Update in HIV treatment – New(ish) Kids on the Block

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Presenter Disclosure

Presenter Name: Osric Sin

I have no current or past relationships with commercial entities

Speaking Fees for current program:

I have received a speaker's fee from CSHP-BC for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

By the end of the session the learner will be able to:

- Describe how Tenfovir Alafenamide (TAF) and Tenofovir Disoproxil Fumarate (TDF) compare with respect to: HIV treatment efficacy, dosing, adverse effects and drug interactions

- List similarities and differences between second generation integrase inhibitors dolutegravir and bictegravir

- Describe the role of 2-drug therapy for HIV treatment in antiretroviral (ARV) Naïve patients

Antiretrovirals on Pharmanet

As per BC Ministry of Health, since May 2020, all antiretrovirals (ARVs) have been included on PharmaNet for patient safety

Overview of HIV ARV regimen selection

Nucleotide/Nucleoside Reverse Transcriptase Inhibitor (NRTI)

"Backbone" = 2 different NRTIs

Tenofovir Disoproxil Fumarate (TDF) + Emtricitabine
Tenofovir Alafenamide (TAF) + Emtricitabine
Abacavir (ABC) + Lamivudine

AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV; 2019 Dec 18 [cited 2020 Aug 15]. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf

History of Tenofovir in HIV

Tenofovir Disoproxil Fumarate (TDF)

2001 – FDA Approval

2003 – Health Canada conditional approval

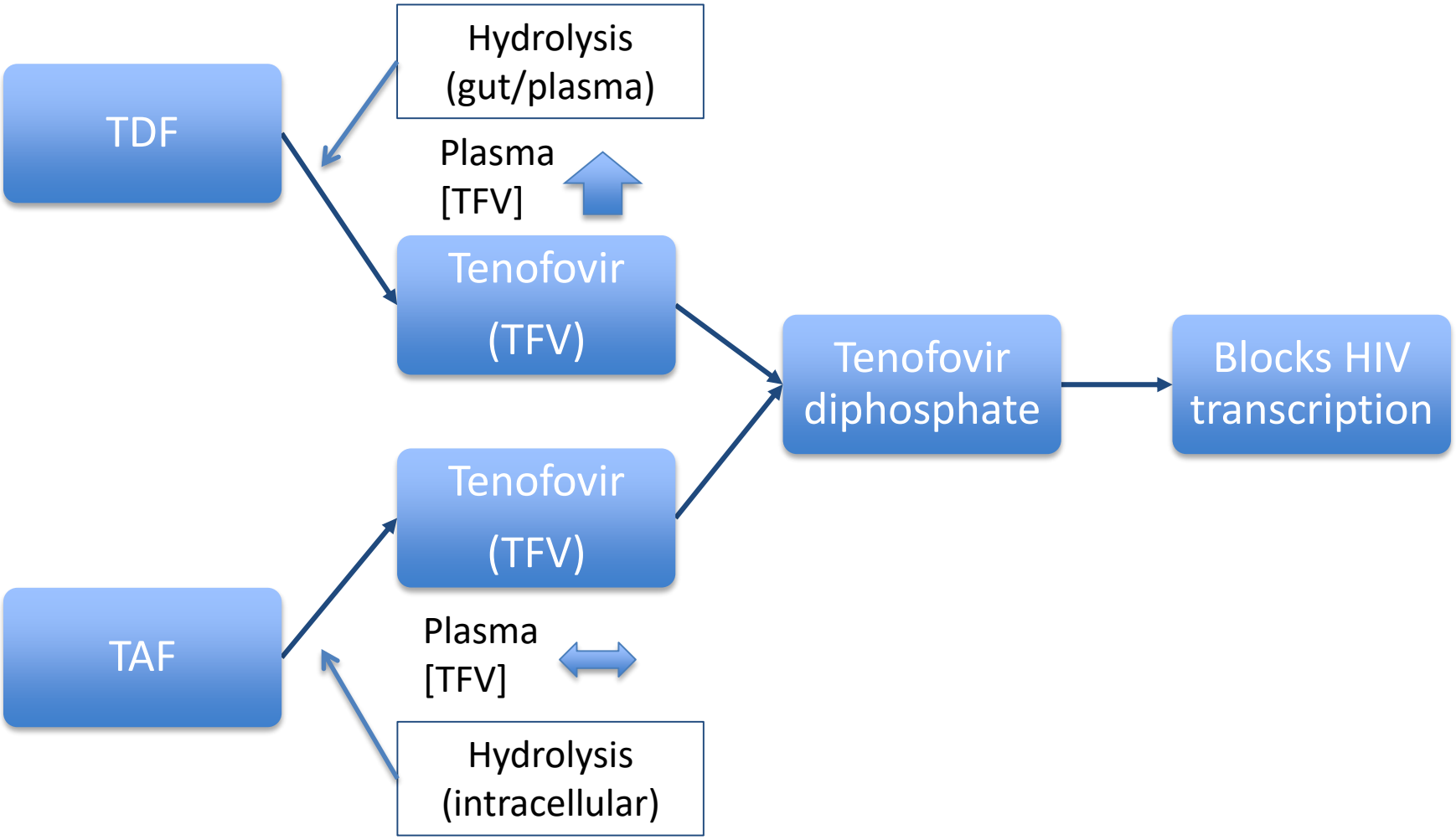
2005 – Health Canada approval (without conditions)

