DCH AURIGA

22nd HIV/AIDS Workshop 2023

Confidence in HIV Treatment and Prevention

Mandarin Hotel Bangkok
Grand Ballroom A, B, C

AGENDA 12.10 - 13.00 | AUGUST 24, 2023

12.10 - 12.15 **Opening & Welcome**
Prof. Sasisopin Kiertiburanakul, MD, MHS

12.15 - 12.35 **Think Big for Today and Tomorrow**
Prof. Sasisopin Kiertiburanakul, MD, MHS

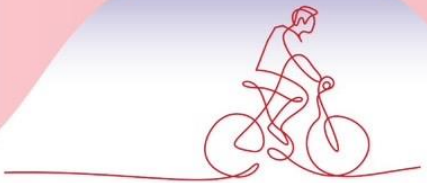
12.35 - 12.55 **Discover the Option in HIV Prevention**
Prof. Thana Khawcharoenporn, MD, MSc

12.55 - 13.00 **Q & A session**

SPEAKER

Prof. Sasisopin Kiertiburanakul, MD, MHS
Faculty of Medicine Ramathibodi Hospital

Prof. Thana Khawcharoenporn, MD, MSc
Faculty of Medicine, Thammasat University



GILEAD
Creating Possible

Think Big for Today and Tomorrow

Prof. Sasisopin Kiertiburanakul, MD, MHS
Department of Medicine,
Faculty of Medicine Ramathibodi Hospital, Mahidol University

Gilead and DCH Auriga Symposium, The 22nd TAS HIV/AIDS Workshop, Mandarin Hotel Bangkok (24 August 2023)

Disclosure

- Speakers Bureau
  - Pfizer, Astellas, MSD, Janssen, AztraZeneca, GSK, DKSH, BMS, AbbVie, Meiji, Siam, Daiichi, Takeda, Sanofi, Mylan, DCH Auriga, Biopharm, BLHua, Roche, Berlin, Zuellig Pharma, Medtronic, Biogenetech, Celltrion, Novartis
- Congress Travel
  - Astellas, Pfizer, MSD, Janssen, BMS, AbbVie, Siam, Daiichi, Takeda, DKSH, AztraZeneca
- Research Grant
  - Gilead, MSD, BMS, Daiichi, Biopharm, Medicago, Atea

Outline

Antiretroviral therapy: What to start

Characteristics of BIC and DTG

Short- and long-term data of BIC/FTC/TAF

Data on switching to BIC/FTC/TAF

Outline

Antiretroviral therapy: What to start

International Guidance on First-line ART

DHHS[1]	IAS-USA[2]	EACS[3]	WHO[4]
Recommended initial regimens for most PLWH—not have a history of using CAB-LA as PrEP ▪ BIC/TAF/FTC ▪ DTG/ABC/3TC* ▪ DTG + XTC + TXF ▪ DTG/3TC†	*Recommended for most PLWH* ▪ BIC/TAF/FTC ▪ DTG + TXF/XTC ▪ DTG/3TC ‡	*Recommended regimens* ▪ BIC/FTC/TAF ▪ DTG/ABC/3TC or DTG + ABC/3TC* ▪ DTG + XTC/TXF ▪ RAL + XTC/TXF ▪ DTG/3TC or DTG + XTC† ▪ TXF/XTC + DOR or TDF/3TC/DOR	*Preferred first-line regimen* ▪ DTG + XTC + TDF

ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; TXF = tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF); XTC = lamivudine (3TC) or emtricitabine (FTC)

*if HLA-B*5701 negative

†Except for individuals with baseline HIV RNA >500,000 copies/mL, with HBV, or for whom results of HIV genotypic resistance testing or HBV testing are not yet available

‡Only if HIV RNA <500 000 copies/mL and HBV coinfection not present. This regimen should not be used for rapid initiation when genotype, HIV RNA, and HBV serology results are not yet available

1. DHHS ART Guidelines. September 2022. 2. Gandhi RT, et al. JAMA 2022;329:63-84. 3. EACS Guidelines. Version 11.1. October 2022. 4. WHO Consolidated Guidelines. July 2021.

Thailand National Guidelines: First-line Regimen

Standard regimen (3 drugs) (prefer single tablet regimen)

NRTIs (backbone)			INSTIs (recommend)
TAF / TDF	3TC / FTC	+	DTG

NRTIs (alternative)			NNRTI (alternative)		
ABC / AZT	3TC	+	EFV	OR	RPV

Optional regimen (2 drugs)

Regimen	Remarks
DTG + 3TC	▪ Contraindication to TDF and TAF ▪ Considerations if ➢ HBsAg negative ➢ Baseline VL <500,000 copies/mL or CD4 count >200 cells/mm^3 ➢ No 3TC resistance

แนวทางการตรวจวินิจฉัย รักษาและป้องกันการติดเชื้อเอชไอวี ประเทศไทย ปี 2564/2565

Thailand National Guidelines: First-line Regimen

- ยากลุ่ม integrase inhibitors ตัวอื่น เช่น BIC อาจเป็นทางเลือกตัวที่ 3 ได้

Outline

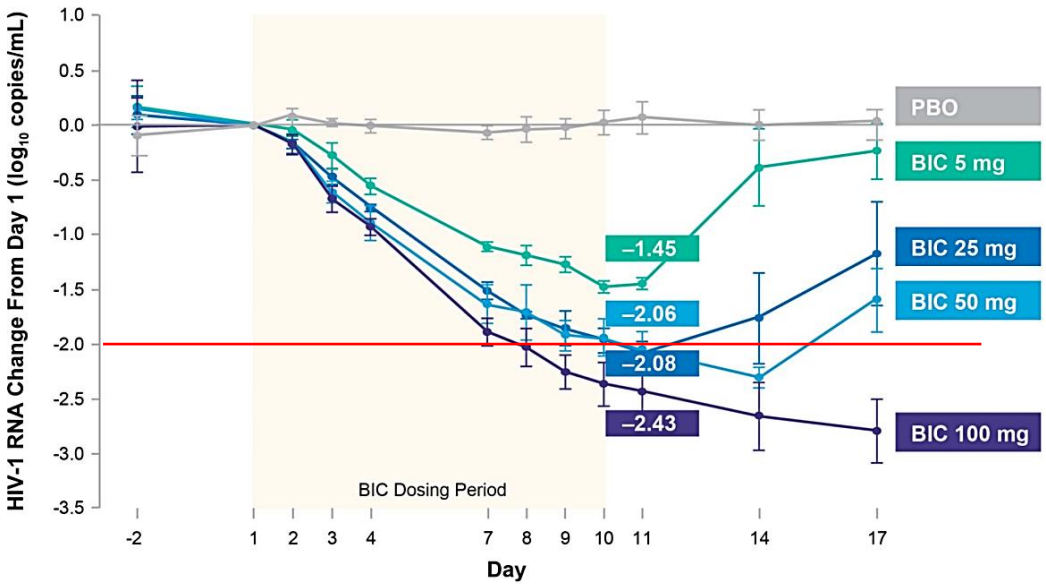
Characteristics of BIC and DTG

Characteristics of BIC and DTG 1

Characteristics	Bictegravir	Dolutegravir
Dosing frequency	Once daily	Once daily or twice daily: depends on situations
STR for ART-naive patients	▪ BIC/TAF/FTC	▪ TAF/FTC/DTG ▪ TDF/3TC/DTG ▪ DTG/ABC/3TC ▪ DTG/3TC
Virologic efficacy against EVG- or RAL-resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available	Yes, for some isolates; effective with DTG 50 mg twice-daily dose
Adverse effects	Weight gain, nausea, diarrhea, headache, insomnia; depression and suicidality are rare, occurring primarily in patients with preexisting psychiatric conditions	
	↑ CPK 4%	Hypersensitivity, hepatotoxicity, ↑ CPK, myositis

Modified from DHHS ART Guidelines. September 2022.

