HIV integrase Inhibitors: A novel mechanisms of action

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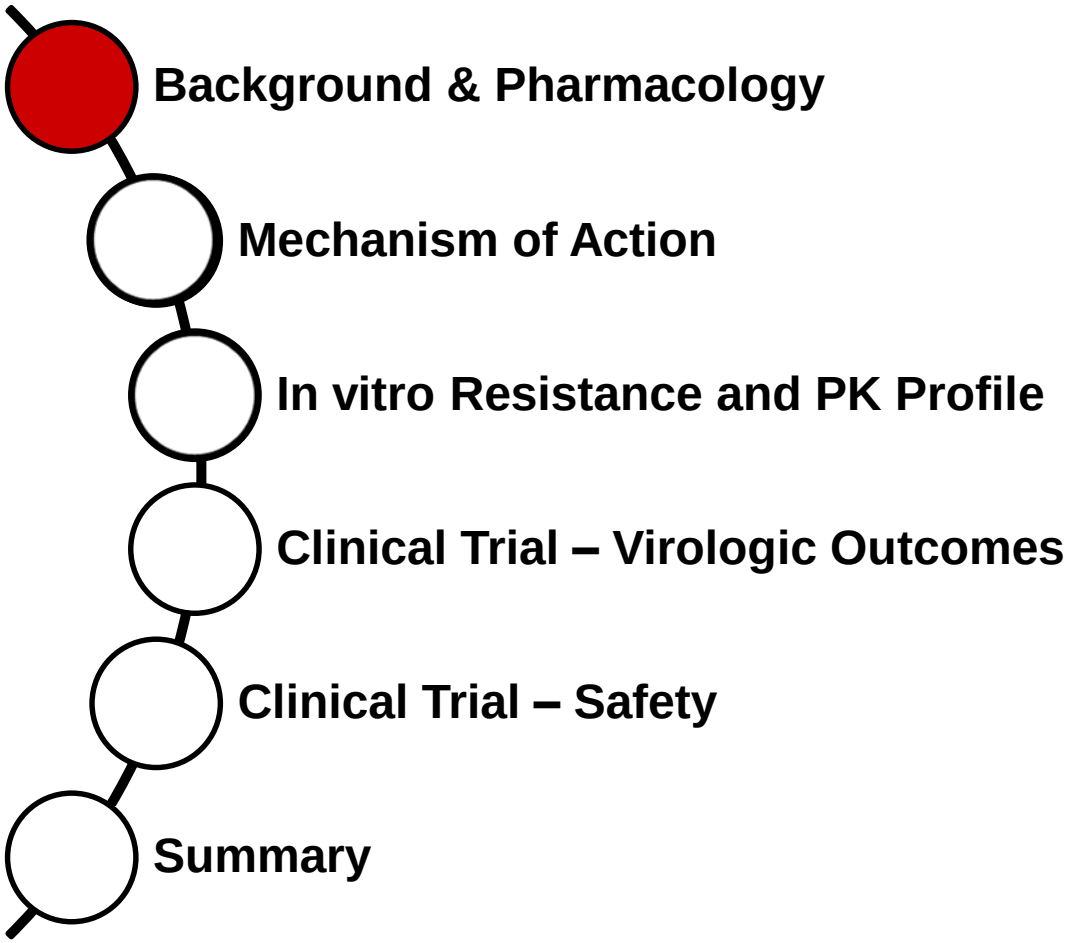
Outline



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Recommended Initial Regimens for Most People with HIV

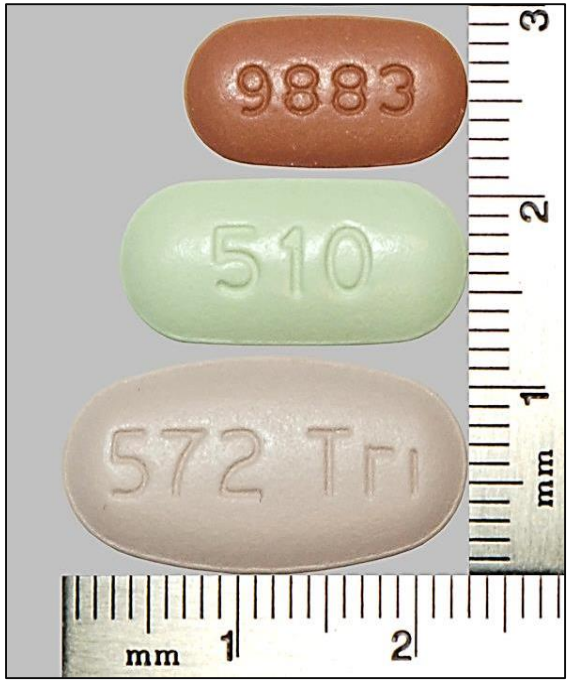
- **Only integrase inhibitor-based regimens are recommended as initial regimens for "Most People with HIV"**

CLASS	RECOMMENDED REGIMEN
Integrase Inhibitor	**BIC/FTC/TAF*† (AI)**
	EVG/COBI/FTC/TAF† (AI) **EVG/COBI/FTC/TDF† (AI)**
	DTG/3TC/ABC‡ (AI)**
	DTG + FTC/TAF† (AI) or FTC/TDF† (AI)**
	RAL§ + FTC/TAF† (AII) or FTC/TDF† (AI)**

* Not for creatinine clearance <30 mL/min, severe liver impairment, persons younger than 18 years of age, and there is insufficient safety information regarding use in pregnant women.
† TAF and TDF are two forms of tenofovir approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost and access are among the factors to consider when choosing between these drugs.
**3TC may substitute for FTC or vice versa
‡ Only for HLA-B*5701 negative
§ RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily

DHHS. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Available at: http://aidsinfo.nih.gov/guidelines October 2017*.
DHHS Statement on the Use of Bictegravir, March 27, 2018. Available at: http://aidsinfo.nih.gov/guidelines

BIC Co-formulated with FTC and TAF



B/F/TAF (721 mg)

E/C/F/TAF (1082 mg)

DTG/ABC/3TC (1750 mg)

Number in parenthesis is the total weight in mg of the tablet.
Note: Tablet size is not intended to compare clinical efficacy and safety, indications, dosing regimens, or treatment adherence.

- Smallest three-drug, INSTI-containing single-tablet regimen for both treatment-naïve and virologically-suppressed patients[2]
- Patient compliance with medication regimens may be influenced by the size and shape of a tablet or capsule, with size frequently being cited as the main reason for the difficulty in swallowing[3]

DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; E/C, elvitegravir/cobicistat; INSTI, integrase strand transfer inhibitor

1. Gilead Sciences. Data on File.
2. Gilead Sciences. Biktarvy US Prescribing Information. February 2018
3. DHHS & FDA CDER. Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules. June 2015

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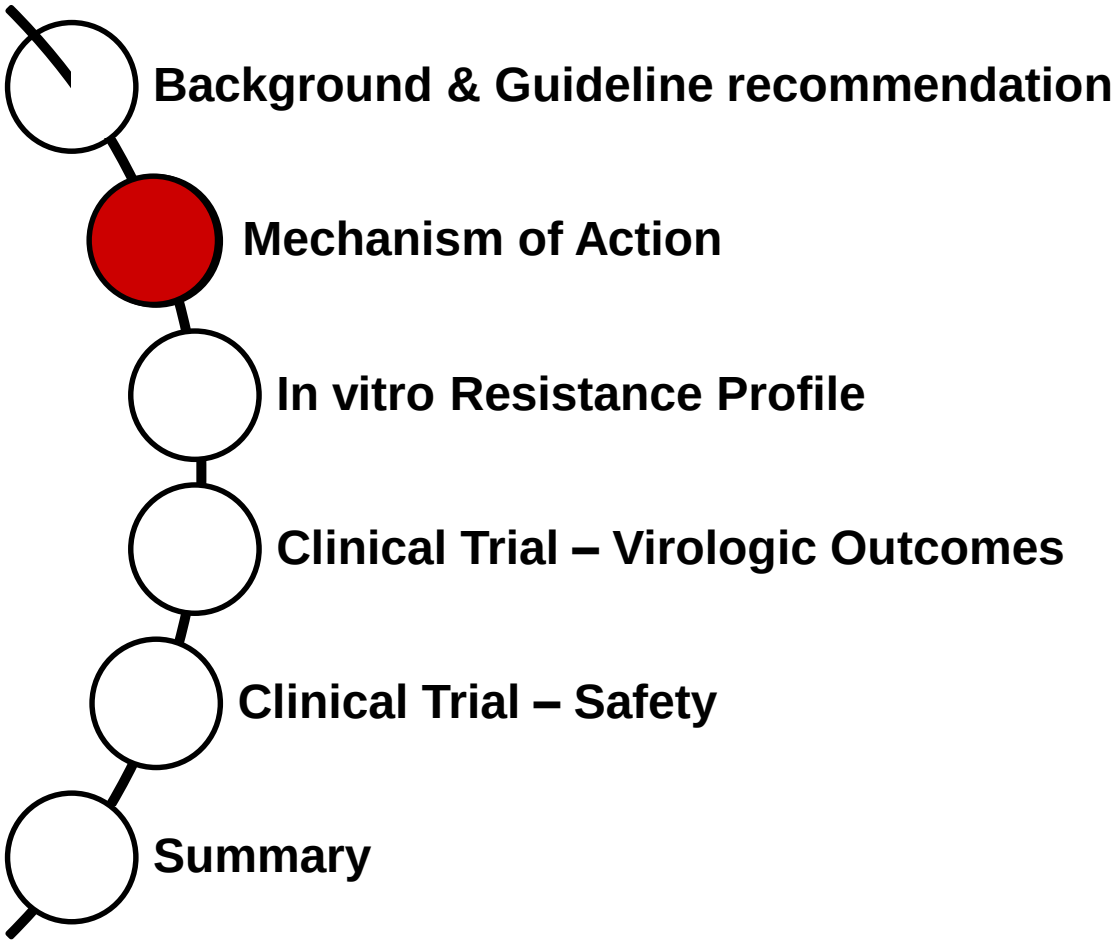

