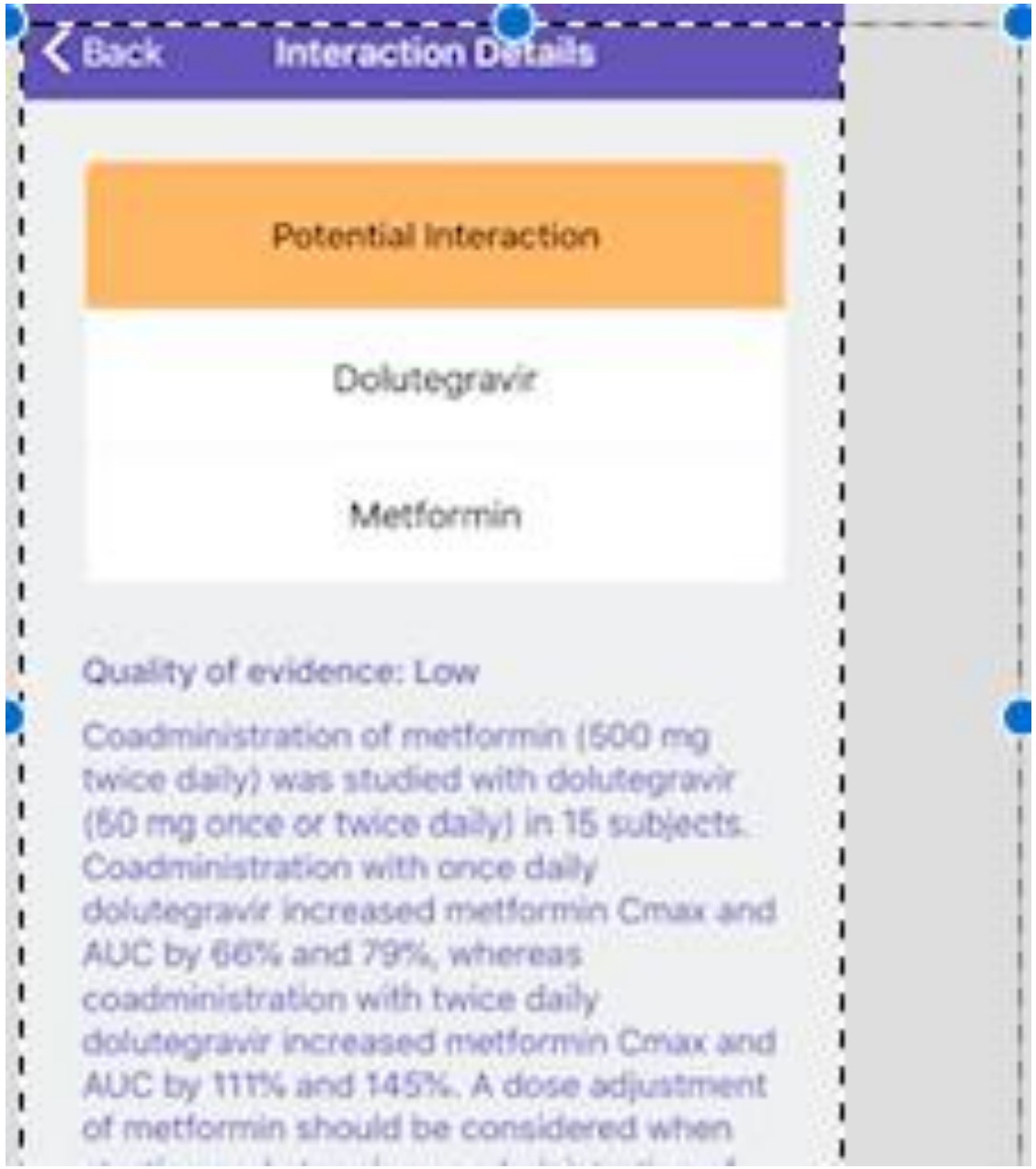