Antiviral Activity and PK of Bictegravir

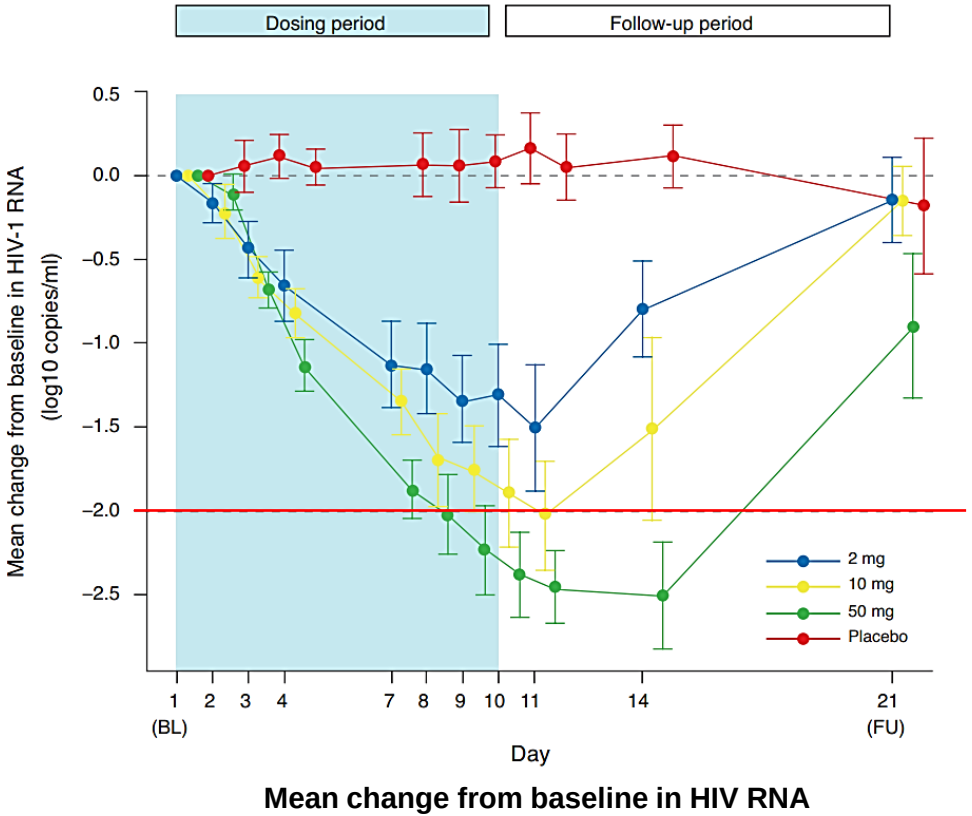


Mean change (95% CI) in HIV RNA

- Significant reductions in plasma HIV RNA from baseline at day 11 for all BIC doses compared with placebo (P <0.001)
- Mean decreases 1.45-2.43 log_{10} copies/mL
- 3 of 8 receiving BIC (50 or 100 mg) achieved plasma HIV RNA <50 copies/mL by end of study (Day 17)

Gallant JE, et al. J Acquir Immune Defic Syndr 2017;75:61-6.

Antiviral Activity and PK of Dolutegravir



Mean change from baseline in HIV RNA

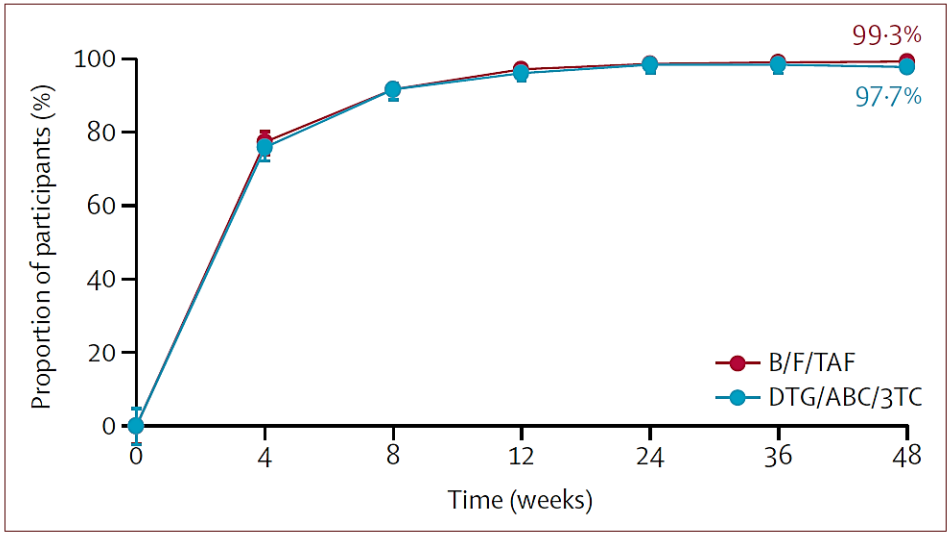
- Significant reductions in plasma HIV RNA from baseline to day 11 for all DTG dose groups compared with placebo ($P < 0.001$)
- Mean decrease 1.51-2.46 $\log_{10}$ copies/mL
- 7 of 10 receiving DTG 50 mg achieved plasma HIV RNA <50 copies/mL during the study (Day 21)

Min S, et al. AIDS 2011;25:1737-45.

BIC/FTC/TAF vs DTG/ABC/3TC for Initial Treatment of HIV Infection

- Double-blind, multicenter, active-controlled, randomized controlled non-inferiority trial at 122 outpatient centers in 9 countries in Europe, Latin America, and North America

Regimens	Proportion of participants with HIV RNA <50 copies/mL	
	At 4 week	At 8 week
BIC/FTC/TAF	**77.4%** (243 of 314)	**91.7%** (286 of 312)
DTG/ABC/3TC	**75.9%** (243 of 314)	**91.6%** (284 of 310)



Proportion of participants with HIV RNA <50 copies/mL (missing-as-excluded analysis)

Gallant J, et al. Lancet 2017;390:2063-72.

Characteristics of BIC and DTG 2

Characteristics	Bictegravir	Dolutegravir
CYP3A4 drug–drug interactions	CYP3A4 substrate	CYP3A4 substrate (minor)
Chelation with polyvalent cation supplements and antacids	Oral absorption of all INSTIs may be reduced by polyvalent cations	
Other key potential drug interaction mechanisms	P-gp substrate, UGT1A1 substrate, OCT2, and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate

MATE: multidrug and toxin extrusion transporter

Modified from DHHS ART Guidelines. September 2022.

Drug-drug Interactions: BIC vs DTG 1

Drugs	Bictegravir		Dolutegravir	
	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments
Rifampicin	BIC AUC ↓ 75%	Contraindication	DTG AUC ↑ 33% and C_{min} ↑ 22%	Use DTG 50 mg twice daily
Rifabutin	BIC AUC ↓ 38% and C_{min} ↓ 56%	Do not coadminister	Rifabutin 300 mg once daily ↔ DTG AUC and C_{min} ↓ 30%	No dose adjustment needed
Metformin	Metformin AUC ↑ 39%	Need to monitor for adverse events of metformin	Metformin AUC ↑ 79% and C_{max} ↑ 66%	Start metformin at the lowest dose and titrate based on glycemic control. Monitor for adverse events of metformin.
Antacids	Al/Mg Hydroxide Antacid ↔ BIC AUC if antacid is administered 2 hrs after BIC and under fasting conditions BIC AUC ↓ 52% if antacid is administered 2 hrs before BIC BIC AUC ↓ 47% to 79% if administered simultaneously with antacid $CaCO_3$ Antacid ↔ BIC AUC if administered with food BIC AUC ↓ 33% if administered under fasting conditions	With Al/Mg Hydroxide Antacid Administer antacids that contain Al/Mg at least 2 hrs after or 6 hrs before BIC With Antacids That Contain Ca Administer BIC and antacids that contain Ca together with food Do not coadminister BIC simultaneously with antacids that contain Ca on an empty stomach	▪ DTG AUC ↓ 74% if administered simultaneously with antacid ▪ DTG AUC ↓ 26% if administered 2 hrs before antacid	Administer DTG at least 2 hrs before or at least 6 hrs after antacids that contain polyvalent cations

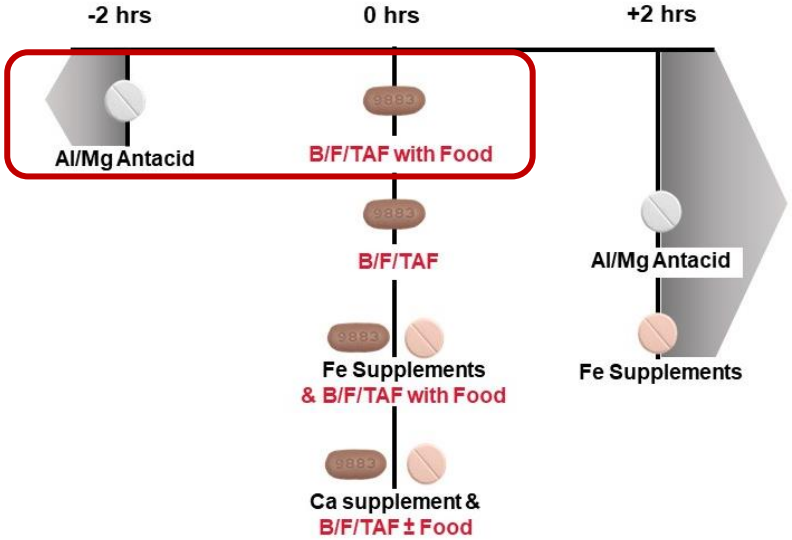
Modified from DHHS ART Guidelines. September 2022.