Long term safety concerns:

- Renal
  - Proteinuria
  - Hypophosphatemia
  - Renal insufficiency/failure
  - Fanconi syndrome
- Bone
  - Reduced bone density
  - Fragility fractures?

Government of Canada. Archived – conditional approval of Viread (tenofovir disoproxil fumarate); 2004 May 10 [cited 2020 Aug 15]. Available from: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2004/14294a-eng.php
J Int Assoc Provid AIDS Care. 2020;19: 2325958220919231.

TDF vs. TAF: Pharmacology



Tenofovir alafenamide tablets [product monograph]; 2019 May 19 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/6115/5959/0213/Vemlidy_English_PM_e193066-GS-002.pdf
Tenofovir disoproxil fumarate tablets [product monograph]; 2018 June 13 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/1915/2970/4534/Viread_English_PM_e131863-GS-0035.pdf

TDF vs. TAF: P-Glycoprotein (p-gp) Drug Interactions

	Effect on TDF	Effect on TAF
Strong p-gp inducers[1]	None	Reduced TAF absorption – **Avoid combination**
Strong p-gp inhibitors (ARVs) (e.g. ritonavir, cobicistat)	None	Increased TAF absorption – **Reduce TAF dose to: 10mg daily**
Strong p-gp inhibitors[2] (non-ARVs)	None	Increased TAF absorption **but no dose adjustment recommended**

[1]Strong p-gp INDUCER examples: Rifampin, Carbamazepine, Phenytoin, St. John's Wort

[2]Strong non-ARV p-gp INHIBITOR examples: Amiodarone, Clarithromycin, Itraconazole, Ketoconazole, Verapamil

Tenofovir alafenamide tablets [product monograph]; 2019 May 19 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/6115/5959/0213/Vemlidy_English_PM_e193066-GS-002.pdf
Tenofovir disoproxil fumarate tablets [product monograph]; 2018 June 13 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/1915/2970/4534/Viread_English_PM_e131863-GS-0035.pdf

TDF and TAF: Dose

3rd agent of ARV Regimen Contains	TDF Dose	TAF Dose
INSTI or NNRTI	300 mg daily “Unboosted TDF”	25 mg daily
PI or cobicistat	300 mg daily “Boosted TDF”	10 mg daily

Tenofovir alafenamide tablets [product monograph]; 2019 May 19 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/6115/5959/0213/Vemlidy_English_PM_e193066-GS-002.pdf
Tenofovir disoproxil fumarate tablets [product monograph]; 2018 June 13 [cited 2020 Aug 10]. Available from: http://www.gilead.ca/application/files/1915/2970/4534/Viread_English_PM_e131863-GS-0035.pdf

TDF vs. TAF: Efficacy

Meta Analysis

9 RCTs – Head to head

- ARV Naïve x 4 RCTs; 48-144 weeks
- Treatment Experienced/Switch studies x 5 RCTs; 24-144 weeks

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety

Meta-analysis end points assessed:

- Death
- Serious adverse events (SAE)
- Renal
- Bone

Methods:

- Adverse event data pooled, risk of AE is estimated and the difference is presented

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety

Death and SAE

11 RCTs – HIV and HBV pooled data

TAF 10mg vs. Boosted TDF	
Endpoint	Risk Estimate [95% CI]
Death (any cause)	0% [0%]
Serious adverse events	0% [-2%, 1%]