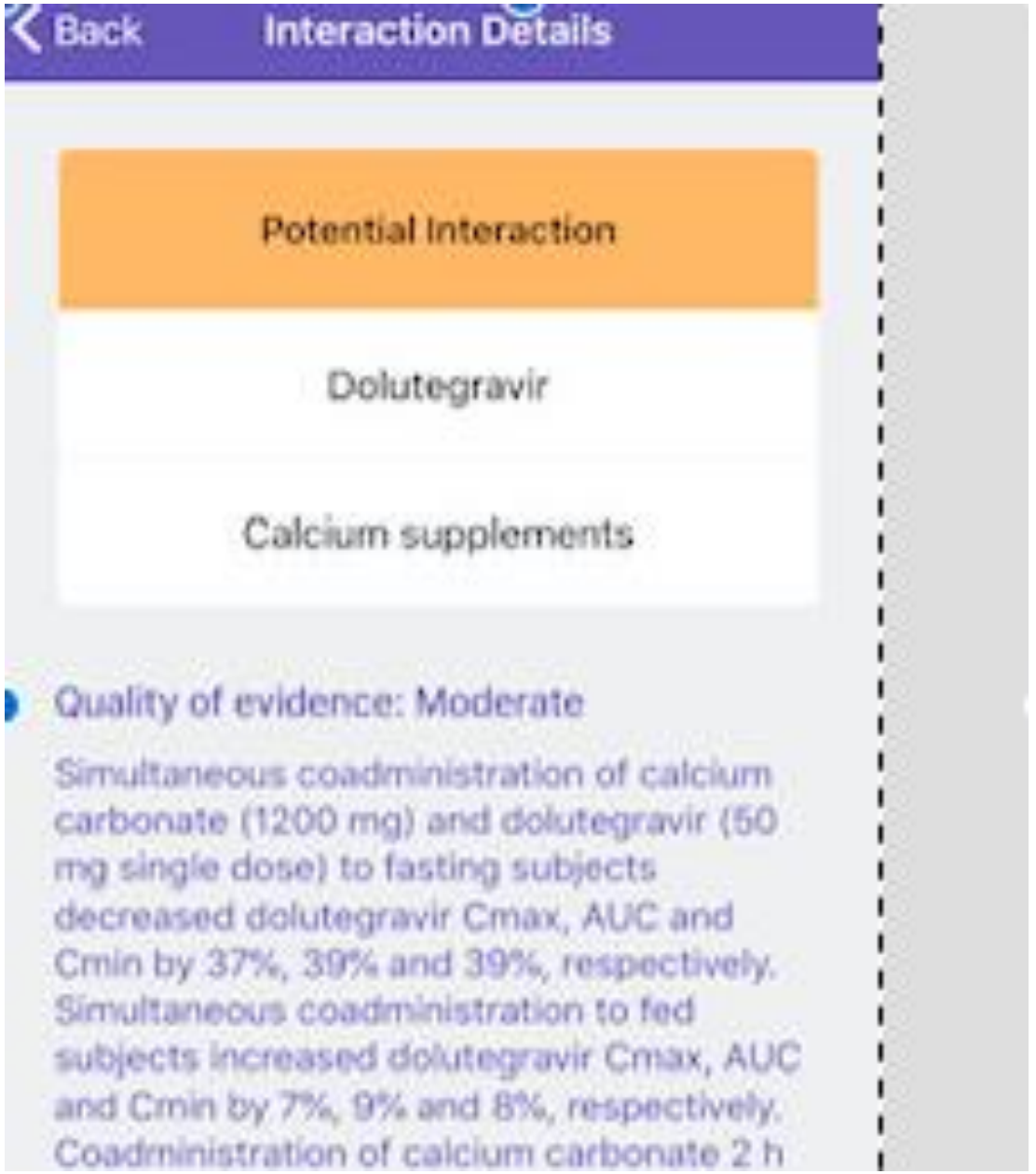