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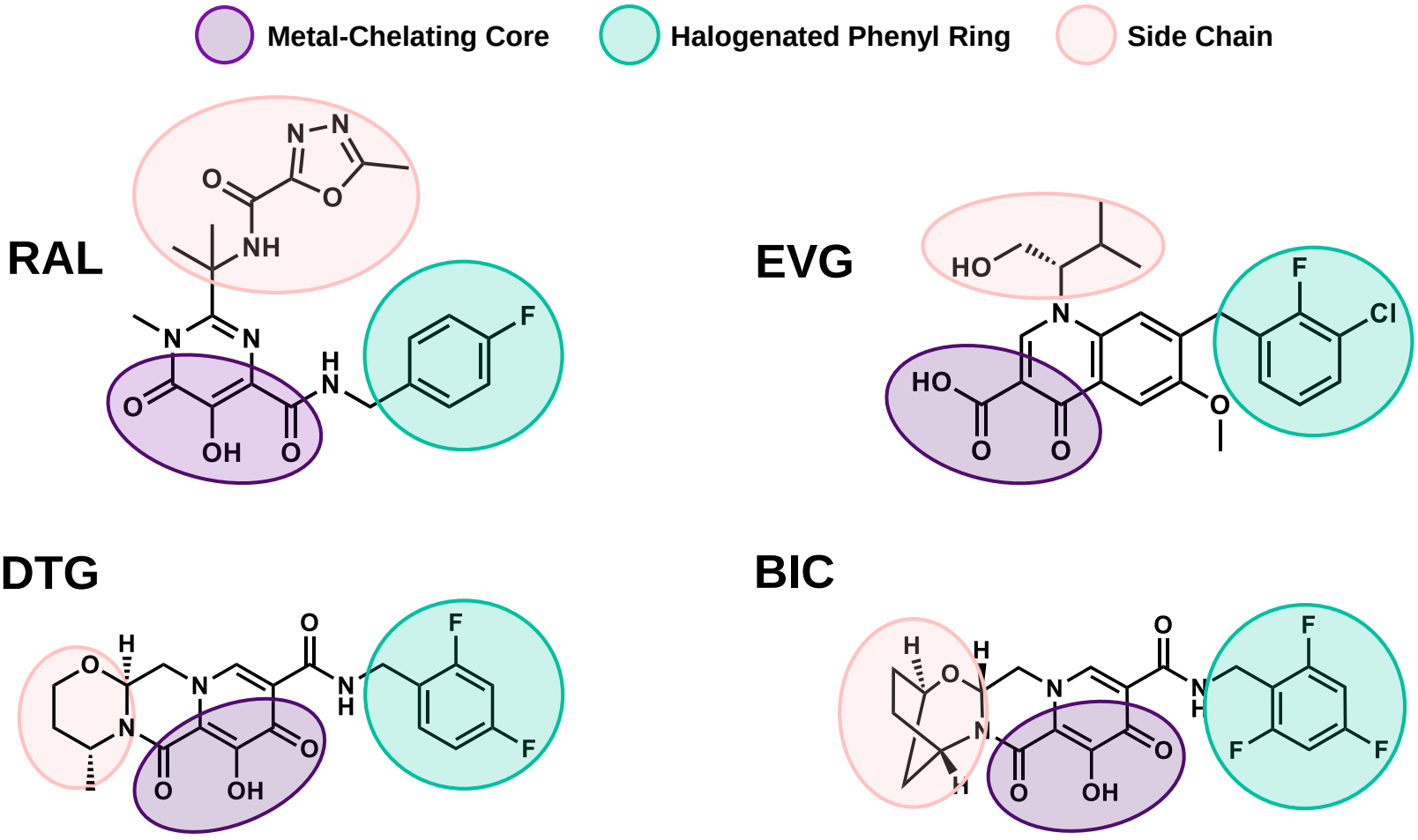
Mechanism of Action



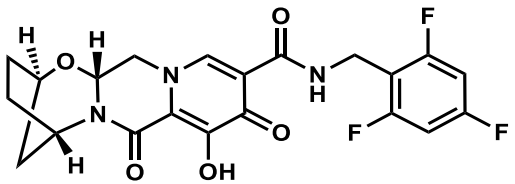
Metal-Chelating Core: Oxygen atoms chelate a pair of Mg^{2+} ions and bind the integrase catalytic active site

Halogenated Phenyl: Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA

1. Lazerwith SE, et al. ASM 2016. Poster #414. 2. Gallant J, et al. ASM 2016. Poster #415. 3. Tsiang M, et al. ASM 2016. Poster #416. 4.Tsiang M, et al., AAC 2016;60:7086-7097.

Novel Chemical Structure and Profile

Bictegravir



- Metal-chelating core
- 2,4,6-trifluorophenyl ring
- [3.2.1] oxaza bridging bicyclic side chain

	RAL	EVG	DTG	BIC
Human Plasma Half-Life	9 hours	8.7 hours	14 hours	18 hours
WT IN-DNA Dissociation Half-life, hours	5.2	1.5	16	38
G140S/Q148H IN-DNA Dissociation Half-life, hours	--	--	0.65	2.5
G140S/Q148H Mean Fold Change vs WT	>143	>150	7.6	3.4
OCT-2 IC_{50}	--	--	0.13 µM	0.49 µM

- BIC is a novel, potent INSTI with a high barrier to resistance and a favorable PK profile (longest plasma $T_{1/2}$ with dose-proportional PK, and fewer DDIs)
- Active against HIV-1 and HIV-2
- BIC vs. DTG demonstrates
  - More potent antiviral activity *in vitro* against multiple integrase mutants including G140/Q148
  - Less impact on estimated creatinine clearance

DDIs, drug-drug interactions; IC, inhibitory concentration; IN, integrase; OCT-2, organic cation transporter-2; PK, pharmacokinetic; $T_{1/2}$, half-life; WT, wild type.

1. Gallant J, et al. ASM 2016. Boston, MA. Poster #415. 2. Isentress US Prescribing Information. Merck & Co. February 2015 3. Lazerwith SE, et al. ASM 2016. Boston, MA. Poster #414.
4. Tivicay US Prescribing Information, ViiV Healthcare. June 2016. 5. Tsiang M, et al., AAC 2016;60:7086-7097 6. Vitekta US Prescribing Information, Gilead Sciences. June 2015.
7. White K, et al. CROI 2017. Seattle, WA. Poster 0893. 8. Zhang H, et al. CROI 2017. Seattle, WA. Oral #40.

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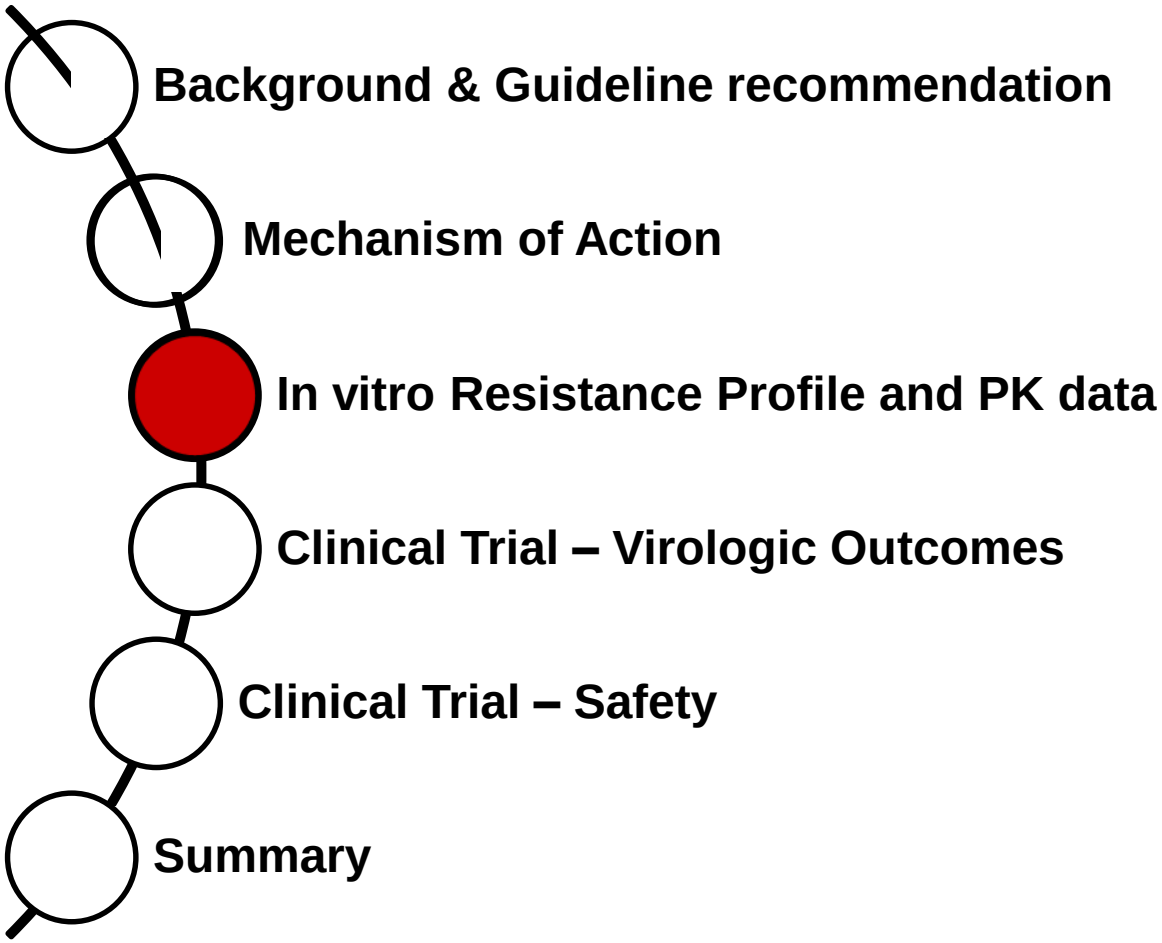