TAF 25mg vs. Unboosted TDF	
Endpoint	Risk Estimate [95% CI]
Death (any cause)	0% [-1%, 1%]
Serious adverse events	0% [-2%, 1%]

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety - Renal

Discontinuations due to renal adverse effects

Intervention	Number of Events (n)	Effect Estimate [95% CI]
TAF 25mg	1/1621 (0%)	0% [0%]
Unboosted TDF	0/1183 (1%)	

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety - Bone

Discontinuations due to bone adverse effects

Intervention	Discontinuations due to bone A/E (n)	Risk Estimate % [95%]
TAF 25mg	1/1621	0% [0%]
Unboosted TDF	0/1183	

Data for these events not specified. Some studies reported these numbers, while others did not

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety - Bone

Intervention	Fracture events (n)	Risk Estimate % [95%]
TAF 10mg	8/978	-1% [-2%, 0%]
Boosted TDF	17/928	
TAF 25mg	6/866	0% [0%, 1%]
Unboosted TDF	1/432	

J Virus Erad. 2018; 4(2): 72-9

TDF vs. TAF: Safety - Weight gain

Observational Pharmaco-Epidemiology Research and Analysis (OPERA) Healthcare database

- HIV Cohort
- 65 cities across USA
- >115,000 HIV+ adults receiving care

Estimated Weight Δ by kg/yr (95% CI)			
Time From TDF to TAF Switch	**3rd agent of ARV Regimen**		
	INSTI (n = 3281)	**NNRTI (n = 1452)**	**Boosted PI (n = 746)**
-60 to 0 mos	+0.42 (+0.26 to +0.59)	+0.66 (+0.51 to +0.81)	+0.31 (-0.02 to +0.64)
0 to 9 mos			
9+ mos			

J Int AIDS Soc 2020; 23(S4):e25547

TDF vs. TAF: Safety - Hyperlipidemia

Switch Studies TDF → TAF	Intervention	Total Cholesterol Δ from baseline (mmol/L)	LDL Δ from baseline (mmol/L)	TC:HDL Δ from baseline
Raffi et al (96 weeks)	TAF	+ 0.36	+ 0.36	+ 0.1
	TDF	+ 0.03	+ 0.1	+ 0.1
		p<0.001	p<0.001	p=0.26
EMERALD (48 weeks)	TAF	+ 0.51	+ 0.41	+ 0.2
	TDF	+ 0.03	+ 0.05	+ 0.1
		p<0.001	p<0.001	P=0.01

J Acquir Immune Defic Syndr. 2017;75(2):226-231.
Lancet HIV. 2018;5(1):e23–e34.

TDF vs TAF Summary

Outcome	Favors TAF	Favors TDF	No Difference
HIV suppression	✓(?) (TAF vs Boosted TDF)	✗	✓ (TAF vs Unboosted TDF)
Death	✗	✗	✓
Serious Adverse Events	✗	✗	✓
Discontinuations 2° Renal ADR	✓(?) (TAF vs Boosted TDF)	✗	✓ (TAF vs Unboosted TDF)
Discontinuations 2° Bone ADR	✓(?) (TAF vs Boosted TDF)	✗	✓ (TAF vs Unboosted TDF)
Weight Gain	✗	✓	✗
Hyperlipidemia	✗	✓	✗

Integrase Strand Transfer Inhibitors (INSTI)

Efficacy

- Non-inferior or superior vs other 3rd agent classes
- Rapid viral suppression vs other 3rd agent classes

Safety

- Generally well tolerated
- Neuropsychiatric effects
  - Sleep disturbances
  - Depression/Anxiety
  - Suicidal Ideation

British Columbia Centre for Excellence in HIV/AIDS. Therapeutic Guidelines for Antiretroviral (ARV) Treatment of Adult HIV Infection; 2020 Jun [cited 2020 Aug 15]. Available from: http://bccfe.ca/therapeutic-guidelines/guidelines-antiretroviral-arv-treatment-adult-hiv-infection

Dolutegravir (DTG) - Efficacy

ARV Naïve:

INSTI Comparison:	NNRTI Comparison:	PI Comparison:
DTG vs Raltegravir : **Non-Inferior** (week 48), Superior (week 96) Randomized, Double-Blind, Double-Dummy, Non-inferiority trial	DTG vs Efavirenz: **Superior** (weeks 48 and 96) Randomized, Double-Blind, Double-Dummy, Non-inferiority trial	DTG vs Darunavir/ritonavir: **Superior** (week 48) Randomized, Open Label, Non-inferiority trial

Treatment Experienced Patients:

INSTI Comparison:

DTG vs Raltegravir – **Non-inferior** (week 48)

- Randomized, Double-Blind, Double-Dummy, Non-inferiority trial
  - Resistance to ≥ 2 ARV classes; INSTI naïve
  - Background regimen contained 1 or 2 fully active drugs

Single Arm DTG in heavily tx experienced patients – **% pts HIV Viral Load < 50 c/mL: 63%** (week 24)

- Open Label
  - Resistance to ≥ 2 ARV classes
  - Low level resistance to raltegravir or elvitegravir/cobicistat
  - ≥ 1 active ARV in regimen

CADTH. Common Drug Review Clinical Report – dolutegravir; 2014 Aug [cited 2020 Aug 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/sr0357_tivicay_cl_report.pdf

Dolutegravir (DTG) – Safety

Common:

- GI: Nausea, diarrhea
- CNS: Headache, insomnia (AM dosing preferred)
  - Less Common: Neuropsychiatric – anxiety, depression, suicidal ideation
- Lab abnormality: increased SCr (~10 umol/L) with preserved glomerular function
  - MOA: inhibition of tubular secretion of creatinine (initial 4 weeks)

Teratogenicity:

- Exposures during initial 12 weeks associated with infant development of neural tube defect (<1%)
  - Avoid if trying to conceive or if child-bearing potential
  - Avoid in 1st trimester of pregnancy

N Engl J Med 2019;381(9):885-887
AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV; 2019 Dec 18 [cited 2020 Aug 15]. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf

Dolutegravir (DTG)

Standard Dose:

- 50 mg po once daily
- Note: no renal dose adjustment required

Dosage Forms:

- DTG 50 mg Tablet
- DTG/lamivudine/abacavir (50/300/600mg) STR
- DTG/lamivudine (50/300mg) STR

Dolutegravir (as dolutegravir sodium) [product monograph]. 2020 Jan 31 [cited 2020 Aug 15]. Available from: https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_CA/tivicay.pdf