Back
Interaction Details
Potential Interaction
Dolutegravir
Metformin
Quality of evidence: Low
Coadministration of metformin (500 mg twice daily) was studied with dolutegravir (50 mg once or twice daily) in 15 subjects. Coadministration with once daily dolutegravir increased metformin Cmax and AUC by 66% and 79%, whereas coadministration with twice daily dolutegravir increased metformin Cmax and AUC by 111% and 145%. A dose adjustment of metformin should be considered when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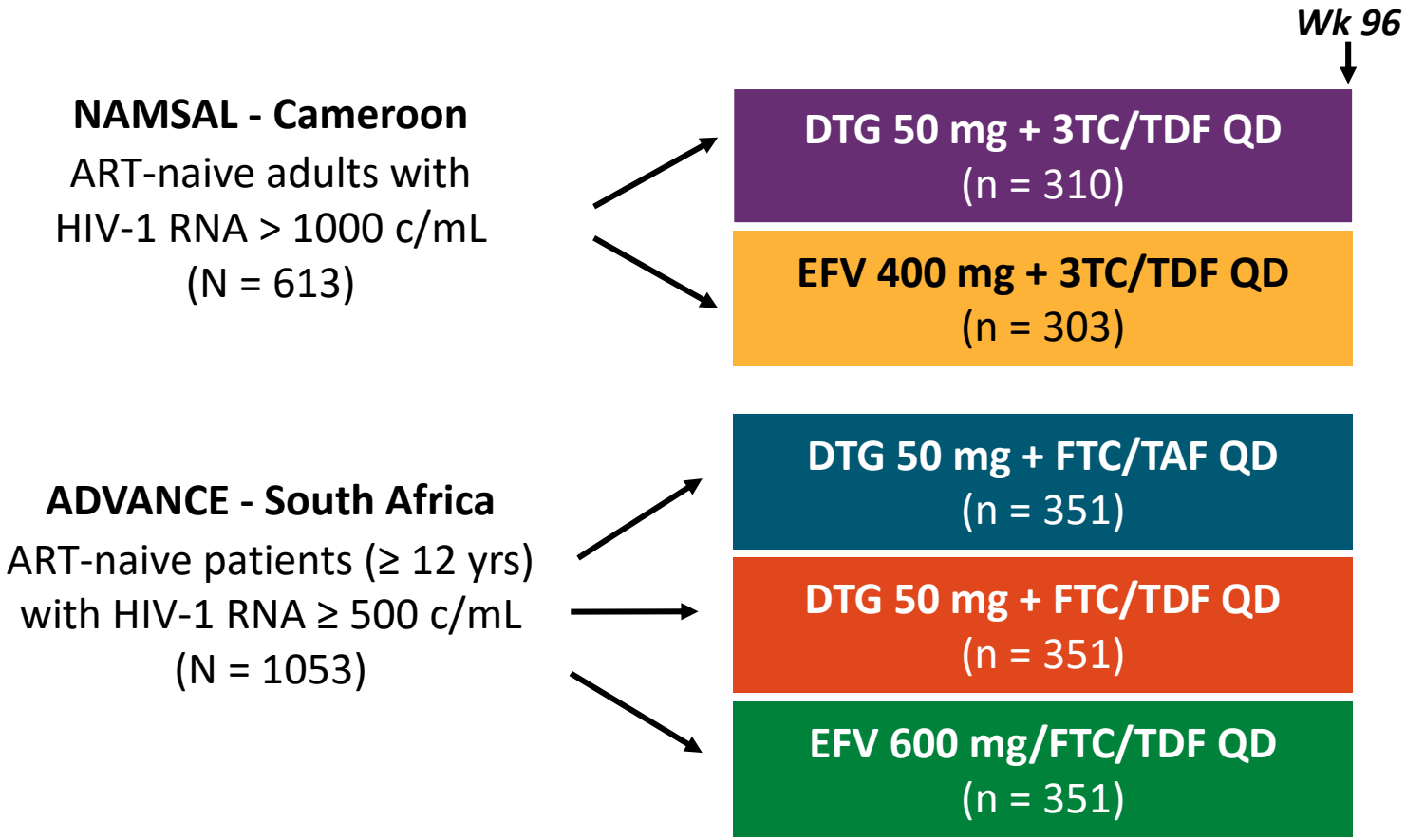
Interaction Details
Potential Interaction
Dolutegravir
Calcium supplements
Quality of evidence: Moderate
Simultaneous coadministration of calcium carbonate (1200 mg) and dolutegravir (50 mg single dose) to fasting subjects decreased dolutegravir Cmax, AUC and Cmin by 37%, 39% and 39%, respectively. Simultaneous coadministration to fed subjects increased dolutegravir Cmax, AUC and Cmin by 7%, 9% and 8%, respectively. Coadministration of calcium carbonate 2 h