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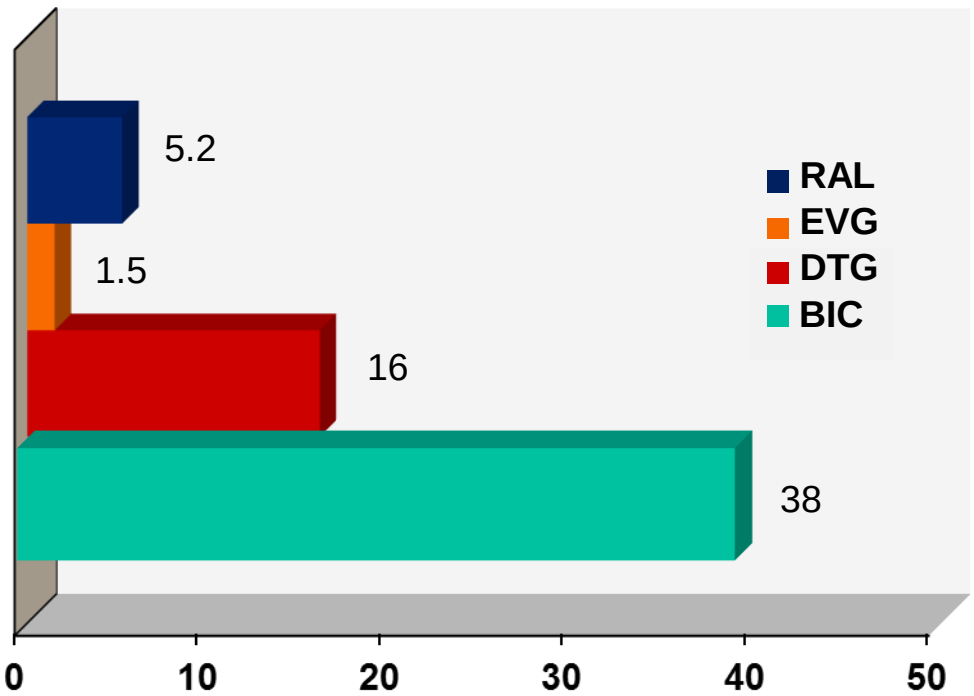
Wild Type HIV-1 Integrase-DNA Complexes

Dissociation Half-life of INSTIs



Wild Type HIV-1 IN Dissociation $T_{1/2}$

- BIC vs DTG (p=0.017)
- BIC vs RAL (p=0.003)
- BIC vs EVG (p=0.0006)

The dissociation half-life of BIC from wild type HIV-1 integrase-DNA complexes is twice as long as DTG

1. White K, et al. HIV Drug Therapy 2016. Glasgow, UK. Poster P025. 2. White K, et al. CROI 2017. Seattle, WA. Poster 0893.

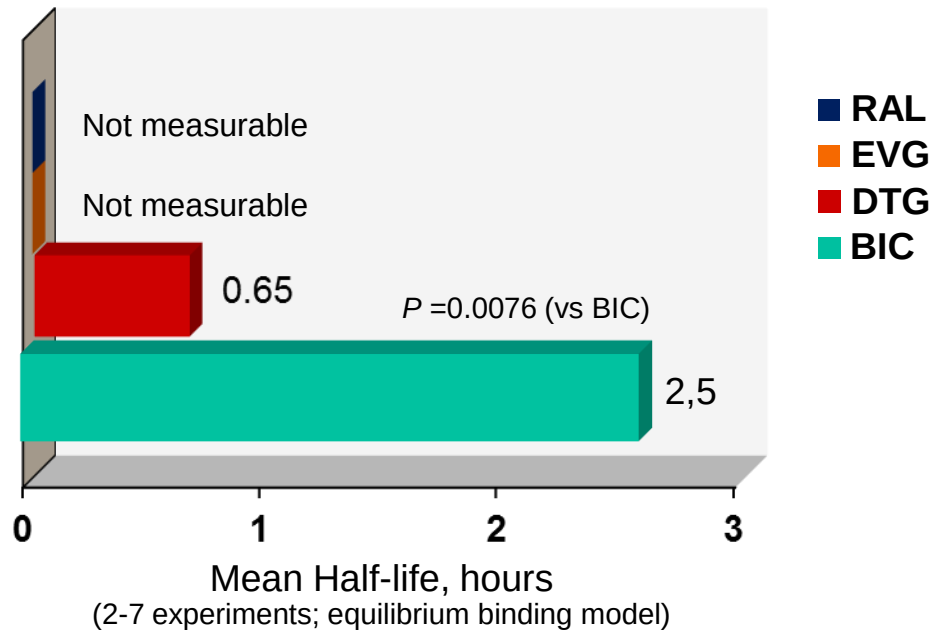
G140S+Q148H Mutant Integrase-DNA Complexes

Phenotypic Analysis of Clinical Isolates G140S + Q148H ± Other INSTI-R (n=16)

INSTI	Fold-Change vs WT*	% of Isolates with EC_{50} FC > 4.0	*P*-value vs BIC
RAL	>143	100%	<0.001
EVG	>150	100%	<0.001
DTG	7.6 ± 4.3	75%	<0.001
BIC	3.4 ± 1.7	25%	--

susceptibility to DTG on the PhenoSense IN assay is 4-fold.

Dissociation Half-life of INSTIs



Previous studies have demonstrated that the dissociation $T_{1/2}$ of DTG from integrase-DNA complexes was longer than RAL or EVG and predicted to correlate with more potent antiviral activity against G140S/Q148H mutants and a higher genetic barrier to resistance.

BIC vs. DTG:

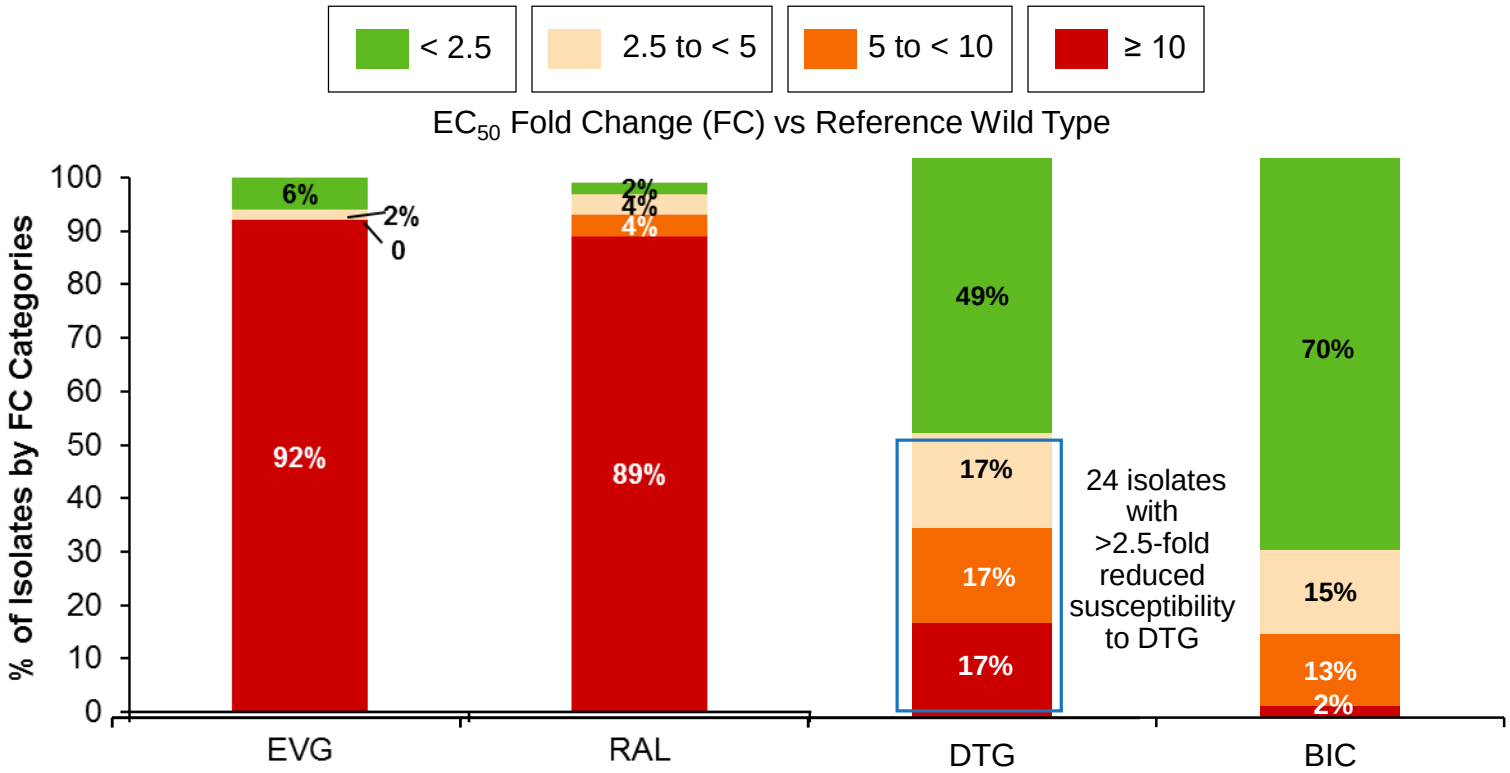
- **More potent antiviral activity against G140S + Q148H integrase mutants**
- **3X longer dissociation $T_{1/2}$ from G140S/Q148H mutant integrase-DNA complexes**

EC=effective concentration; FC=fold change; IN=Integrase; $T_{1/2}$=half-life.