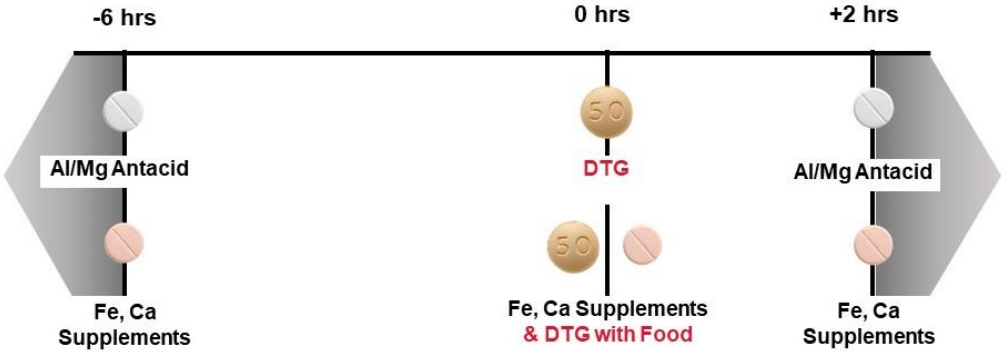
Drug-drug Interactions: BIC vs DTG 2

Drugs	Bictegravir		Dolutegravir	
	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments
Polyvalent Cation Supplements **Mg, Al, Fe, Ca, Zn, including multivitamins with minerals**	BIC AUC ↓ 33% if administered simultaneously with Ca under fasting Conditions BIC AUC ↓ 63% if administered simultaneously with Fe under fasting conditions ↔ BIC AUC if administered simultaneously with Fe or Ca and food	With Supplements That Contain Ca or Fe BIC should be administered at least 2 hrs before iron supplements, or taken together with food BIC and calcium-containing supplements can be taken together, without regard to food Do not coadminister BIC under fasting conditions simultaneously with, or 2 hrs after, supplements that contain Fe	DTG AUC ↓ if administered simultaneously with Ca or Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	With Supplements That Contain Ca or Fe Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hrs before or at least 6 hrs after supplement Do not coadminister DTG under fasting conditions simultaneously with, or 2 hrs after, supplements that contain Ca or Fe

Modified from DHHS ART Guidelines. September 2022.

BIC and DTG Co-administration with Antacids or Polyvalent Cations Supplement





Always refer to the SmPC full prescribing advice on DDIs

1. Modified from DHHS ART Guidelines. September 2022. 2. Triumeq EPAR Product Information (accessed 4 August 2023). 23. Biktarvy EPAR Product Information (accessed 4 August 2023)

Drug-drug Interactions: BIC vs DTG 3

Drugs	Bictegravir		Dolutegravir	
	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments	Effect on INSTI or concomitant drug concentrations	Dosing recommendations and clinical comments
Carbamazepine	↓ BIC possible	Do not coadminister	DTG AUC ↓ 49%	Increase DTG dose to 50 mg twice daily
Oxcarbazepine Phenobarbital Phenytoin	↓ BIC possible	Do not coadminister	↓ DTG possible	Do not coadminister
Dexamethasone Systemic	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.	↔ DTG expected	No dose adjustment needed
Prednisone, Prednisolone Systemic	↔ glucocorticoid expected	No dose adjustment needed	↔ glucocorticoid expected	No dose adjustment needed
Contraceptives: Oral	↔ ethinyl estradiol, norgestimate ↔ BIC	No dose adjustment needed	↔ ethinyl estradiol, norgestimate ↔ DTG	No dose adjustment needed

Modified from DHHS ART Guidelines. September 2022.

BIC: Advantage and Disadvantage

Advantage(s)	Disadvantage(s)
▪ Coformulated with TAF/FTC ▪ Higher barrier to resistance than EVG and RAL ▪ No food requirement	▪ Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing **polyvalent cations** (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals) ▪ **Inhibits tubular secretion of Cr** without affecting glomerular function ▪ **CYP3A4 and UGT1A1 substrate** (but not a CYP3A4 inducer or inhibitor); potential for drug–drug interactions ▪ **Weight gain** ▪ Should **not be used in pregnancy** because of lack of data for BIC

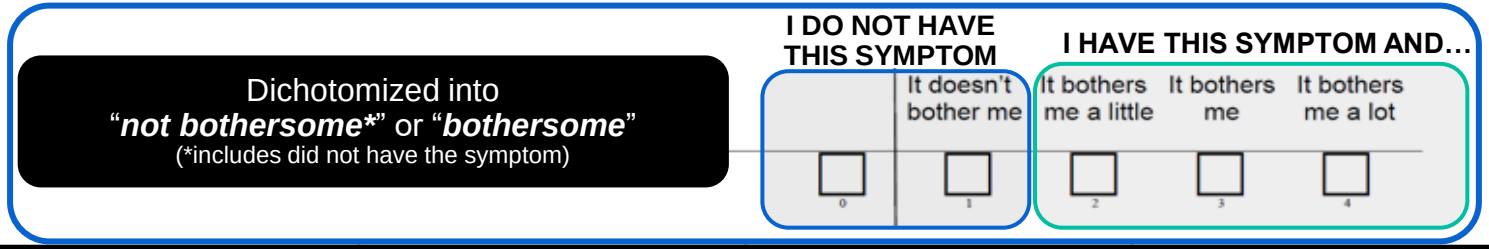
Modified from DHHS ART Guidelines. June 2021.

DTG: Advantage and Disadvantage

Advantage(s)	Disadvantage(s)
▪ Higher barrier to resistance than EVG or RAL ▪ Coformulated with TXF/XTC ▪ No food requirement ▪ Minimal CYP3A4 interactions ▪ Favorable lipid profile	▪ Oral absorption of DTG can be reduced by simultaneous administration with drugs containing **polyvalent cations** (e.g., Al-, Ca-, or Mg-containing antacids or supplements or multivitamin tablets with minerals) ▪ **Inhibits renal tubular secretion of Cr** and can **increase serum Cr** without affecting glomerular function ▪ **UGT1A1 substrate**; potential for drug–drug interactions ▪ **Depression and suicidal ideation** (rare; usually in patients with preexisting psychiatric conditions) ▪ **Weight gain** ▪ DTG exposure during conception may be associated with a small risk of **NTDs** in the infant compared with non-DTG ARV drugs (1.9 per 1000 vs 1.1 per 1000), that was not statistically significant

Modified from DHHS ART Guidelines. June 2021.

Patient-reported Outcomes: HIV Symptom Index Tool and Analysis



Nausea/Vomiting	Loss of appetite	Diarrhea	Bloating
Nervous/Anxious	Sad/Down/Depressed	Fatigue	Dizzy/Lightheaded
Trouble remembering	Headache	Fevers/Chills	Difficulty sleeping
Pain in hands/feet	Skin problems	Cough	Muscle aches
Sex problems	Weight gain	Weight loss	Hair loss

- Treatment differences assessed at Week 4, 12, and 48:
  - Logistic regression models adjusting for:
    - Age, sex, race, baseline HIV Symptom Index score, VACS Index, history of serious mental illness, baseline SF36 physical and mental scores, and years since diagnosis (for Study 1844 only)
  - Longitudinal modeling of prevalence of bothersome symptoms over time
    - Generalized mixed models including treatment, time, time-by-treatment interaction, and the covariates above

Wohl D, et al. Patient 2018;11:561-73. Wohl D, et al. AIDS 2018 (poster TUPEB148).