NAMSAL and ADVANCE: Study Design

- Multicenter, randomized, open-label phase III trials[1-3]



Primary Endpoint (Both Trials)
HIV-1 RNA < 50 c/mL at Wk 48 by FDA Snapshot in ITT population (noninferiority margin: -10%)[4,5]

1. Hill. IAS 2019. Abstr MOAX0102LB. 2. NCT02777229. 3. NCT03122262.
4. NAMSAL ANRS 12313 Study Group. N Engl J Med;2019:[Epub]. 5. Venter. N Engl J Med;2019:[Epub].

NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

Outcome	NAMSAL			ADVANCE			
	DTG + 3TC/TDF (n = 293)	EFV + 3TC/TDF (n = 278)	*P* Value	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF	*P* Value
Mean Δ in weight, kg							
▪ Wk 48	+5	+3	< .001	+6	+3	+1	< .001
▪ Wk 96	NA	NA		+8	+5	+2	
Mean Δ in BMI at Wk 48	+1.7	+1.2	< .001	NR	NR	NR	
Treatment-emergent overweight (BMI 25-29.9), %							
▪ Wk 48	16	17	NS	23	14	9	NS
▪ Wk 96	NA	NA		25	13	11	
Treatment-emergent obesity (BMI ≥ 30), %							
▪ Wk 48	12	5	< .01	14	7	6	< .01
▪ Wk 96	NA	NA		19	8	4	

Hill. IAS 2019. Abstr MOAX0102LB.

Switching From Suppressive ART to an STR: Key Studies With Contemporary Regimens

- Noninferior efficacy for all switch regimens vs baseline regimen; all FDA approved to treat virologically suppressed patients

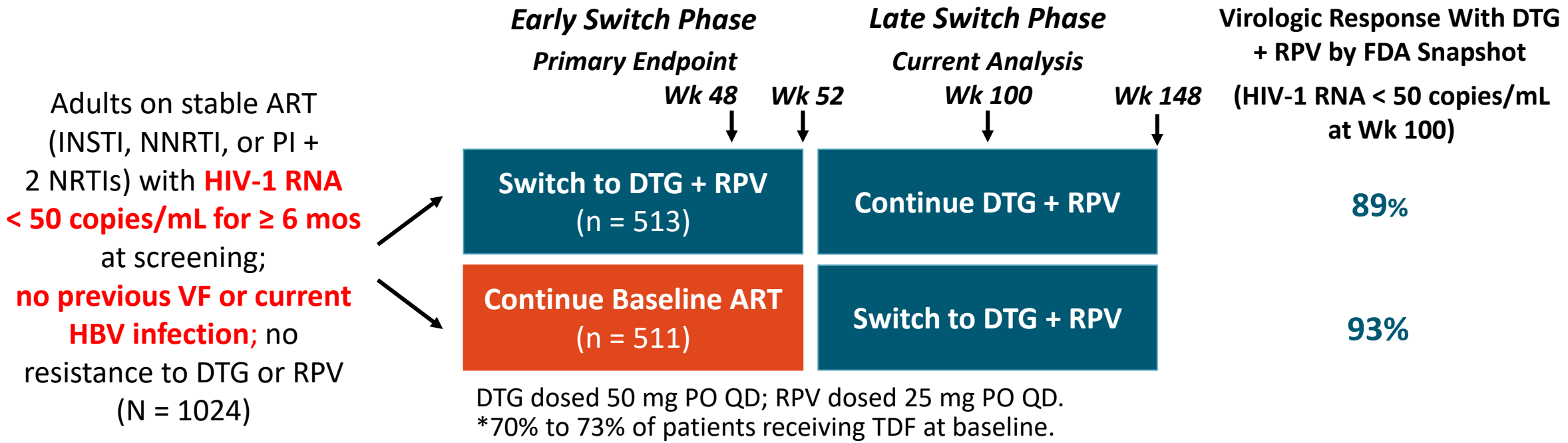
Key Studies	Switch From	Switch to
380-1878[1] or 380-1844[2] or 380-4030[3]	Boosted PI + 2 NRTIs or DTG/ABC/3TC or DTG + FTC/(TAF or TDF)	BIC/FTC/TAF
SWORD 1 & 2[4]	Third agent + 2 NRTIs	DTG/RPV
STRIIVING[5]	Third agent + 2 NRTIs	DTG/ABC/3TC
EMERALD[6]	Boosted PI + FTC/TDF	DRV/COBI/FTC/TAF
GS-109[7]	TDF-based regimen	EVG/COBI/FTC/TAF
GS-1216[8] or GS-1160[9]	RPV/FTC/TDF or EFV/FTC/TDF	RPV/FTC/TAF

Most recent FDA approvals: for BIC/FTC/TAF and DTG/RPV, must have no history of treatment failure and no resistance to regimen components; for DRV/COBI/FTC/TAF, must have no resistance to DRV, TFV.