1. Hightower K, et al. Antimicrob Agents Chemo 2011;55(10):4552-4559. 2. White K, et al. CROI 2017. Seattle, WA. Poster 0893.

Patient Isolates with INSTI Resistance Mutations: Resistance Profile of BIC and Other INSTIs

Stratification of 47 HIV-1 Clinical Isolates Based on Fold Change in Resistance



Each of 47 patient-derived clinical isolates (from Monogram Biosciences) had ≥ 1 primary and/or other INSTI mutations with phenotypic resistance to INSTIs and comprised *all* available INSTI resistant variants in the Monogram library). EC_{50}, effective concentration of half maximal response.

Mean fold changes: BIC 2.8 (ref) ; DTG 5.8, p=0.042; RAL >100, p<0.001; EVG >106, p<0.001

BIC has a statistically improved resistance profile compared to RAL, EVG, and DTG

1. White K, et al., European Workshop HIV & Hep 2016. Rome, Italy. Poster O-01. 2. Tsiang M, et al., AAC 2016;60:7086-7097.

24 HIV-1 Patient Isolates with Reduced Susceptibility to DTG: Resistance Profile of BIC vs DTG

Stratification of Clinical Isolates Based on Fold Change in Resistance

< 2.5	2.5 to < 5	5 to < 10	≥ 10

EC_{50} Fold Change (FC) vs Reference Wild Type

	DTG	BIC
G140S,Q148H	3.44	2.12
* E92Q,N155H	3.49	1.72
G140S,Q148H	3.52	2.03
G140S,Q148H	3.59	2.42
G140S,Q148H	3.60	1.99
G140S,Q148H	4.00	2.17
* E92Q,N155H,G163R	4.12	2.02
E138K,G140S,Q148H	4.73	2.46

	DTG	BIC
* E138K,G140S,Q148H	5.34	2.52
G140S,Q148H	5.46	2.92
* G140S,Q148H	5.56	2.49
* G140S,Q148H,G163K	5.68	2.48
* G140S,Q148R	6.15	3.01
E138K,G140C,Q148R	8.58	5.32
L74L/M,G140A,Q148R	8.81	5.38
L74M,G140C,Q148R	9.06	8.36

	DTG	BIC
G140S,Q148H,E138A	10	7.23
* G140S,Q148H	11	3.81
* E138K,G140S,Q148H	13	2.62
* G140S,Q148H	13	4.37
T97A,G140S,Q148H	14	7.62
* T97A,G140S,Q148H	15	4.39
* G140S,Q148R	17	7.05
* E138K,G140A,Q148K	63	19

These 24 isolates are a subset of the 47 patient-derived clinical isolates (from Monogram Biosciences) with ≥ 1 primary and/or other INSTI mutations with phenotypic resistance to INSTIs and comprised *all* available INSTI resistant variants in the Monogram library.

BIC has an improved resistance profile compared to DTG

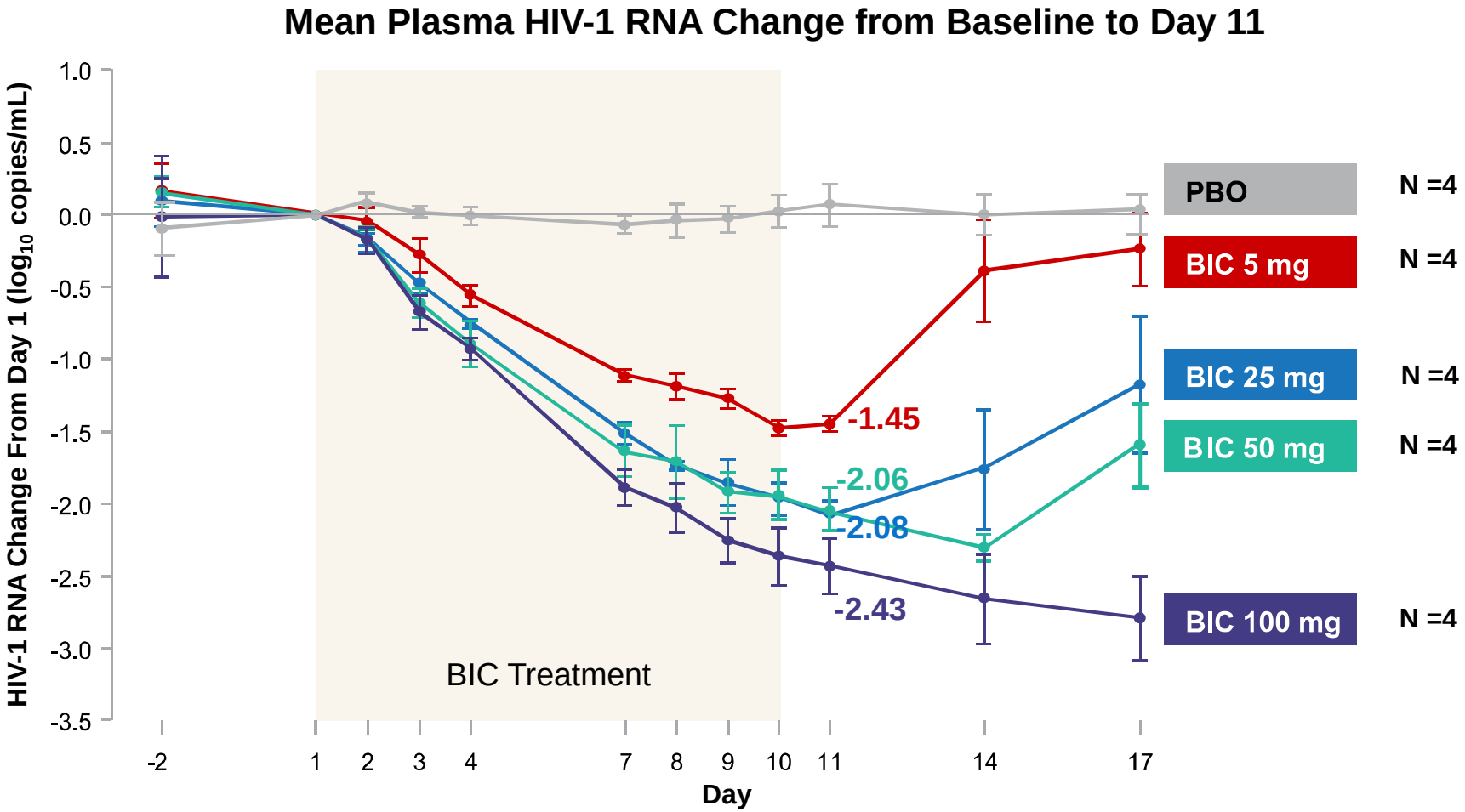
- E92Q + N155H (p=0.031)
- G140C/S + Q148R/H/K (p=0.037)

*BIC, compared to DTG, displayed more activity (≥2-fold) against multiple INSTI-resistant isolates

EC_{50}=effective concentration of half maximal response.

1. White K, et al., European Workshop HIV & Hep 2016. Rome, Italy. Poster O-01. 2. Tsiang M, et al., AAC 2016;60:7086-7097.

BIC Multiple-Dose: Viral Dynamics



- **BIC has a rapid, dose-response antiviral effect with no emergent resistance**
- **Three participants achieved HIV-1 <50 copies/mL (1 on BIC 50mg, 2 on BIC 100mg)**

Gallant J, et al. ASM 2016. Boston, MA. Poster #415

BIC Clinical Pharmacology

- BIC has a plasma half-life of ~18 hours, supportive of once daily dosing
- B/F/TAF can be dosed *without* food (food PK effect: BIC concentration ↑24%)

Hepatic Profile

✓ Hepatic metabolism (UGT1A1 + CYP3A4)

✓Substrate of UGT1A1 + CYP3A4

✓BIC is not an inhibitor or inducer of UGT1A1 and CYP3A4

✓ Moderate hepatic impairment

Renal Profile

✓ Severe renal impairment ($eGFR_{CG}$ 15-29 mL/min)

✓No effect on actual GFR

✓Minimal impact on eGFR (↓10%)

✓Metformin (↑39%)

Drug Interaction Profile

Data shown are % change in coadministered drug or BIC exposure

Drug	[Drug]	[BIC]
midazolam	↑13%	--
ledipasvir	↓13%	--
sofosbuvir	↑7%	--
norgestimate	↑8%	--
ethinyl estradiol	↑4%	--
2 hours before antacids	--	↓13%
2 hours after antacids	--	↓52%
darunavir/cobicistat	--	↑74%
voriconazole	--	↑61%
rifabutin	--	↓38%

DRV/COBI=CYP3A4 inhibitor; Rifabutin=weak dual inducer of UGT1A1 and CYP3A4; Voriconazole=CYP3A4 inhibitor.

BIC has a favorable PK profile with minimal drug interactions

Zhang H, et al. CROI 2017. Seattle, WA. Oral 0860. CG=Cockcroft-Gault; PK=pharmacokinetics.

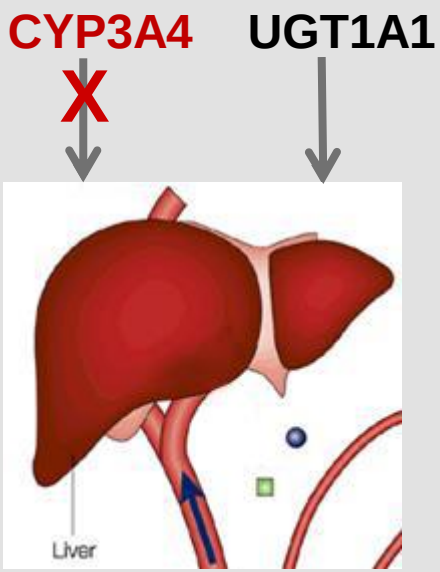
Drug Interaction Profile

- BIC's dual alternative metabolic pathways minimize drug interactions
  - UGT1A1 (glucuronidation) & CYP3A4 (oxidation)

Inhibitor or inducer of either • UGT1A1 *or* CYP3A4	Expect similar BIC exposures

Inhibition of Single Pathway

- Alternative metabolism pathway operates to eliminate BIC when the other is inhibited



1. Zhang H, et al. CROI 2017. Seattle, WA. Oral #40. 2. Isentress USPI. Merck & Co., Inc. February 2011. 3. Tivicay USPI. Viiv Healthcare. August 2013.