Patient-Reported Outcomes: HIV Symptom Index on B/F/TAF vs DTG/ABC/3TC*

Favors B/F/TAF	No differences between arms	Favors DTG/ABC/3TC**

	Study 1489 Treatment-naïve	Study 1844 Virologically suppressed
Nausea/vomiting	Favors B/F/TAF	Favors B/F/TAF
Loss of appetite	Favors B/F/TAF	Favors B/F/TAF
Difficulty sleeping	Favors B/F/TAF	Favors B/F/TAF
Fatigue/loss of energy	Favors B/F/TAF	
Dizzy/lightheadedness	Favors B/F/TAF	Favors B/F/TAF
Sad/down/depressed		Favors B/F/TAF
Nervous/anxious		Favors B/F/TAF

*Statistically significant (P <0.05) favoring B/F/TAF group over DTG/ABC/3TC group (at ≥2 time points in adjusted logistic regression model, or at 1 time point in adjusted logistic regression model and in longitudinal model)
**No symptom favored DTG/ABC/3TC.

In these double-blind studies in ART-naive and virologically suppressed adults, B/F/TAF was associated with a significantly lower bothersome symptoms than DTG/ABC/3TC

Wohl D, et al. Patient 2018;11:561-73. Wohl D, et al. AIDS 2018 (poster TUPEB148).

Outline

Short- and long-term data of BIC/FTC/TAF

BIC-NOW: Rapid Start with B/F/TAF in ART-naïve PLWH (Phase IV, Prospective, Open-label Study)

N = 160

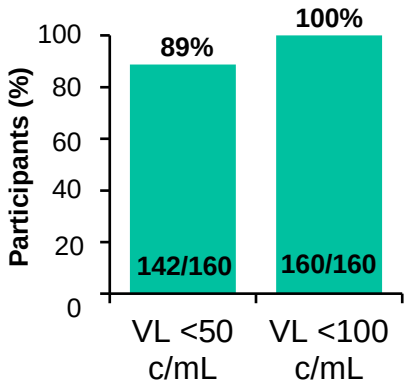
ART-naïve PLWH initiating B/F/TAF as part of a rapid start strategy

Outcomes at 24 weeks

Virologic suppression (HIV-1 RNA <50 c/mL or HIV-1 RNA <100 c/mL); B/F/TAF discontinuation; missed doses; safety and tolerability; laboratory parameters; BMI; weight

Dec 2020–Jun 2022

Efficacy and Safety/Tolerability at Week 24



HIV-1 RNA at Week 24 (ITT)

Persistence at Week 24: 100%

Missed doses at Week 24: 0%

Grade 3 or 4 AEs at Week 24: 0%

Changes in Laboratory Parameters and Body Mass at Week 24*

Parameter	Baseline	24 weeks
CD4, cells/μL, mean (SD)	393 (247)	599 (NR)
CD4/CD8 ratio, mean (SD)	0.4 (0.3)	3.8 (1.1)
Creatinine clearance, mL/h, mean (SD)	110 (15)	102 (21)
Total cholesterol, mg/dL, mean (SD)	159 (38)	169 (38)
HDL cholesterol, mg/dL, mean (SD)	41 (10)	47 (10)
LDL cholesterol, mg/dL, mean (SD)	106 (54)	110 (32)
TC/HDL ratio, mean (SD)	4.7 (1.3)	3.8 (1.1)
Triglycerides, mg/dL, mean (SD)	106 (50)	108 (58)
Weight, kg, median (IQR)	74 (66, 83)	76 (68, 87)
BMI, kg/m^2, median (IQR)	24 (22, 26)	25 (23, 27)
Abdominal circumference, cm, median (IQR)	85 (78, 94)	90 (81, 95)

B/F/TAF was associated with reduction in HIV-1 RNA, expected changes in laboratory parameters, and was generally well tolerated among PLWH rapidly starting treatment

Hidalgo Tenorio C, et al. HIV Glasgow 2022 (poster P058).

*All changes significant apart from LDL cholesterol and triglycerides;

OPERA: Discontinuation and Virologic Failure Rates with B/F/TAF vs DTG-based Regimen

N = 3810 Treatment-naïve PLWH in US

- B/F/TAF (n = 3114)
- DTG/3TC (n = 360)
- DTG-based 3DR (n = 336)

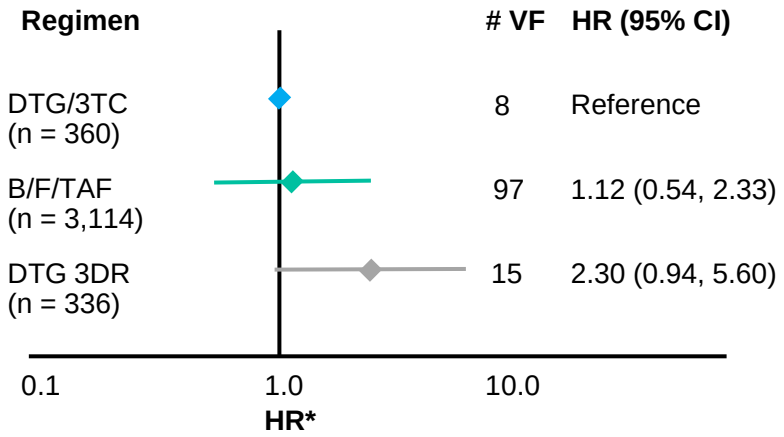
Outcome: Discontinuation (switch to another regimen or prescription gap >45 days) and virologic failure (2 consecutive HIV RNA >200 c/mL after 24 weeks on regimen)

May 2019–Apr 2021

Duration of Follow-up and Regimen Discontinuation

	B/F/TAF (n = 3114)	DTG/3TC (n = 360)	DTG 3DR (n = 336)
Follow-up, months, median (IQR)	15.8 (11.0, 23.2)	15.0 (8.9, 21.5)	14.6 (9.9, 22.9)
Regimen discontinuation N (%)	370 **(12)**	69 **(19)**	121 **(36)**
IR per 100 person-years (95% CI)	**8.5** (7.7, 9.4)	**14.9** (11.8, 18.9)	**27.9** (23.4, 33.4)
Type of discontinuation (%)			
Switch to another regimen‡	38	75	56
Prescription gap >45 days	62	25	44
Resumed index regimen	32	35	23

Association* Between Regimen and Confirmed VF†



*Marginal structural model with inverse probability of treatment weights controlled for baseline age (quadratic), female, black race, Hispanic ethnicity, Southern U.S., $\log_{10}$ HIV RNA, comorbidities; †defined as 2 consecutive HIV RNA >200 c/mL at 24 weeks; ‡ data on regimen to which PLWH were switched were not available.

Pierone G Jr, et al. HIV Glasgow 2022 (poster P057).

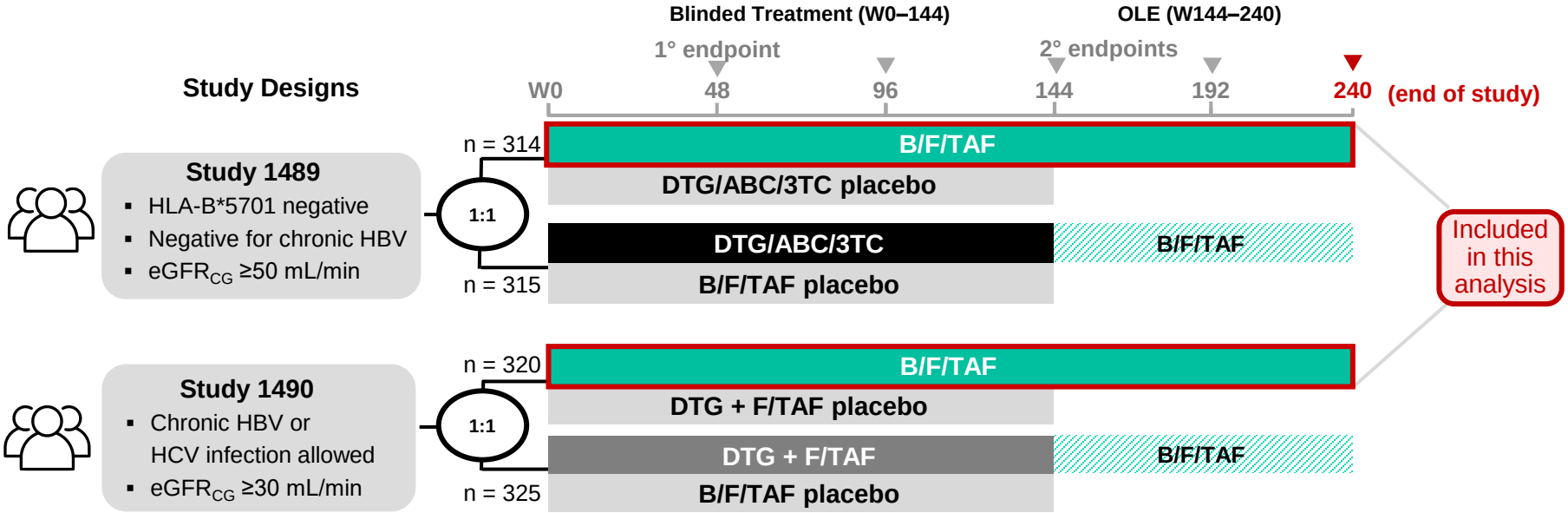
5-year Outcomes of B/F/TAF in Treatment-naïve Adults with High Baseline HIV RNA and/or Low CD4 Count