Dolutegravir (DTG) – Drug Interactions

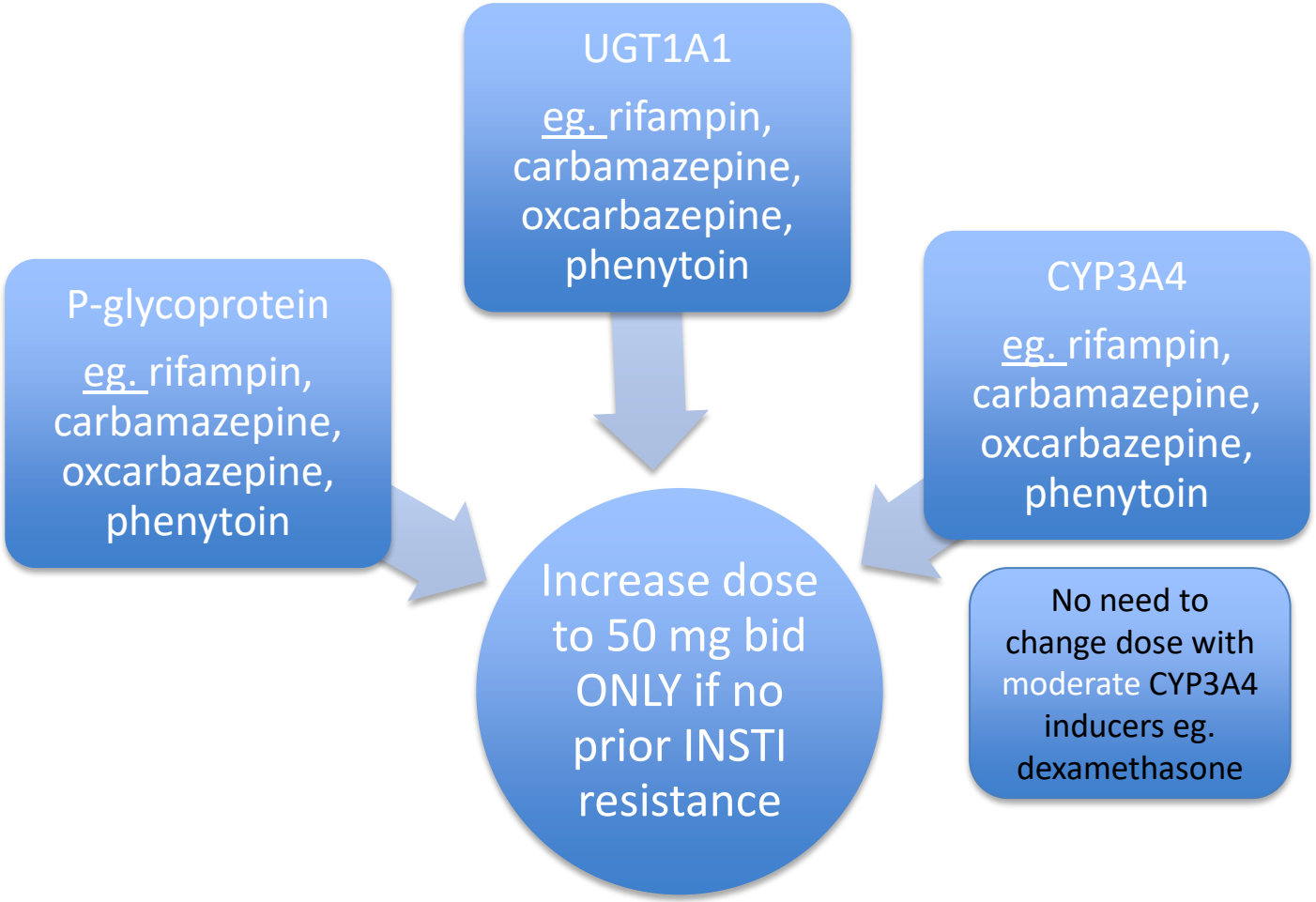
Polyvalent cations: Bind DTG → Reduced DTG absorption

	Al^{3+} or Mg^{2+}	Ca^{2+}	Fe^{2+}	Multivitamin with minerals
Space DTG 2 hours before or 6 hours after cation?	Always	YES - if taking DTG on **empty stomach** (No spacing needed if taking DTG with food)	YES - If taking DTG on **empty stomach** (No spacing needed if taking DTG with food)	YES - If taking DTG on **empty stomach** (No spacing needed if taking DTG with food)

Dolutegravir (as dolutegravir sodium) [product monograph]. 2020 Jan 31 [cited 2020 Aug 15]. Available from: https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_CA/tivicay.pdf

Dolutegravir (DTG) – Drug Interactions

Effect on DTG in the Presence of Strong Inducers



Dolutegravir (as dolutegravir sodium) [product monograph]. 2020 Jan 31 [cited 2020 Aug 15]. Available from: https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_CA/tivicay.pdf

Bictegravir (BIC) – Efficacy

ARV Naïve:

INSTI Comparison:

BIC vs DTG:
Non-Inferior (week 96)
Randomized, Double-Blind, Double-Dummy, Non-inferiority trials x 2

Switch Studies (Treatment Experienced Patients):

INSTI Comparison:	**PI Comparison:**
BIC vs DTG: **Non-inferior (week 48)** Randomized, Double-Blind, Double-Dummy, Non-inferiority trial	BIC vs Darunavir/Atazanavir boosted with ritonavir/cobicistat **Non-inferior (week 48)** Randomized, Open Label, Non-inferiority trial
BIC vs EVG/cobicistat: **Non-inferior (week 48)** Randomized, Open Label, Non-inferiority trial	

Drugs 2018;78(17):1817–1828
CADTH. Clinical Review Report - bictegravir/emtricitabine/tenofovir alafenamide. 2018 Oct [cited 2020 Aug 10]. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0567_Biktarvy_CL_Report.pdf

Bictegravir (BIC) – Safety

Common:

- GI: Nausea, diarrhea
- CNS: Headache, insomnia
  - Less Common: Neuropsychiatric effects - anxiety, depression, suicidal ideation
- Lab abnormality – increased SCr with preserved glomerular function
  - MOA: inhibition of tubular secretion of creatinine (initial 4 weeks)

Pregnancy:

- Avoid due to lack of data

Drugs 2018;78(17):1817–1828

Bictegravir (BIC)