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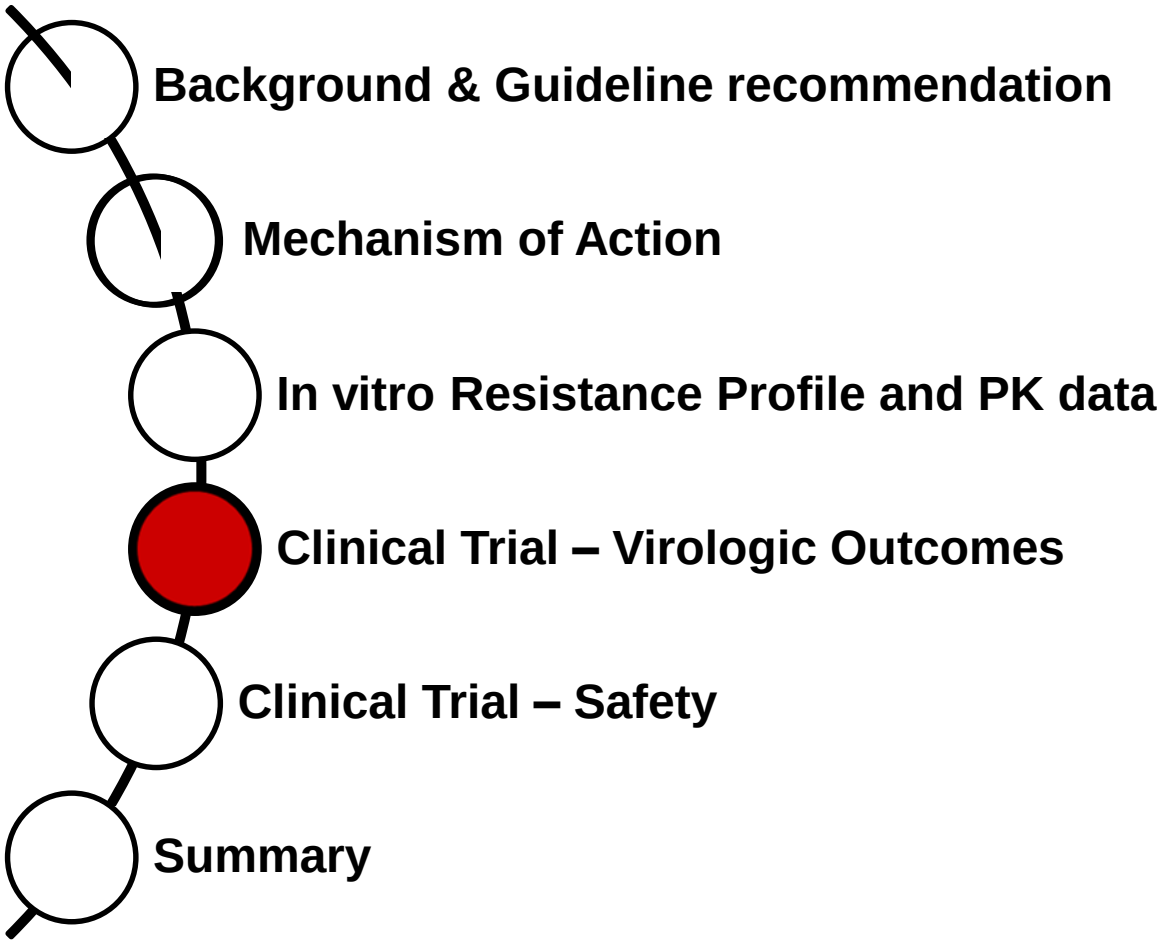

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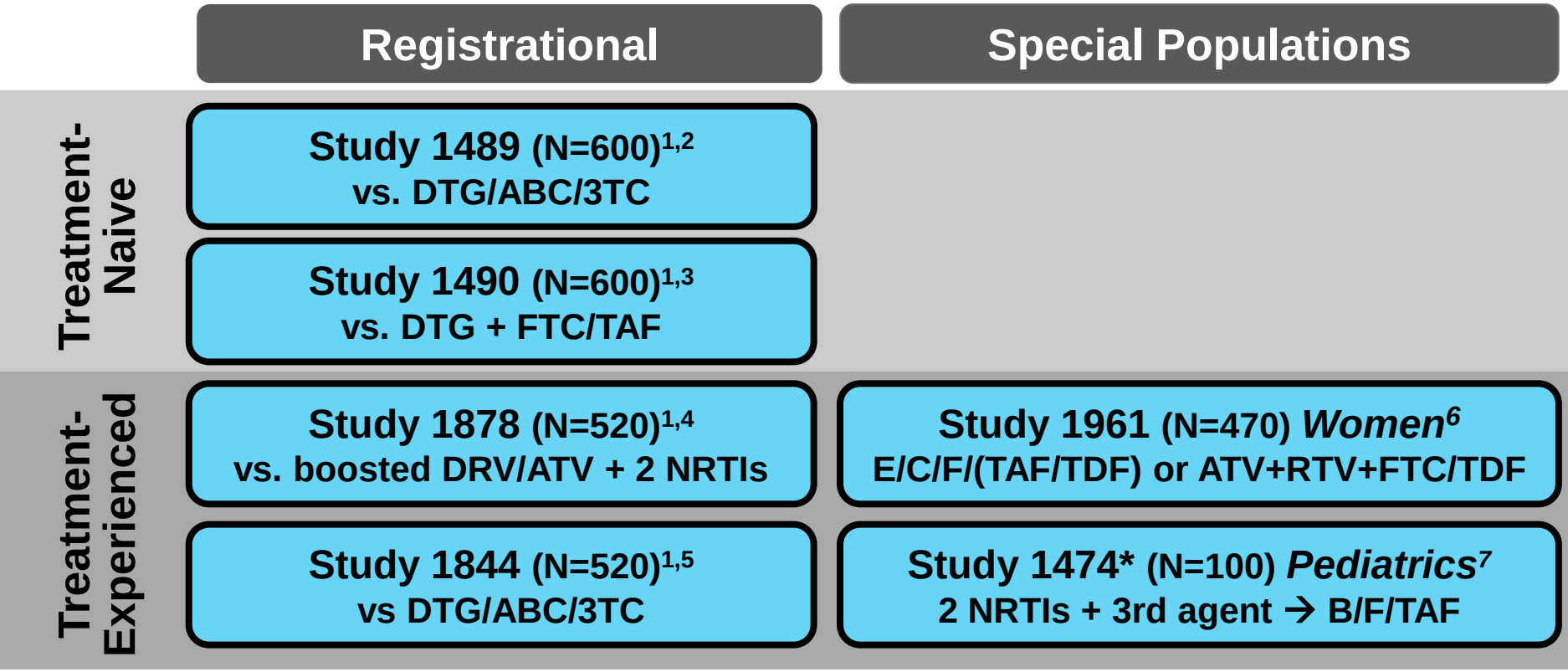
B/F/TAF Phase 3 Clinical Development Program*

- Through 48 weeks, B/F/TAF demonstrated high HIV suppression rates, non-inferior efficacy to DTG- & PI-based regimens with zero resistance development and less drug-related adverse events



= presented at CROI

* Study 1474 is a Phase 2/3 and has a single arm

1. Gilead Sciences. Biktarvy US Prescribing Information. February 2018. 2. Gallant J, et al. Lancet 2017;390:2063-72. 3. Sax P, et al. Lancet 2017;390:2073-82. 4. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4. 5. Molina JM, et al. CROI 2018. Boston, MA. Oral 22. 6. Kityo C, et al. CROI 2018. Boston, MA. Poster 500. 7. Gaur A, et al. CROI 2018. Boston, MA. Poster 844

‡

B/F/TAF Phase 3 Efficacy through Week 48

Study	Population	Comparator	Efficacy	Resistance
1489[1]	Naïve	DTG/ABC/3TC	Non-inferior*	0
1490[2]	Naïve	DTG+FTC/TAF	Non-inferior*	0
1844[3]	Suppressed	DTG/ABC/3TC	Non-inferior†	0
1878[4]	Suppressed	Boosted PI + 2 NRTIs	Non-inferior†	0‡
1961[5]	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior†	0**

* For ART-naïve studies: Treatment outcomes [between treatment groups] were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.[6]

† For virologically suppressed studies: Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region.[5,6]