N = 634

ART-naïve PLWH with no known resistance to FTC, TFV, ABC, or 3TC HIV RNA ≥500 c/mL

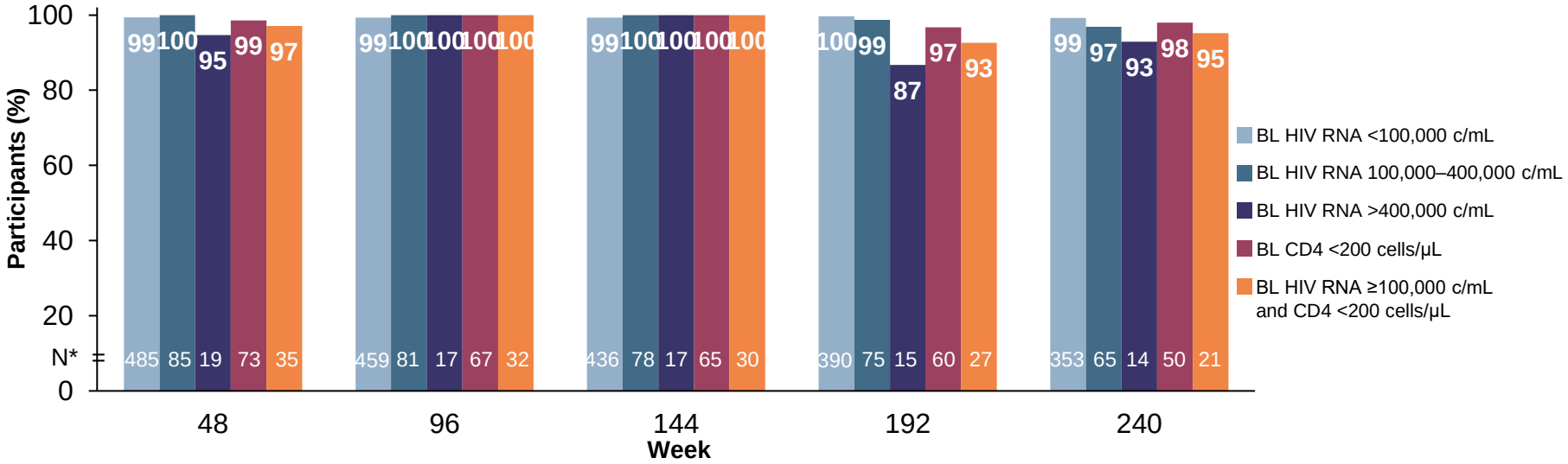
Outcome Pooled safety and efficacy through W240 in participants initially randomized to B/F/TAF, stratified by baseline HIV RNA and CD4 cell count

Baseline–W240



Ramgopal M, et al. IDWeek 2022 (poster 1251). Sax PE, et al. Lancet 2023;59:101991.

Virologic Outcomes by Baseline HIV RNA and CD4 Through Week 240: HIV RNA <50 c/mL



By Week 8, 16/20 participants with baseline HIV RNA >400,000 c/mL achieved HIV RNA <200 c/mL

High rates of virologic suppression with B/F/TAF were maintained through Week 240, regardless of baseline HIV RNA and CD4 count

*Participants with non-missing HIV-1 RNA value. BL= baseline; M = E = missing = excluded

Ramgopal M, et al. IDWeek 2022 (poster 1251). Sax PE, et al. Lancet 2023;59:101991.

Safety Through Week 240

Participants, %	HIV RNA <100,000 c/mL (n = 515)	HIV RNA 100,000–400,000 c/mL (n = 99)	HIV RNA >400,000 c/mL (n = 20)	CD4 <200 cells/μL (n = 80)	HIV RNA ≥100,000 c/mL and CD4 <200 cells/μL (n = 39)
Any study drug-related AE	28	30	20	25	21
Drug-related AE ≥2% overall					
Headache	4	7	10	8	10
Diarrhea	4	7	10	6	8
Nausea	5	4	0	4	3
Fatigue	3	4	0	3	3
Dizziness	2	3	5	0	0
Insomnia	2	1	0	3	3
Study drug-related SAE	1	0	0	0	0
AEs leading to premature D/C	2	1	0	3	0

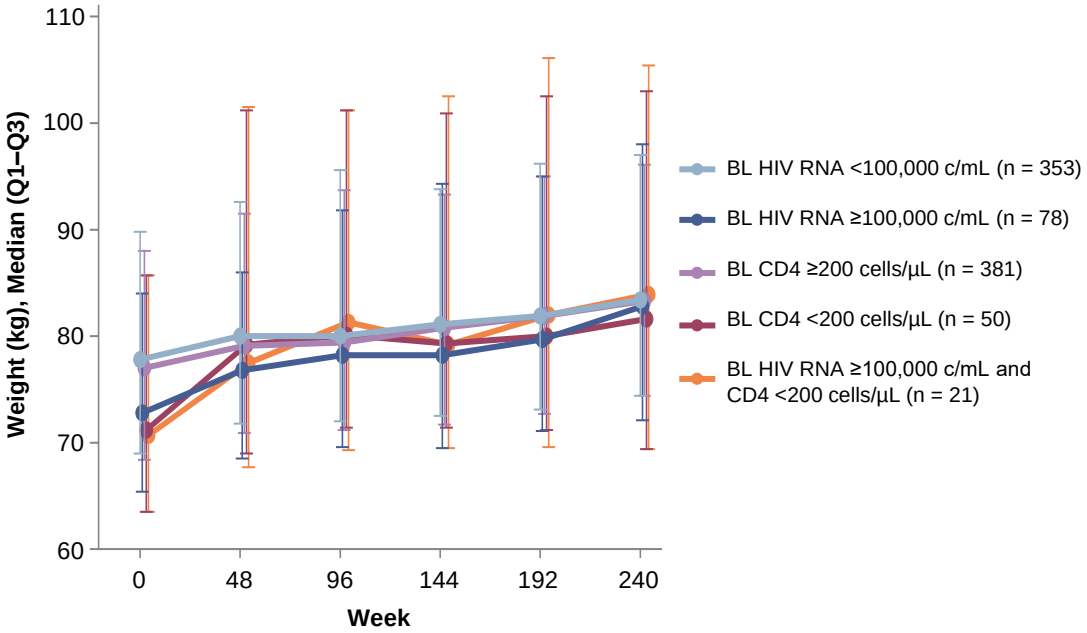
5 cases of IRIS were reported*; all occurred within the first 48 weeks and resolved without interruption of B/F/TAF treatment

*4 cases were associated with HBV, psoriasis, night sweats or *Mycobacterium avium* complex; 1 case had unknown cause

B/F/TAF was generally well tolerated, with few discontinuations due to AEs through 240 weeks, regardless of baseline HIV RNA and CD4 count

Ramgopal M, et al. IDWeek 2022 (poster 1251). Sax PE, et al. Lancet 2023;59:101991.

Actual Weight Over 240 Weeks*



Greater median weight changes in the first year for participants with advanced disease, consistent with a "return to health" phenomenon[2]

At Week 48, participants with:

- Baseline CD4 <200 cells/µL experienced greater weight change than those with CD4 ≥200 (8.3 vs 2.7 kg; *P* <0.001)
- Baseline HIV RNA ≥100,000 c/mL experienced greater weight change than those with HIV RNA <100,000 (4.1 vs 3.0 kg; *P* <0.05)

Subgroups with various baseline HIV RNA and CD4 had comparable median actual weights at Week 240

*Includes participants with weight data at BL and Week 240

Ramgopal M, et al. IDWeek 2022 (poster 1251). Sax PE, et al. Lancet 2023;59:101991. Sax PE, et al. Clin Infect Dis 2020;71:1379-89.