Standard Dose:

- 50 mg daily
- No renal dose adjustment

Dosage Form:

- BIC/TAF/Emtricitabine (50/25/200mg) STR

Drugs 2018;78(17):1817–1828
Bictegravir/emtricitabine/tenofovir alafenamide tablets [product monograph]. 2020 Feb 28 [cited 2020 Aug 15]. Available from: http://www.gilead.ca/application/files/7715/9476/3064/Biktarvy_English_PM_e203718-GS-002_dated_08_July_2020.pdf

Bictegravir (BIC) – Drug Interactions

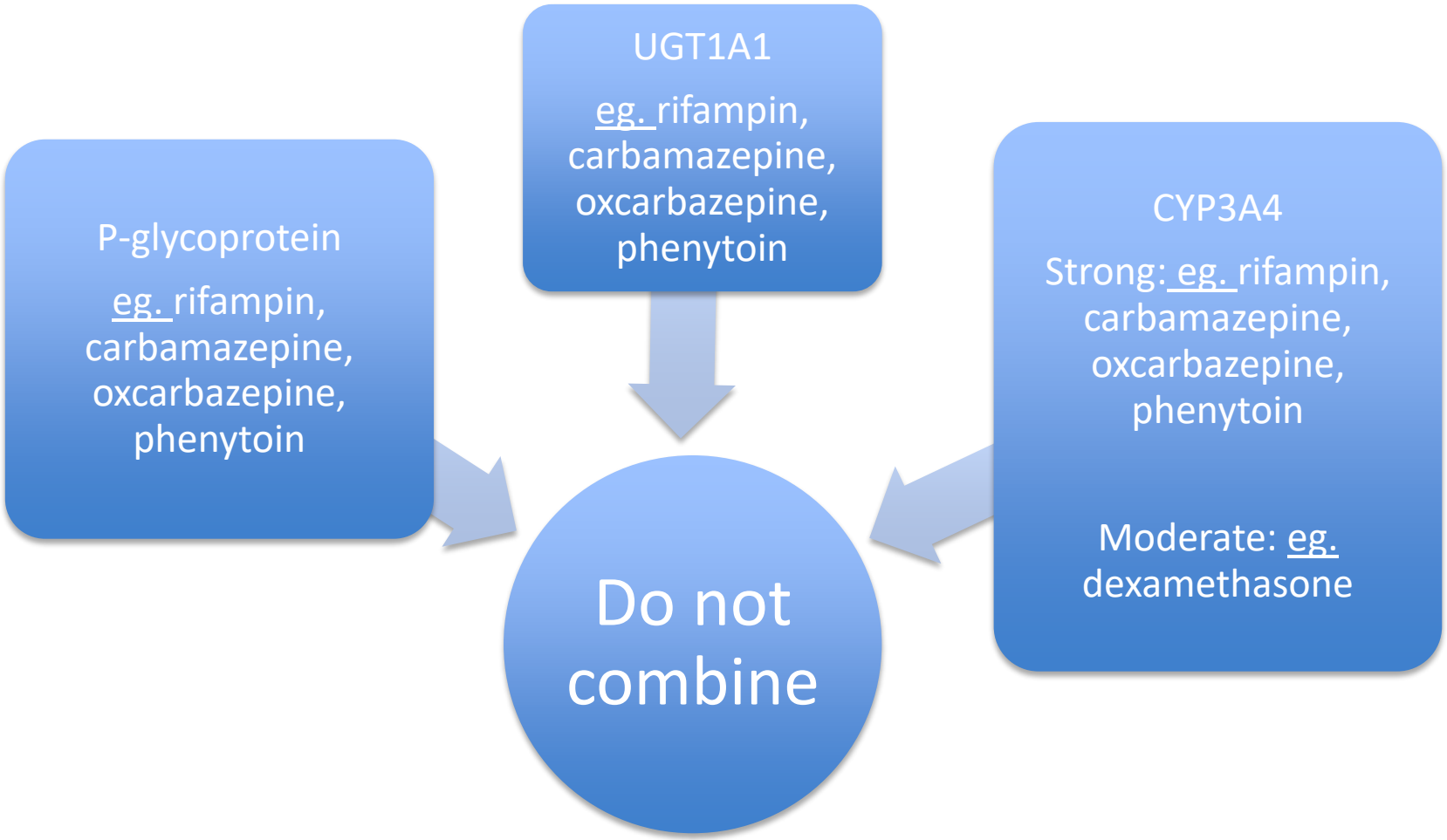
Polyvalent cations: Bind BIC→ Reduced BIC absorption