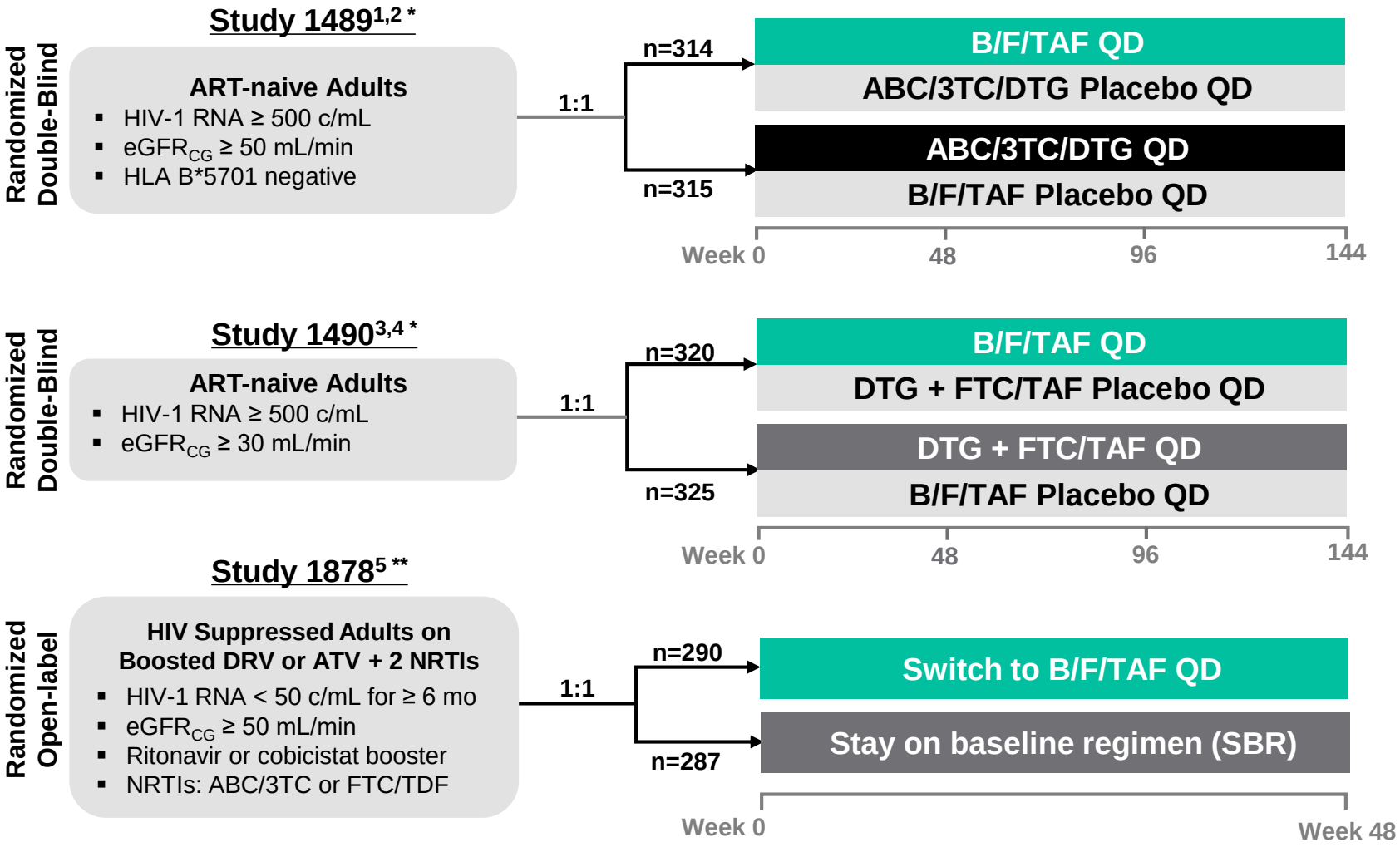
‡ One boosted PI regimen participant on DRV+RTV+ABC/3TC developed ABC mutation L74V

** One E/C/F/TAF participant developed FTC mutation M184M/I/V

In five Phase 3 trials of 1,440 patients through Week 48
B/F/TAF had non-inferior efficacy with zero emergent resistance

1. Gallant J, et al. Lancet 2017;390:2063-72.
2. Sax P, et al. Lancet 2017;390:2073-82.
3. Molina JM, et al. CROI 2018. Boston, MA. Oral 22
4. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4
5.Kityo C, et al. CROI 2018. Boston, MA. Poster 500.
6.Gilead Sciences. Biktarvy US Prescribing Information. February 2018.

Study Designs

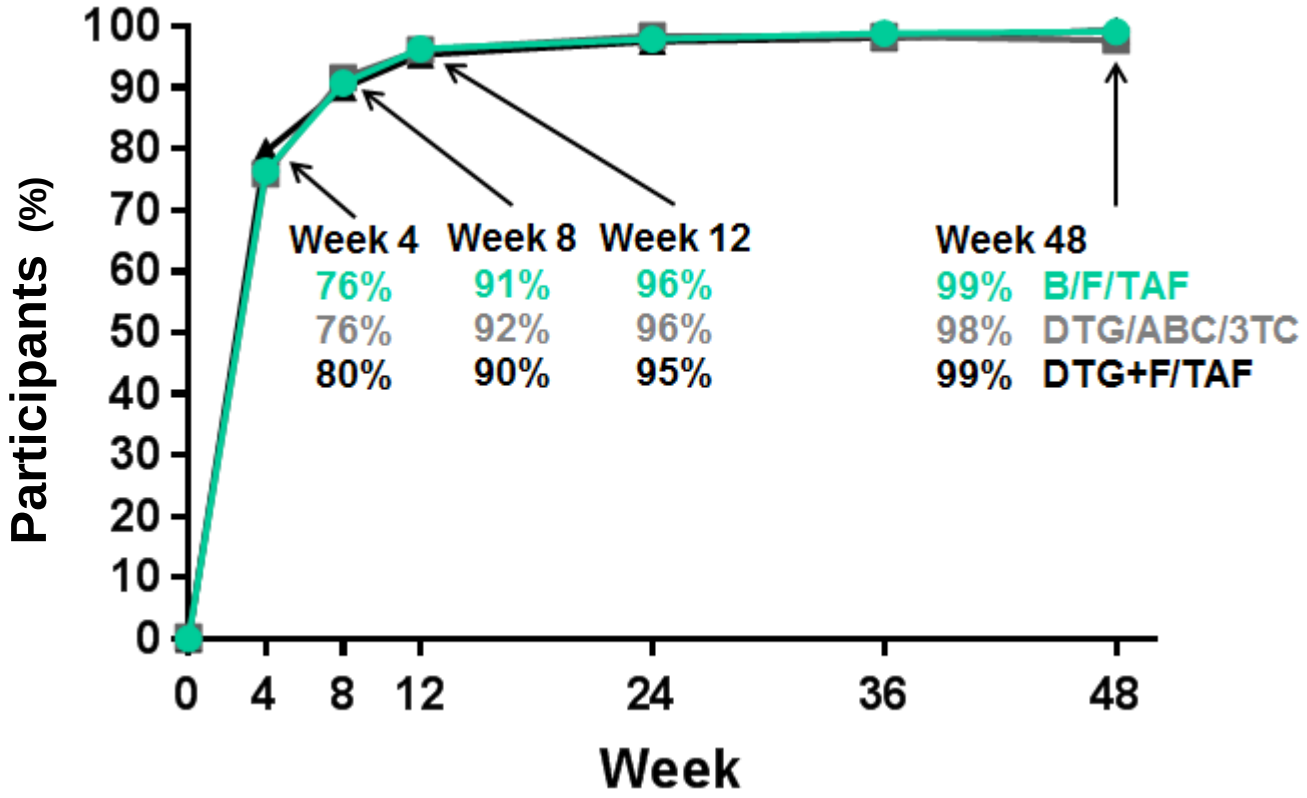


1. Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
2. Gallant J, et al. Lancet 2017;390:2063-72
3. Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
4. Sax P, et al. Lancet 2017;390:2073-82
5. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

* Primary endpoint: HIV-1 RNA <50 c/mL at Week 48 (FDA snapshot)
** Primary endpoint: HIV-1 RNA ≥50 c/mL at Week 48 (FDA snapshot)

Pooled ART-naïve Studies 1489 and 1490

Virologic Efficacy: HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis

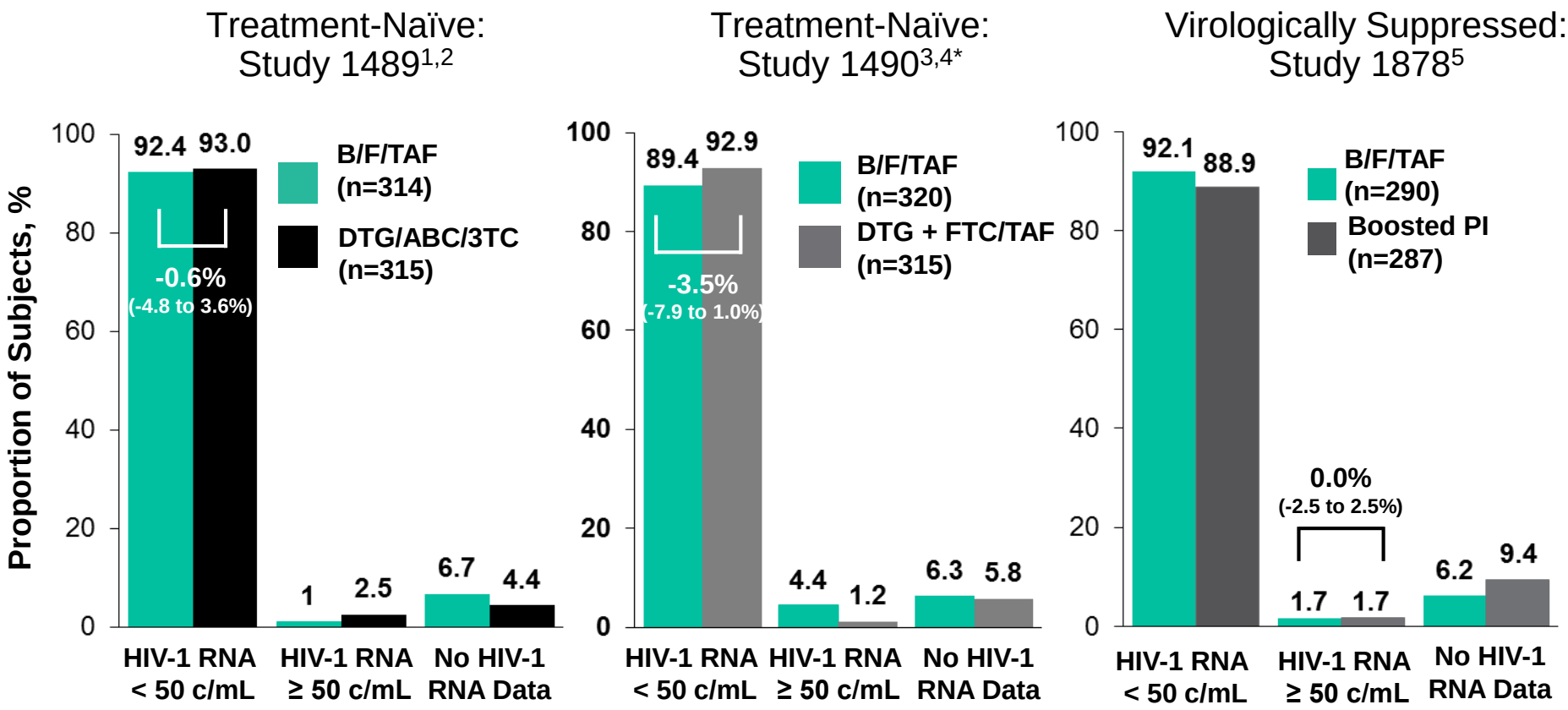


B/F/TAF displayed rapid viral suppression (M=E)[1] and non-inferior efficacy[2,3]* vs. DTG-based regimens at Week 48

* Based on Snapshot analysis

1. White K, et al . CROI 2018. Boston, MA. Poster 532.
1. Gallant J, et al. Lancet 2017;390:2063-72.
2. Sax P, et al. Lancet 2017;390:2073-82.