Outline

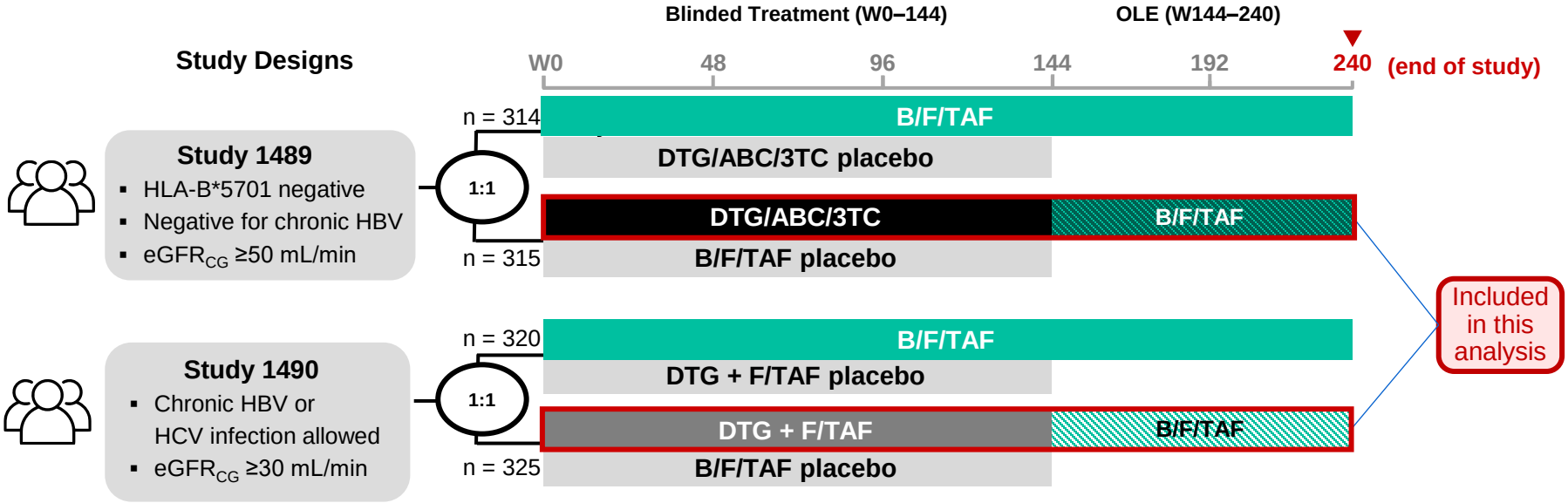
Data on switching to BIC/FTC/TAF

Switching from DTG-based Regimens to B/F/TAF

ART-naïve PLWH with no known resistance to FTC, TFV, ABC, or 3TC; HIV RNA ≥500 c/mL

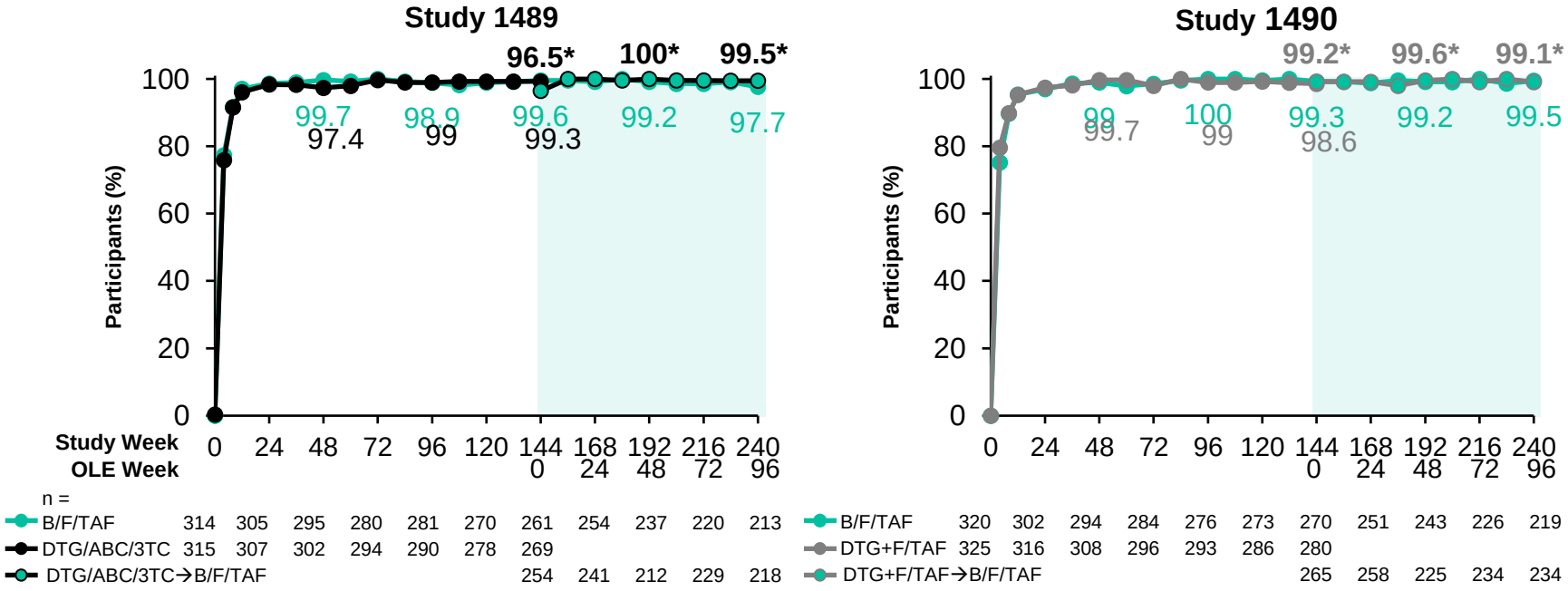
Outcome 96-week outcomes on B/F/TAF in an OLE that followed 144 weeks of blinded DTG-based treatment in 2 Phase 3 studies of treatment-naïve PLWH

Baseline–W240



Orkin C, et al. HIV Glasgow 2022 (poster P088).

Virologic Outcomes Through Week 240 and OLE Week 96: HIV RNA <50 c/mL (M = E)



High rates of virologic suppression were maintained after switching to B/F/TAF through Week 240 (OLE Week 96)

*M = E data for participants who switched from DTG-based regimens to B/F/TAF.

Orkin C, et al. HIV Glasgow 2022 (poster P088).

Virologic Resistance During OLE: Week 144–240

Participants, n	Study 1489 DTG/ABC/3TC→B/F/TAF (n = 254)	Study 1490 DTG + F/TAF→B/F/TAF (n = 265)
Met criteria for resistance testing*	3	1
NRTI resistance detected	0	0
INSTI resistance detected	0	0

2 participants on blinded DTG/ABC/3TC had HIV RNA ≥200 c/mL at time of switch, both of whom were later found to have the M184V mutation and resuppressed on open-label B/F/TAF

No cases of treatment-emergent resistance to any of the components of B/F/TAF after 96 weeks in the OLE (Study Week 240)

*Final resistance analysis population; resistance testing performed for participants with confirmed HIV RNA ≥200 c/mL or ≥200 c/mL at last visit, with no resuppression of HIV RNA to <50 c/mL while on study drug.

Orkin C, et al. HIV Glasgow 2022 (poster P088).