1. Daar. Lancet HIV. 2018;5:e347. 2. Molina. Lancet HIV. 2018;5:e357. 3. Sax. IAS 2019. Abstr MOAB0105. 4. Llibre. Lancet. 2018;391:839. 5. Trottier. Antivir Ther. 2017;22:295. 6. Orkin. Lancet HIV. 2018;5:e23. 7. Mills. Lancet Infect Dis. 2016;16:43. 8. Orkin. Lancet HIV. 2017;4:e195. 9. DeJesus. Lancet HIV. 2017;4:e205.

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: HIV-1 RNA < 50 copies/mL maintained in 95% of patients in each arm at Wk 48; 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.

SWORD-1 and -2: Resistance

- 10/990 (1%) confirmed virologic withdrawals through Wk 100
  - Treatment-emergent NNRTI resistance mutations documented in 3/10, all from early switch arm*

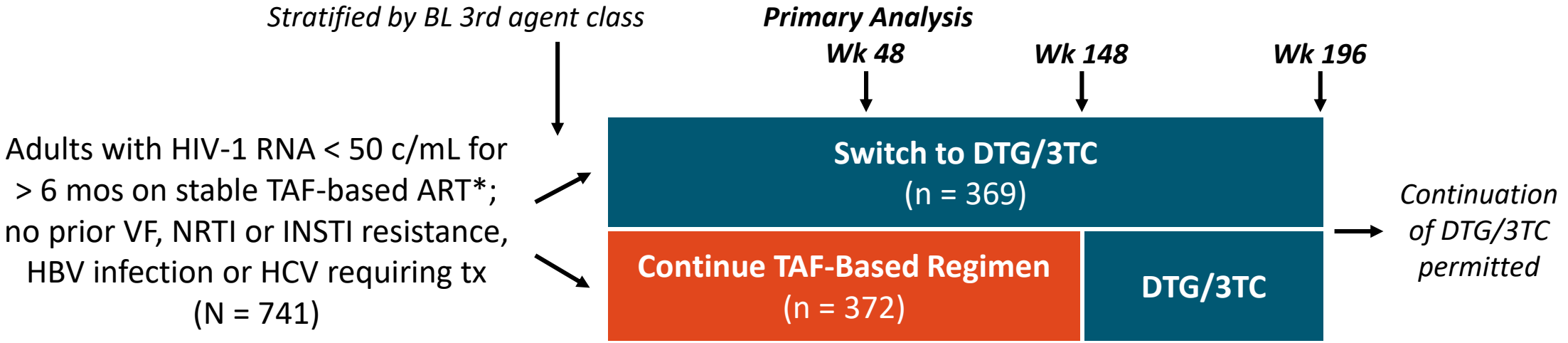
Time of Failure	Previous Regimen	Mutations at Baseline		Mutations at Confirmed Virologic Withdrawal	
		NNRTI	INSTI	NNRTI	INSTI
Wk 36	EFV/TDF/FTC	None	None	K101K/E	None
Wk 88	DTG/ABC/3TC	None	None	E138E/A	None
Wk 100	EFV/TDF/FTC	K101E, E138A	G193E	K101E, E138A, M230M/L	Assay failure

*For these 3 patients, HIV-1 RNA at last measurement: < 50 copies/mL, 55 copies/mL, 300 copies/mL, respectively.

Aboud. AIDS 2018. Abstr THPEB047.