Virologic Outcome at Week 48 (FDA Snapshot Analysis)



B/F/TAF has non-inferior efficacy vs comparators in treatment-naïve and virologically-suppressed populations at Week 48

* 6 participants on B/F/TAF and 0 participant on DTG+FTC/TAF did not have post-baseline virologic data, and were reported as virologic failure.

1. Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
2. Gallant J, et al. Lancet 2017;390:2063-72
3. Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
4. Sax P, et al. Lancet 2017;390:2073-82
5. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

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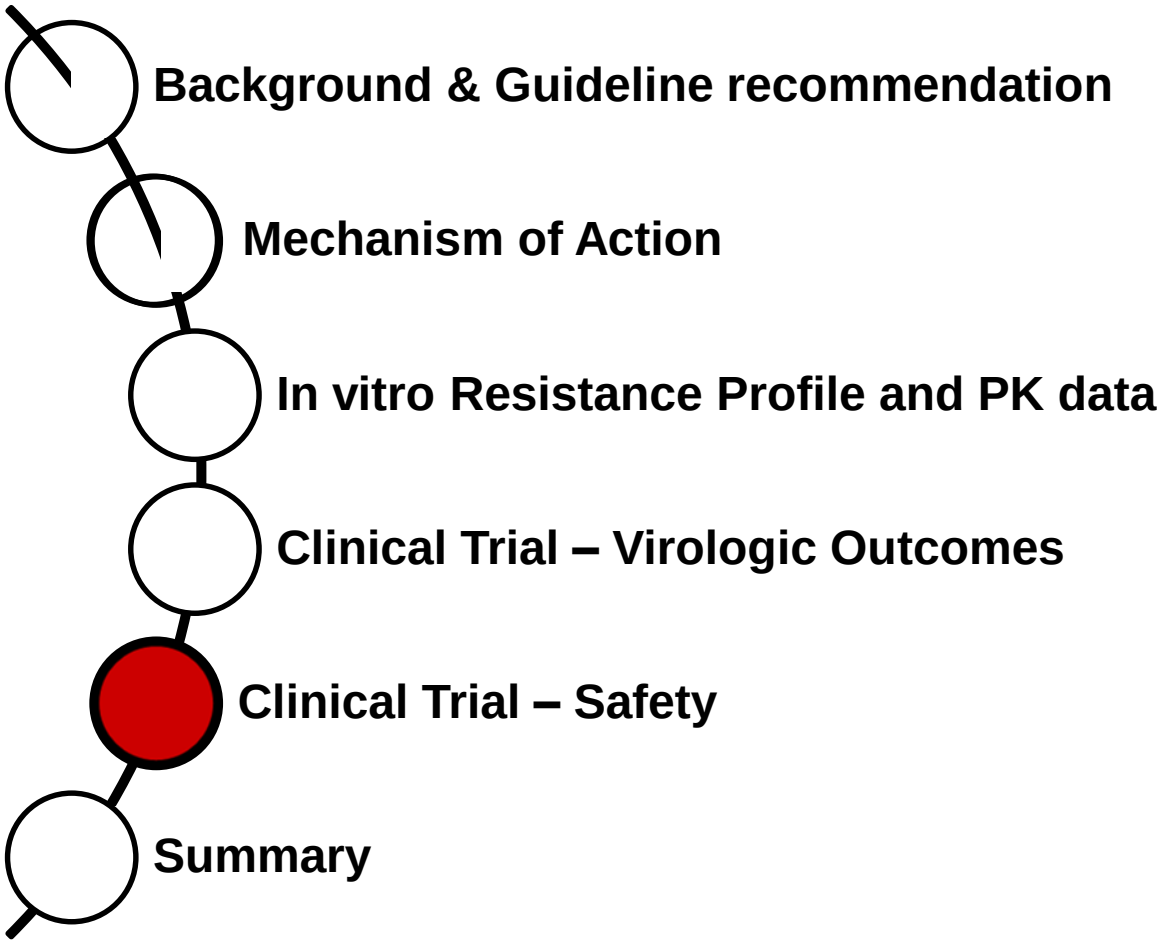

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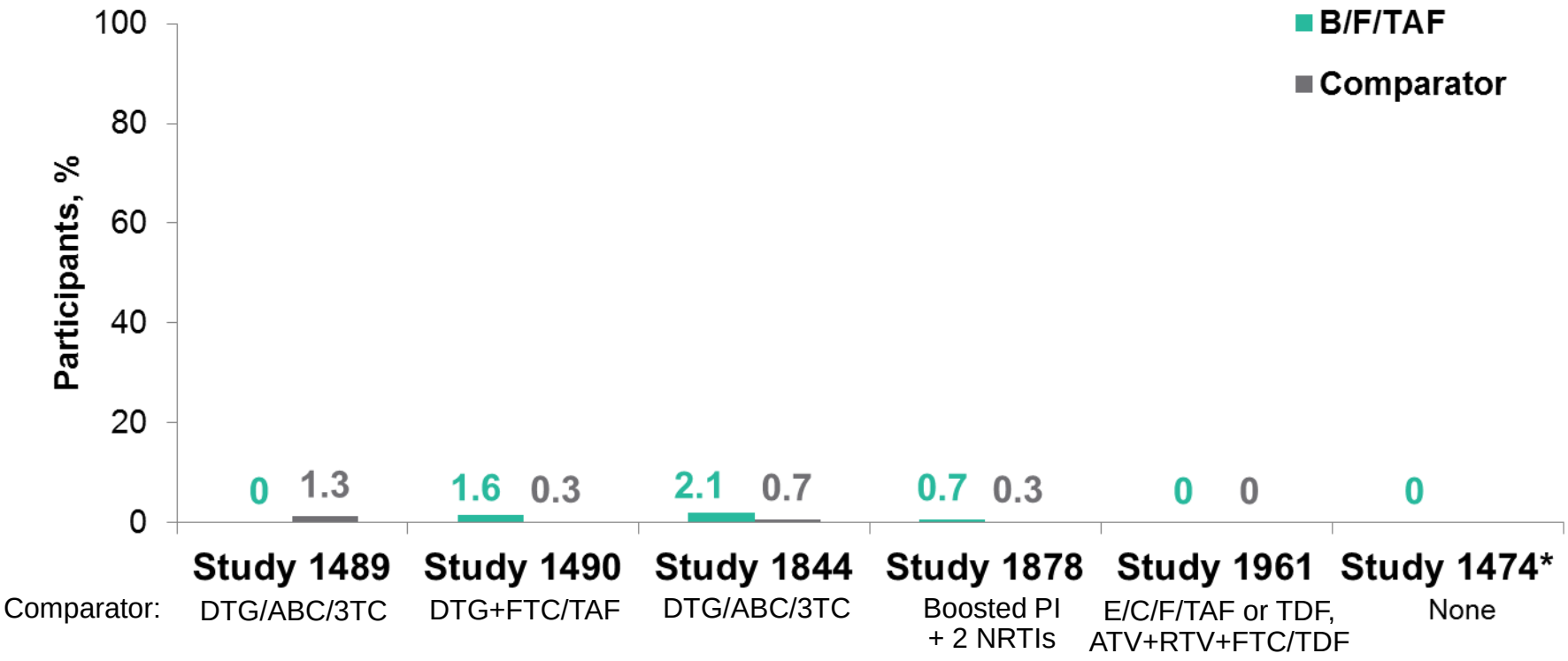
Discontinuation Rates due to AEs through Week 48



B/F/TAF was well tolerated with <1% (13/1440) overall discontinuation due to AEs through 48 weeks

*Study 1474 adolescent primary outcomes are from Week 24

1. Gallant J, et al. Lancet 2017;390:2063-72.
2. Sax P, et al. Lancet 2017;390:2073-82.
3. Molina JM, et al. CROI 2018. Boston, MA. Oral 22
4. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4
5. Kityo C, et al. CROI 2018. Boston, MA. Poster 500
6. Gaur A, et al. CROI 2018. Boston, MA. Poster 844