AEs and Laboratory Abnormalities: OLE Week 144 to Week 240

N (unless specified)	Study 1489 DTG/ABC/3TC→ B/F/TAF (n = 254)	Study 1490 DTG + F/TAF→ B/F/TAF (n = 265)
AEs		
Any study drug-related AEs	5%	3%
AEs leading to discontinuation	2*	0
Death	2	3
Laboratory abnormalities		
Any Grade 3 or 4 laboratory abnormality	13%	16%
Increased amylase†	2%	2%
Non-fasting hyperglycemia	1%	3%
Increased fasting low-density lipoprotein	1%	3%
Glycosuria‡	1%	3%

Study Drug-related Nausea and Diarrhea

Prevalence declined after switching to B/F/TAF in the OLE

- Nausea (3.7% [Study 1489], 0.7% [1490] to 0%)
- Diarrhea (0.4% [Study 1489],1.1% [1490] to 0%)

Renal Safety

- 0 cases of proximal renal tubulopathy
- 0 discontinuations due to renal AEs

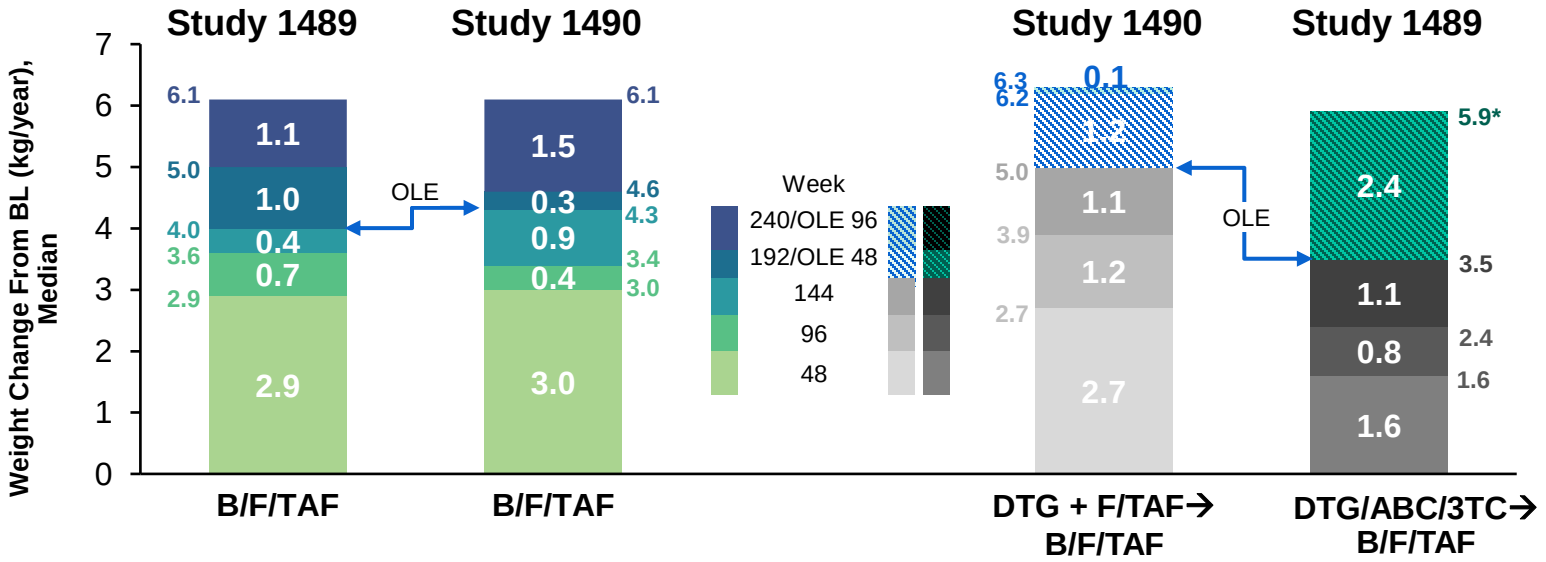
Fasting Lipid Changes

- Small changes in lipid fractions
- Initiated lipid-lowering therapy after switch:
  - Study 1489: 2%; Study 1490: 5%

*Participant 1: Died due to seizure unrelated to study drug on OLE Day 335/Study Week 192; Participant 2: Weight increase attributed to study drug during blinded-phase Day 29, D/C on OLE Day 506/Study Week 228; †No clinical symptoms of pancreatitis; ‡No cases of glycosuria occurred in participants without diabetes or concomitant hyperglycemia

Orkin C, et al. HIV Glasgow 2022 (poster P088).

Annual Median Weight Change, BL Through Week 240



Similar cumulative weight changes at Year 5 for all groups.
Greater weight changes in those who switched from DTG/ABC/3TC vs DTG + F/TAF, consistent with the loss of the weight-suppressive effect of ABC noted in Year 1.

*Median cumulative change at Week 192 (no change from Week 192 to 240).

Orkin C, et al. HIV Glasgow 2022 (poster P088).

B/F/TAF: Data from 16 Studies in ~27,000 PLWH

Rapid start

Rapid start and reinitiation with B/F/TAF was effective and generally well tolerated[1-3]

Viral suppression (treatment-naïve)

Initiating therapy with B/F/TAF resulted in high rates of virologic suppression,[1-13] including in PLWH presenting late to care[5,6]

Viral suppression (treatment-experienced)

Switching to B/F/TAF maintained high rates of virologic suppression,[8,9,11-13] including in PLWH with pre-existing NRTI resistance on bPI[11]

Safety

B/F/TAF was generally well-tolerated, with low rates of discontinuation[1-3,7,9,12-16]

Persistence

Improved persistence for B/F/TAF compared with DTG/3TC and other DTG regimens in both treatment-naïve and treatment-experienced PLWH[13-15]

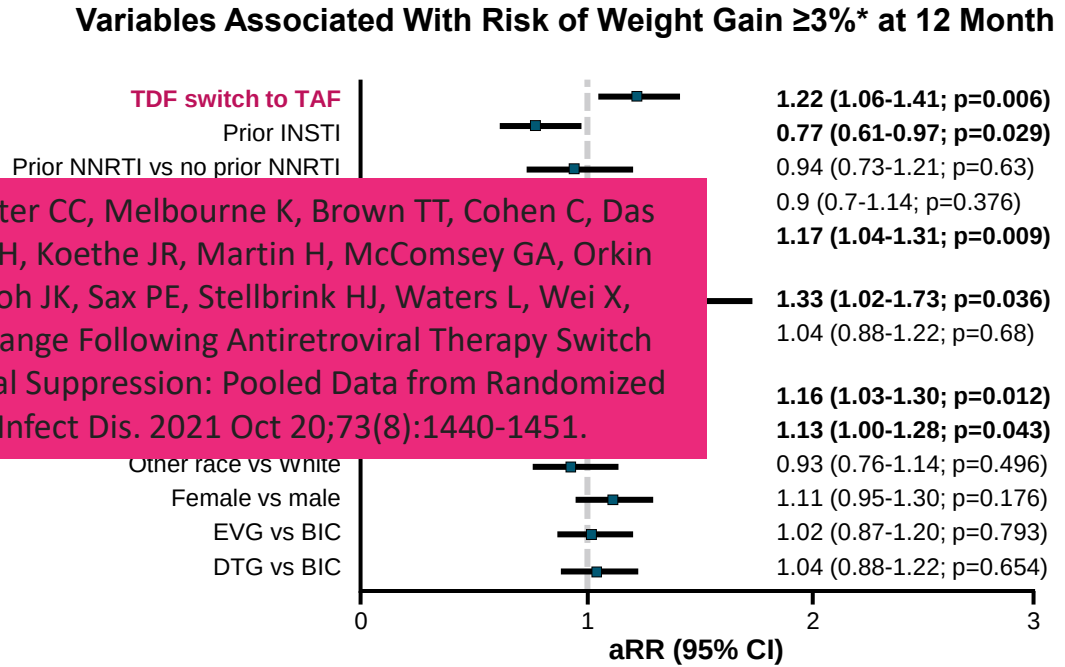
1. Dai L, et al. HIV Glasgow 2022 (oral O24). 2. Hidalgo Tenorio C, et al. HIV Glasgow 2022 (poster P058). 3. Roden L, et al. IDWeek 2022 (poster 1466).
4. Trottier B, et al. HIV Glasgow 2022 (poster P067). 5. Tavelli A, et al. HIV Glasgow 2022 (poster P060). 6. Pérez-Valero I, et al. HIV Glasgow 2022 (poster P052).
7. Nasreddine R, et al. HIV Med 2023 Apr 10. 8. D'Arminio Monforte A, et al. HIV Glasgow 2022 (poster P098). 9. Leleux O, et al. HIV Glasgow 2022 (poster P097).
10. Marcelin A-G, et al. HIV Glasgow 2022 (poster P225). 11. Iwuji C, et al. HIV Glasgow 2022 (poster P089). 12. Kwakwa H, et al. IDWeek 2022 (poster 1268).
13. Pierone G, et al. IDWeek 2022 (poster 1284 and rapid-fire poster 2255). 14. Pierone G Jr, et al. HIV Glasgow 2022 (poster P057).
15. Chastek B, et al. HIV Glasgow 2022 (poster P103). 16. Havens JP, et al. IDWeek 2022 (poster 1258).

Thank You for Your Attention

Weight Gain After Switching INSTIs

- Retrospective analysis
- Adults with viral suppression at BL and through 12-months period who switched to new
- No differences a different INSTIs i with weight gain or 10% after accounting for
  - Patient characteristics
  - Prior and current drug class
  - TDF-to-TAF switch vs no TDF-to-TAF switch

Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, Esser S, Huang H, Koethe JR, Martin H, McComsey GA, Orkin C, Post FA, Rockstroh JK, Sax PE, Stellbrink HJ, Waters L, Wei X, Lake JE. Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials. Clin Infect Dis. 2021 Oct 20;73(8):1440-1451.