TANGO: Switch to DTG/3TC vs Continuing TAF-Based 3-Drug Regimen

- International, randomized, open-label phase III noninferiority study

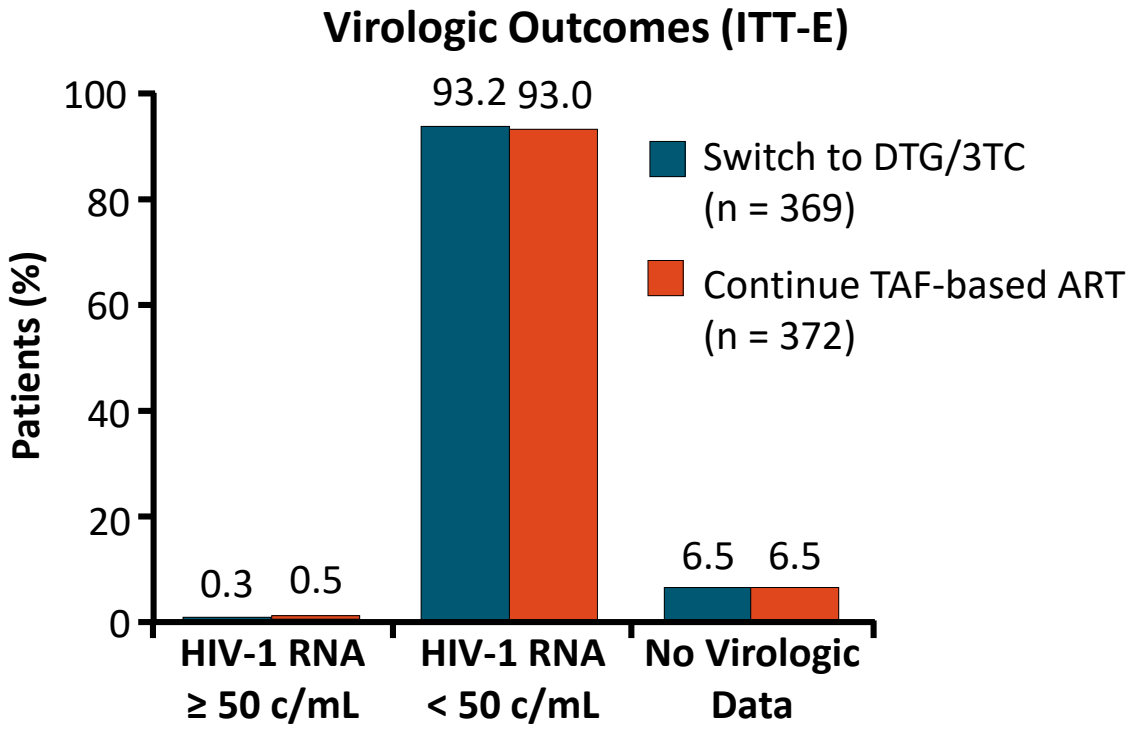


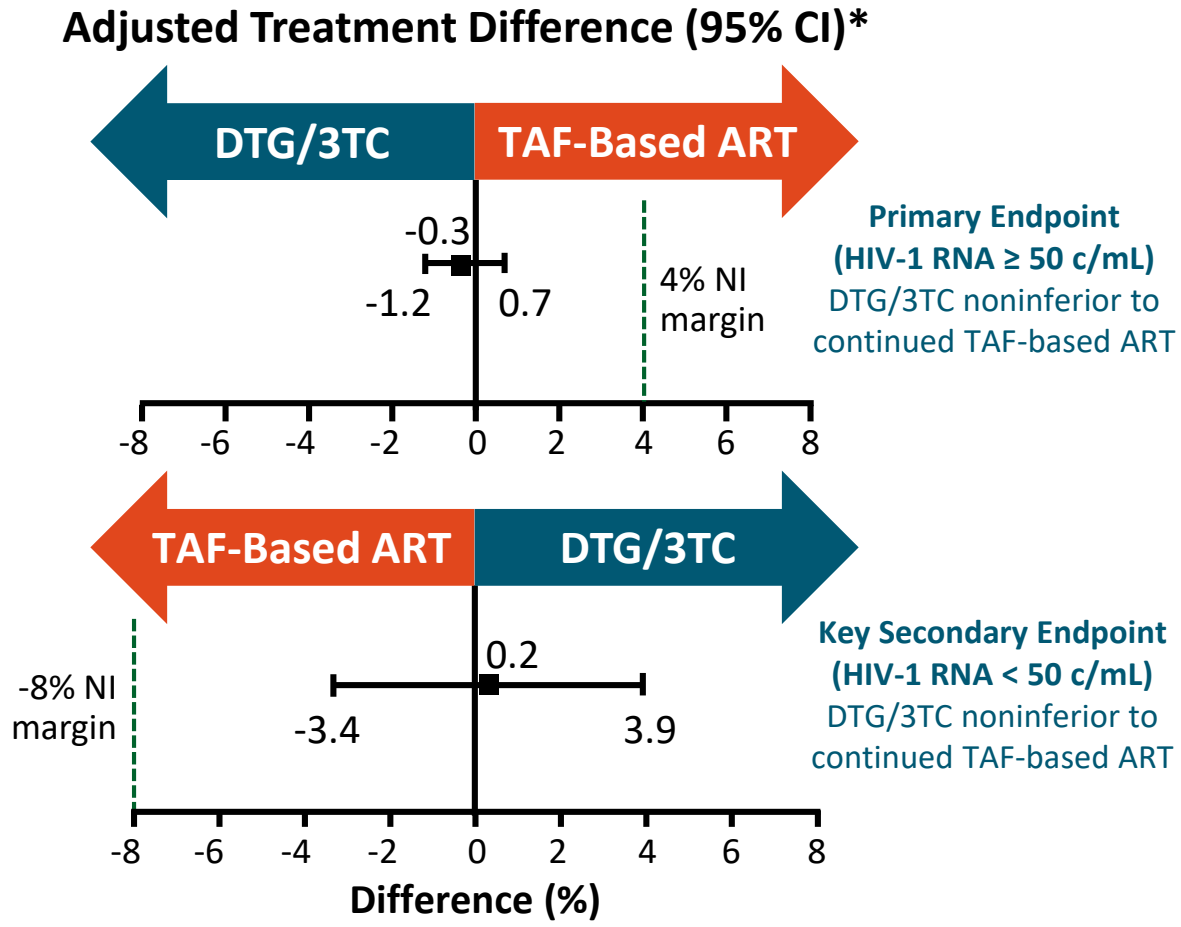
*Initial regimen of FTC/TAF + PI, NNRTI, or INSTI, or TDF switched to TAF ≥ 3 mos prior to screening with no other regimen changes.