Reasons for Discontinuations due to AEs through Week 48

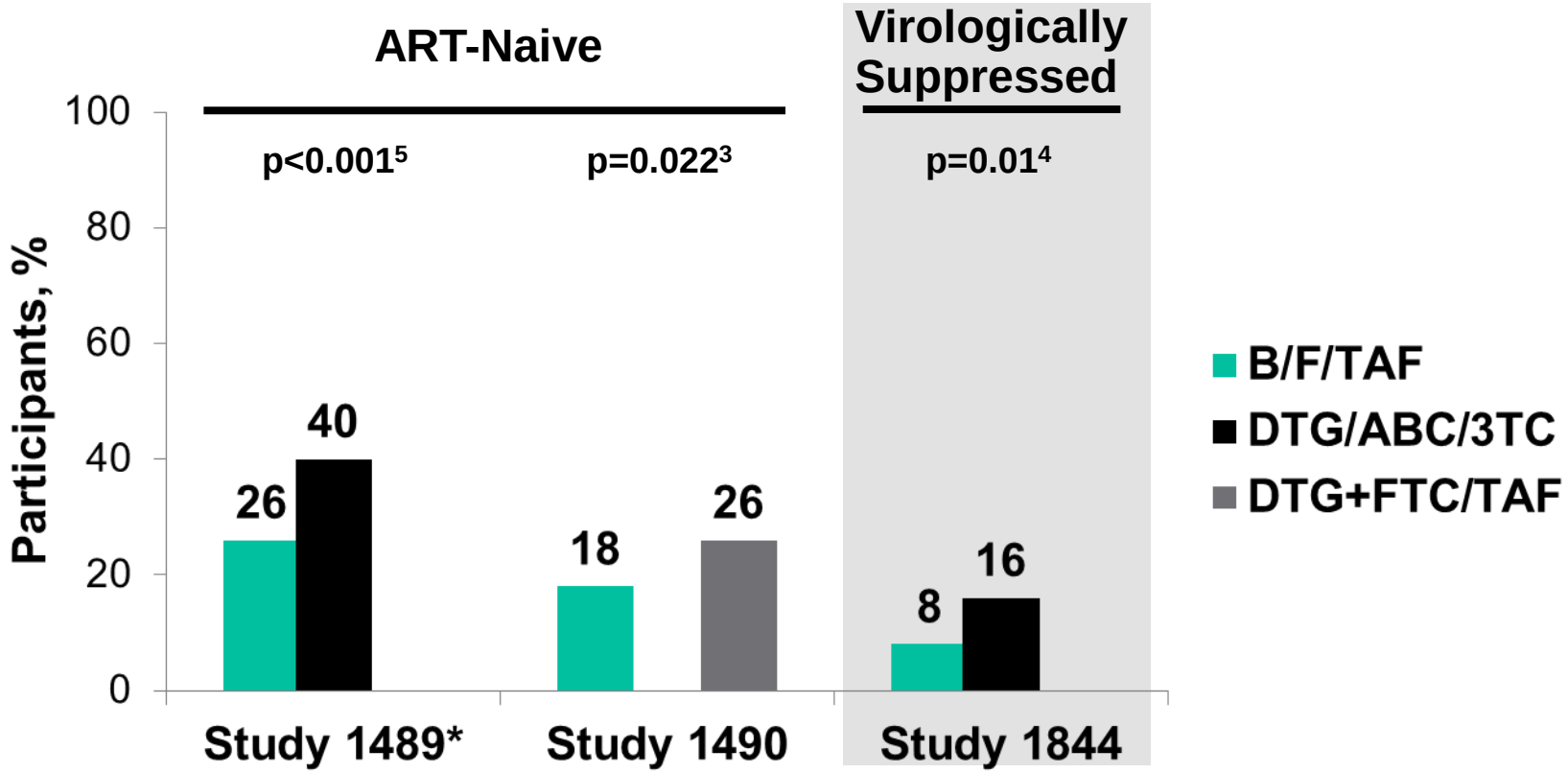
Study 1489[1,2]	Study 1490[3,4]	Study 1844[5,6]	Study 1878[6,7]
B/F/TAF	**B/F/TAF**	**B/F/TAF**	**B/F/TAF**
0	**5 (1.6%)**	**6 (2.1%)**	**2 (0.7%)**
	- Abdominal distention（腹胀） - Cardiac arrest（心脏骤停）* - Chest pain（胸痛） - Paranoia（偏执）, crystal methamphetamine use（冰毒使用）* - Sleep disorder/insomnia （失眠） dyspepsia,（消化不良） tension headache（紧张性头痛）, depressed mood（情绪低落）	- Headaches (n=2) - Vomiting（呕吐） - Cerebrovascular accident（脑血管意外） - Abnormal dreams（异梦） - Suicidal ideation（自杀想法）*	- Rash（皮疹）* - Schizophrenia（精神分裂）
DTG/ABC/3TC	**DTG + FTC/TAF**	**DTG/ABC/3TC**	**Boosted PI Regimen**
4 (1.3%)	**1 (0.3%)**	**2 (0.7%)**	**1 (0.3%)**
- Nausea, rash - Thrombocytopenia（血小板减少） - Chronic pancreatitis（慢性胰腺炎）, steatorrhea（脂肪瘤） - Depression（抑郁）	-Erythema（红疹）, pruritis（瘙痒）*	- Headache（头痛） - Pruritus（瘙痒）	- Acetabular fracture（脱臼性骨折）, acute kidney injury（急性肾衰）*

* Investigator deemed not related to study drug

None of the B/F/TAF discontinuations were due to renal or bone AEs

1. Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
2. Gallant J, et al. Lancet 2017;390:2063-72
3. Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
4. Sax P, et al. Lancet 2017;390:2073-82
5. Molina JM, et al. CROI 2018. Boston, MA. Oral 22
6. Gilead Sciences. Data on File.
7. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

B/F/TAF vs. DTG Regimens: Drug-Related Adverse Events through Week 48

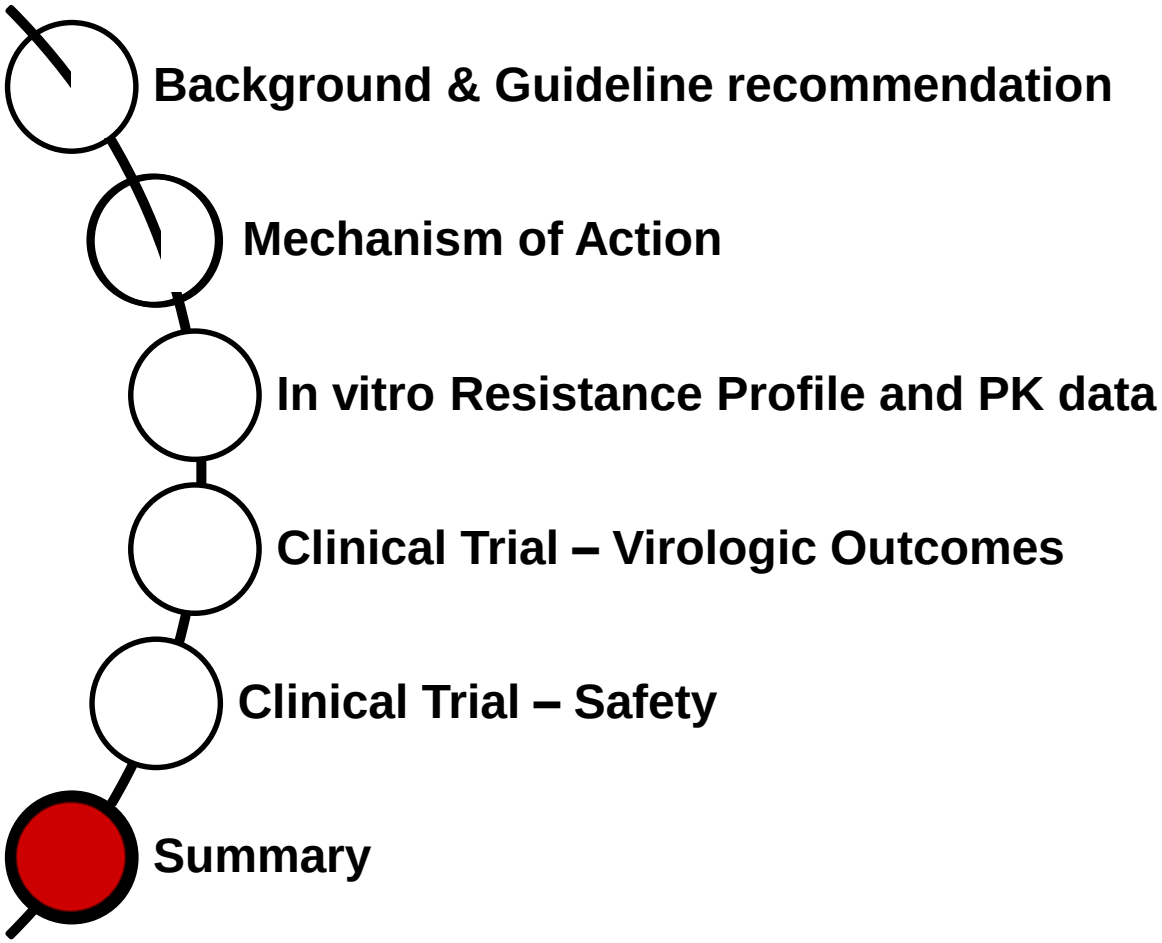


Significantly fewer drug-related AEs with B/F/TAF in all 3 randomized, double-blinded comparisons to DTG based regimens through Week 48

1. Gilead Sciences. Biktarvy US Prescribing Information. February 2018
2. Gallant J, et al. Lancet 2017;390:2063-72.
3. Sax P, et al. Lancet 2017;390:2073-82.
4. Molina JM, et al. CROI 2018. Boston, MA. Oral 22.
5. Gilead Sciences. Data on File.

*B/F/TAF participants had significantly less drug-related nausea compared to DTG/ABC/3TC (5% vs 17%; p<0.0001)[2]

Outline



In presentation mode click circle to hyperlink to specific section

Summary

- BIC: a novel, potent INSTI with an unsurpassed *in vitro* barrier to resistance and a favorable PK profile

- B/F/TAF's target pharmacologic/clinical profile
  - High rate of HIV suppression with no emergent resistance
  - Well-tolerated; no associated renal, bone, or cardiovascular adverse effects
  - Suitable for a variety of patient types
  - Minimal potential for drug-drug interactions
  - 1 tablet dosed once daily without regard for food
  - No dose adjustment in renal impairment down to an eGFR of 30 mL/min