*≥5% weight gain associated with: female sex (aRR 1.3; 95% CI: 1.1-1.6), black race (aRR 1.2; 95% CI 1.0-1.4), BL BMI underweight/normal (aRR 1.4; 95% CI 1.2-1.6), TDF-to-TAF switch (aRR 1.3; 95% CI 1.1-1.6)

*≥10% weight gain associated with: female sex (aRR 2.2; 95% CI 1.5-3.2), BL BMI underweight/normal (aRR 2.3; 95% CI 1.7-3.1), prior non-INSTI regimen (aRR 2.2; 95% CI 4.1-1.2), TDF-to-TAF switch (aRR 1.66; 95% CI 1.1-2.4)

McComsey G, et al. CROI 2021. Abstract 503.

Take-home Points

- INTSIs-based regimens, especially BIC and DTG, are recommended for initial ART
- INSTIs are generally well tolerated, but emerging data of weight gain is reported
- As a class, oral absorption can be impaired if taken with divalent or trivalent cations
  - Infrequently cause metabolism-related DDIs
- Multiple switch strategies to enhance adherence, tolerability and/or decrease toxicity that have demonstrated maintained virologic efficacy
- BIC/FTC/TAF is an option for switching with favorable reasons
  - Resulted in high levels of virologic suppression regardless of preexisting resistance and viral blips

INSTI vs Boosted PIs as First-line ART: Current Role of Boosted PIs

Settings where boosted PI regimens might be considered[1]

- If starting ART before availability of resistance data
- If high risk for poor adherence

Challenges with boosted PI use

- Drug–drug interactions[2,3]
- GI intolerance[2,3]
- Hyperlipidemia[3]
- CV risk with some PIs[4]

1. DHHS. clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines. September 2022.
2. ATV PI. 3. DRV/COBI/FTC/TAF PI. 4. Worm. J Infect Dis. 2010;201:318.

NNRTIs vs INSTIs as First-line ART: Possible Role of NNRTIs Today

Possible role for NNRTIs[1]

- Patient experiencing AE(s) with INSTIs
- If patient is experiencing weight gain with INSTIs[2]

Challenges with NNRTI use

- Low barrier to resistance at VF with EFV, RPV[3,4]
- Neuropsychiatric AEs with EFV[3]
- Higher rates of VF in RPV patients[5] with HIV-1 RNA >100,000 copies/mL and CD4+ cell counts <200 cells/mm³
- RPV must be taken with a meal[4]
- Fixed-dose combination with DOR includes TDF not TAF[6]
- Lipid increases with EFV[3]
- Drug-drug interactions with EFV, RPV[3,4]

1. DHHS. clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines. September 2022.
2. McCann. EACS 2019. Abstr PS3/3. 3. EFV PI. 4. RPV PI. 5 Cohen. AIDS. 2014;28:989. 6. DOR/TDF PI.

The Role of TDF and TAF in Today's First-line Regimens

Supporting TDF

- Longer experience with greater number of patients with TDF vs TAF
- Coformulations with many regimens
- Lipid decreases of uncertain clinical significance seen with use of TDF regimens
- Weight gain signal with TAF[1,2]
- Available as generic NRTI combinations with 3TC and FTC

Supporting TAF

- At Wk 144, TAF superior to TDF[3]
  - At Wk 48, TAF also superior to TDF for HBV DNA <29 IU/mL in patients with HIV/HBV coinfection[4]
- Less impact than TDF on bone mineral density (comparable to ABC)[5]
- Less impact on markers of renal tubular dysfunction
- Low dose allows small tablet (co)formulations

1. NAMSAL ANRS 12313 Study Group. NEJM;2019;381:816. 2. McCann. EACS 2019. Abstr PS3/3. 3. Arribas. JAIDS. 2017;75:211.
4. Sax. Lancet. 2015;385:2606. 5. Avihingsanon. AIDS 2022. Abstr OALBX0105.

Key Take-home Points

- All preferred initial regimens contain an unboosted INSTI plus NRTIs
  - DTG and BIC have high barrier to resistance
  - FTC/TAF has improved safety, tolerability vs FTC/TDF and ABC/3TC, but appears to be associated with greater weight gain
  - DTG/3TC now recommended alongside 3-drug ART options
- Potential AEs with INSTIs include weight gain, CNS AEs, and possible small potential risk to newborn if taken at the time of conception
- Several single-tablet regimens available, now representing all ARV drug classes

Tivicay SmPC (Dolutegravir)

Antidiabetics		
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg once daily: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg twice daily: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Antimycobacterials		
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓72% (induction of UGT1A1 and CYP3A enzymes)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin in the absence of integrase class resistance. In paediatric patients the weight-based once daily dose should be administered twice daily. In the presence of integrase class resistance this combination should be avoided (see section 4.4).

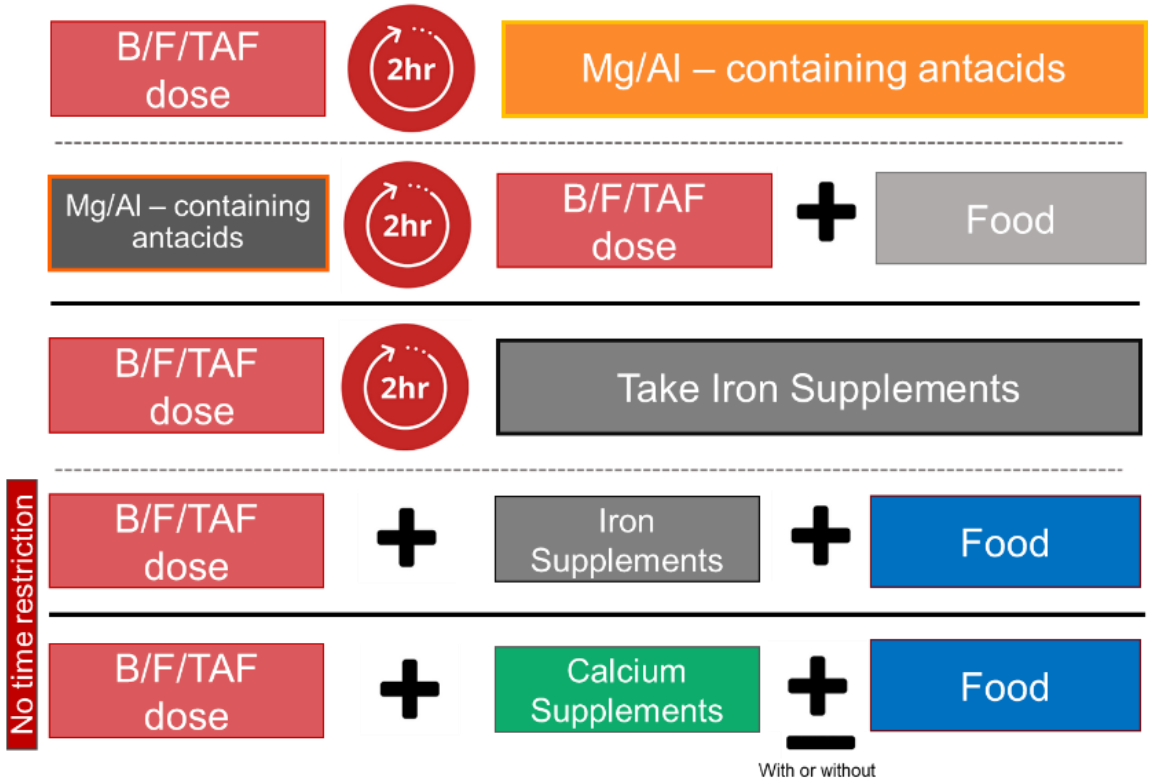
BIKTARVY SmPC (B/F/TAF)

Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Coadministration with alternative anticonvulsants should be considered.

Tivicay SmPC (Dolutegravir)

Anticonvulsants		
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternatives to carbamazepine should be used where possible for INI resistant patients.
Oxcarbazepine Phenytoin Phenobarbital	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.

B/F/TAF-Co-administration With Cations



B/F/TAF UK SmPC via medicines.org.uk; B/F/TAF EU (for Ireland and Northern Ireland) SmPC via medicines.ie both accessed July 2021;