- Primary endpoint: virologic failure at Wk 48 by FDA Snapshot analysis (ITT-E)
  - Noninferiority margin: 4%
- Secondary endpoint: safety

van Wyk. IAS 2019. Abstr WEAB0403LB. NCT03446573.

TANGO: Virologic Outcomes by FDA Snapshot at Wk 48





- 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 for baseline third agent class.

van Wyk. IAS 2019. Abstr WEAB0403LB.

Case#3

- Present history: DM, GERD and hyperlipidemia
- HIV history:

-Diagnosed in 1994 (after blood transfusion)

-Started on ART in 1999: saquinavir, 3TC and AZT

-Nadir CD4: 60, currently ranges from 400-550

-Viral load ranges from 5000-22000 c/ml

-Because he never had a suppressed virus he received multiple regimens

Continue case presentation

NRTI	DDI, D4T, AZT, and tenfovir
NNRTI	Efavirenz
PI	Saquinavir, Nelfinavir, Indinavir, Lopinavir/ritonavir, Darunavir
INSTI	Raltegravir

HIV-1 Genotypic Drug Resistance, P

HIV-1 Genotypic Drug Resistance, P	INTERP	SDL
Test Note: Interpretation of following results: RESIST= Resistant SUSC= No evidence of resistance PR= Possible resistance IE= Insufficient evidence		
Reverse Transcriptase Mutations		SDL
Test Note: L74V, K103N, V108I, V118I, V179E, M184V, T215Y mutations		
Zidovudine	PR	SDL
Test Note: M184V, T215Y mutations		
Didanosine	RESIST	SDL
Test Note: L74V mutation		
Lamivudine	RESIST	SDL
Test Note: M184V mutation		
Emtricitabine	RESIST	SDL
Test Note: M184V mutation		
Stavudine	PR	SDL
Test Note: M184V, T215Y mutations		
Abacavir	RESIST	SDL
Test Note: L74V, M184V, T215Y mutations		
Tenofovir	SUSC	SDL
Nevirapine	RESIST	SDL
Test Note: K103N, V108I, V179E mutations		
Efavirenz	RESIST	SDL
Test Note: K103N, V108I, V179E mutations		
Protease Mutations		SDL
Test Note: I13V, K20I, M36I, K43T, M46I, I54V, L63P, H69K, L89M mutations		
Saquinavir with Ritonavir	SUSC	SDL
Indinavir	RESIST	SDL
Test Note: M46I mutation		
Indinavir with Ritonavir	PR	SDL
Test Note: M46I mutation		
Nelfinavir	PR	SDL
Test Note: M36I, M46I, I54V mutations		
Fosamprenavir	RESIST	SDL
Test Note: M46I, I54V mutations		
Fosamprenavir with Ritonavir	PR	SDL
Test Note: M46I, I54V mutations		
Lopinavir with Ritonavir	PR	SDL
Test Note: K43T, M46I, I54V, L63P, L89M mutations		
Atazanavir	PR	SDL
Test Note: K20I, M36I, M46I, I54V mutations		
Atazanavir with Ritonavir	PR	SDL
Test Note: M36I, M46I, I54V mutations		
Tipranavir with Ritonavir	PR	SDL
Test Note: I13V, M36I, K43T, I54V, H69K mutations		
Darunavir with Ritonavir	SUSC	SDL