	Al^{3+} or Mg^{2+}	Ca^{2+}	Fe^{2+}	Multivitamin with minerals
Space BIC 2 hours before or 2 hours after cation?	Always	YES - if taking BIC on **empty stomach** (No spacing needed if taking BIC with food)	YES - If taking BIC on **empty stomach** (No spacing needed if taking BIC with food)	YES - If taking BIC on **empty stomach** (No spacing needed if taking BIC with food)

Bictegravir/emtricitabine/tenofovir alafenamide tablets [product monograph]. 2020 Feb 28 [cited 2020 Aug 15]. Available from: http://www.gilead.ca/application/files/7715/9476/3064/Biktarvy_English_PM_e203718-GS-002_dated_08_July_2020.pdf

Bictegravir (BIC) – Drug Interactions

Effect on BIC in the Presence of Inducers



Bictegravir/emtricitabine/tenofovir alafenamide tablets [product monograph]. 2020 Feb 28 [cited 2020 Aug 15]. Available from: http://www.gilead.ca/application/files/7715/9476/3064/Biktarvy_English_PM_e203718-GS-002_dated_08_July_2020.pdf

INSTI – Safety: Weight Gain

GOAL: Explore Risk Factors associated with weight gain in HIV+ patients

- Antiretroviral components

METHOD: Pooled analysis of 8 RCTs + longitudinal modeling

- ARV Naïve; 40-100% USA; 2003 – 2015
- 96 - 144 week duration

ARV Class	Mean weight gain at 96 weeks, kg (95% CI)
INSTI	+3.24 (+3.02 to +3.46)
NNRTI	+1.93 (+2.58 to +2.28)
PI	+1.72 (+1.01 to +2.42)

Clin Infect Dis 2020; 71(6):1379-89

INSTI – Safety: Weight Gain

Weight Gain by Individual INSTI

Integrase Inhibitor*	Mean weight gain at 96 weeks, kg (95% CI)
BIC	+4.24 (+3.71 to +4.78)
DTG	+4.07 (+3.51 to +4.62)
EVG/c	+2.72 (+2.45to +3.0)

*Raltegravir not included in analysis

Clin Infect Dis. 2020 Sep; 71(6): 1379-89.

INSTI – Safety: Weight Gain

ADVANCE Study Observations:

- South Africa
- ARV Naïve
- Randomized, Open Label, non-inferior trial

Intervention	Mean weight gain at 96 weeks (kg)	
	Men	Women
TAF/FTC[1]/DTG	+ 5.4	+ 8.1
TDF/FTC[1]/DTG	+ 3.6	+ 4.8
TDF/FTC/EFV[2]	+ 1.1	+ 3.2

[1]FTC = emtricitabine

[2]EFV = efavirenz

J Int AIDS Soc 2020; 23(S4):e25547

2nd Generation INSTI Summary

	DTG	BIC
HIV treatment Efficacy – ARV Naïve	✓	✓
HIV treatment Efficacy – Treatment Experienced with presence of ARV resistance	✓	✗
Pregnancy Use	✗ 1st trimester teratogenicity	✗ No data
Neuropsychiatric adverse events	✓	✓
Weight Gain	✓	✓
Safe to combine with p-gp, 3A4 and/or UGT1A1 inducers?	✓ Only if: No INSTI resistance and increased DTG dose	✗

2-Drug Regimen: DTG/Lamivudine (3TC)

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC): Efficacy

GEMINI 1 and 2:

Proportion of patients with HIV VL < 50 copies/mL at **week 48**

	DTG/3TC	DTG/FTC/TDF	Non-inferiority met?
GEMINI 1	90%	93%	Yes
GEMINI 2	93%	94%	Yes

Pre-specified Non-inferiority margin: -10%

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC): Efficacy

GEMINI 1 and 2: Confirmed Virologic Withdrawal

Proportion of patients with HIV VL > 50 copies/mL:

(GEMINI 1 and 2 pooled data)

	DTG/3TC n (%)	DTG/FTC/TDF n (%)
Week 48	6/716 (0.8%)	4/717 (0.6%)
Week 96	11/716 (1.5%)	7/717 (1.0%)