Testing was done by DNA sequencing method (Trugene HIV-1 Genotyping Kit; Bayer HealthCare LLC), and results were

DHHS : Management of ART Failure of second line ARV failure

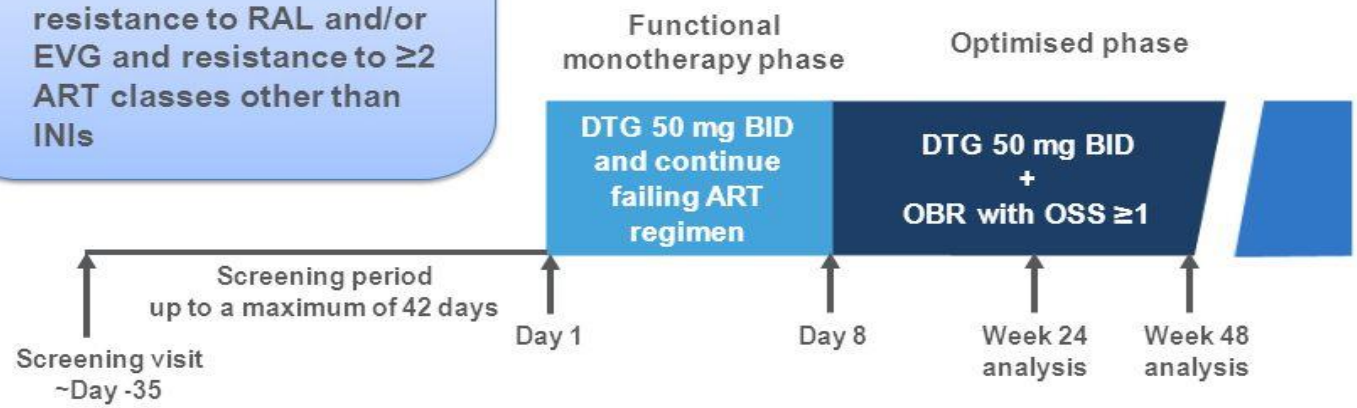
- **Goal : Fully suppressive ARV regimen**
  - If **susceptible** to boosted PI → regimen can be similar for those with first line failure
  - If **NOT** susceptible to boosted PI → new regimen should have a minimum of 2 (preferably 3) fully active drugs if possible
    - Susceptibility to drug predicted from patient treatment history, prior and current resistance and tropism testing, MoA of novel drug class
- Not recommended to add single agent to failing regimen due to risk of developing resistance to entire regimen

DHHS guideline

VIKING-3: STUDY DESIGN (N=183)

Main eligibility criteria:

- HIV-1 RNA ≥500 c/mL
- Screening or documented historic evidence of resistance to RAL and/or EVG and resistance to ≥2 ART classes other than INIs



OSS, overall susceptibility score, determined by Monogram Biosciences net assessment

. Nichols G, et al. IAS 2013. Poster TULBPE19

conclusion

- Integrase inhibitors are the first line of choice for naïve patients, in absence of genotype testing choose DTG or BIC
- Certain 2-drug regimens appear to be as effective as 3-drug strategies, although long-term data are not yet available
- switching for toxicities can be done with many safe options
- For treatment experienced patients, use 2 preferably 3 potent drugs.
- As more our patients are living longer, the need for a durable regimen with minimal toxicity, high genetic barrier, non-booster single tablet is important.