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC): Efficacy

GEMINI 1 and 2: Subgroup Analysis

Baseline VL > 500,000 copies/mL

Intervention	Number of pts, n	HIV VL < 50 c/mL at Week 96, n (%)
DTG/3TC	13/716	9/13 (69%)
DTG/FTC/TDF	15/717	12/15 (80%)

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC): Safety

GEMINI 1 and 2: Safety Analysis (Pooled data)

Intervention	Deaths (n)		Serious Adverse Event (% of pts)		Treatment discontinuations - any reason (% of pts)		Treatment related adverse events reported (% of pts)	
	Wk 48	Wk 96	Wk 48	Wk 96	Wk 48	Wk 96	Wk 48	Wk 96
DTG/3TC	2*	3**	7.0%	8.9%	2.1%	3.4%	17.6%	19.6%
DTG/FTC/TDF	0	0	7.7%	9.3%	2.2%	3.2%	23.6%#	25.0%#

All deaths deemed unrelated to study treatment
*Burkitt Lymphoma n=1, Acute MI n=1
** Additional ACS n=1

#Higher frequency of grade 1 nausea

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC): Safety

GEMINI 1 and 2: Renal Safety Analysis (Pooled data)

Intervention	Δ in Cystatin C eGFR from baseline (ml/min/1.73m^2)		Δ in Serum Cr from baseline (umol/L)		Δ in creatinine eGFR from baseline (ml/min/1.73m^2)	
	Wk 48	Wk 96	Wk 48	Wk 96	Wk 48	Wk 96
DTG/3TC	+6.3	+10.7	+10.4	+12.3	-12.1	-14.6
DTG/FTC/TDF	+4.1	+8.8	+13.5	+15.4	-15.5	-18.2
P-value	<0.0004	<0.005	<0.0001	<0.001	<0.0001	<0.001

Lancet 2019; 393(10167):143-155
J Acquir Immune Defic Syndr. 2020:83(3): 310-318

2-Drug Regimen: DTG/Lamivudine (3TC) Summary

Outcome	Favors 2-drug	Favors 3-drug	No Difference
HIV treatment: ARV Naïve	✗	✗	✓ Non-Inferior if: HIV VL < 500,000 c/mL and CD4 > 200 cells/mm^3
HIV treatment: Presence of ARV resistance	✗	✓	✗
Risk of Death or Serious Adverse Events	✗	✗	✓
Risk of Renal Adverse Effects	✓	✗	✗
Risk of Bone Adverse Effects	?	?	?
Risk of GI Adverse Effects	✓	✗	✗
Risk of treatment failure and development of ARV resistance	✗	✗	✓

Learning Summary

Objective #1:

Describe how Tenfovir Alafenamide (TAF) compares to Tenofovir Disoproxil Fumarate (TDF) with respect to: HIV treatment efficacy, dosing, adverse effects and drug interactions

Summary:

- TAF non-inferior to TDF for HIV treatment

- TDF requires dose adjustment for mild to severe renal impairment,
- TAF does not require dose adjustment in mild-moderate renal impairment; TAF not recommended in severe renal impairment

- No difference between TAF vs TDF – death, serious adverse events

- Compared to TDF, TAF associated with less renal and bone adverse effects, but more weight gain and hyperlipidemia

- Drug interactions through p-gp are clinically significant with TAF but not with TDF

Learning Summary

Objective #2:

List similarities and differences between second generation integrase inhibitors dolutegravir (DTG) and bictegravir (BIC)

Summary:

- DTG and BIC – 2nd generation INSTI with higher barrier to resistance vs 1st generation INSTI
- BIC non-inferior to DTG for HIV treatment (ARV naïve)
- DTG potential option in treatment experienced pts with low level ARV resistance (BIC is not)
- DTG dose adjustment possible for p-gp, UGT1A1, CYP 3A4 inducers (BIC should not be used)

Learning Summary

Objective #3:

Describe the role of 2-drug therapy for HIV treatment in ARV Naïve patients

Summary:

- 2-drug regimen (DTG/3TC) non-inferior and better tolerated vs 3-drug regimen

- 2-drug regimen (DTG/3TC) recommended only if:
  - no Hepatitis B co-infection,
  - HIV VL < 500,000 c/mL, and
  - CD4 > 200 cells/mm^3

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