22nd HIV/AIDS Workshop 2023

สมาคมโรคเอดส์แห่งประเทศไทย
Thai AIDS Society

The Third 95: Challenging Issue in TLD Transition

Interactive-case Discussion

22nd HIV/AIDS Workshop, 24th August 2023, 13.00-14.30

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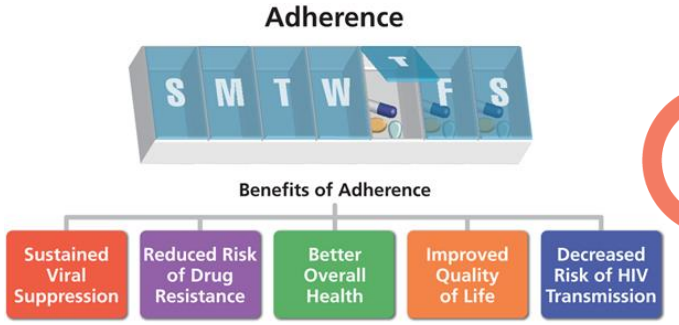
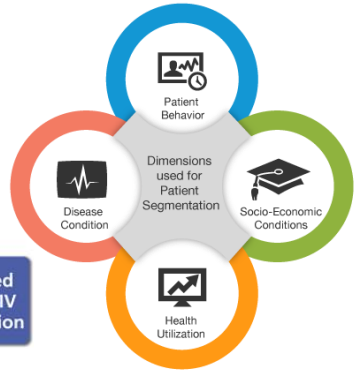




Panel Discussants

Assistant Professor

Thanomsak Anekthananon, M.D.

Assistant Professor

Tavatchai Jariyasethpong, M.D.

Associate Professor

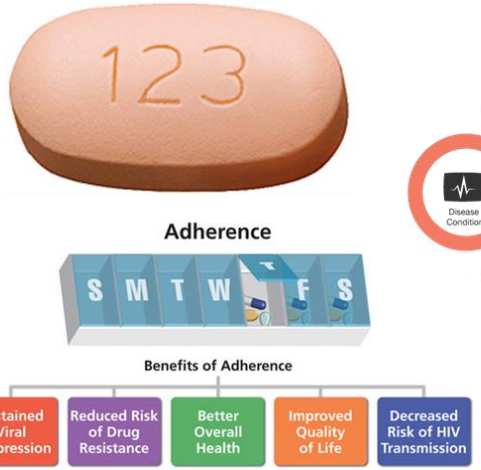
Opass Putcharoen, M.D.

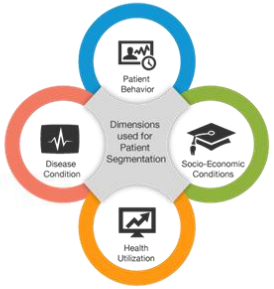
Professor

Thana Khawcharoenporn, M.D.

Case 1

A young Thai male with weight gain





Case 1: A young Thai male with weight gain

Case 35 yrs., male, government officer, live in Bangkok

- **Occupation**: government officer, **Health scheme**: civil servant medical benefit
- **First diagnosis**: Asymptomatic HIV infection (2017), Late latent syphilis
- **Physical examination**: unremarkable, BW: 85 kg, Height: 175 cm [BMI: 24.5 kg/m^2]
- **Initial laboratory assessment**

- Anti-HIV: reactive
- CD4+ T cell: 480 cell/µL (30%)
- Lipid profile: Cholesterol: 208, LDL: 113 mg/dL
- HBsAg: non-reactive, Anti-HBS: negative
- Anti-HCV: negative
- LFT: ASL: 20 IU/L, ALT: 27 IU/L
- RPR : reactive [1:2], TPHA: positive
- Cr.: 0.85 mg/dL (eGFR: 85 mL/min/1.73 m^2)

- **Start TDF/FTC/EFV 1 tab oral at 22.00**
- **Benzathine penicillin 2.4 mU IM x 3 wks.**

Case 1: A young Thai male with weight gain

Date	Treatment	CD4+ T cell (%) [cell/µL]	HIV-1 VL [copies/mL]
APR-2017	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00 - Late latent syphilis	480 (30)	NA
OCT-2017	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00	742 (35)	<20
OCT-2018	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00	906 (38)	<20
OCT-2019	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00	636 (36)	<20
NOV-2020	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00	728 (39)	<20
OCT-2021	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00 - Insomnia, nightmare: switch to TDF/FTC/DTG at 22.00	795 (42%)	<20

Adherence: Good (90-95%)

Case 1: A young Thai male with weight gain

Date	Treatment	HIV-1 VL [copies/mL]	BW [kg]/ BMI [kg/m^2]	BP [mmHg]	Triglyceride [mg/dL]	LDL/HDL [mg/dL]	AST/ALT [IU/L]
APR-2017	TDF/FTC/EFV	NA	75/24.5	120/70	147	113/36	20/27
OCT-2018	TDF/FTC/EFV	<20	80/26	125/70	144	133/39	31/36
OCT-2019	TDF/FTC/EFV	<20	85/27.7	130/70	150	123/44	25/36
NOV-2020	TDF/FTC/EFV	<20	80/26	125/70	155	125/44	28/35
OCT-2021	TDF/FTC/DTG	<20	83/27.1	130/80	148	119/39	30/32
JAN-2022	TDF/FTC/DTG	NA	85/27.7	125/80	151	130/39	50/60
MAY-2022	TDF/FTC/DTG	NA	**90/29.4**	**145/90**	**341**	**163/45**	**69/130**
NOV-2022	TDF/FTC/DTG	<20	**95/31.1**	**150/90**	**301**	**188/40**	**58/137**
MAR-2023	TDF/FTC/DTG	NA	**100/32.6**	**160/90**	**360**	**190/39**	**114/278**

Case 1: A young Thai male with weight gain

Additional history

- Increased appetite, remarkable gaining of body weight, denied history of snoring or sleep apnea.
- Denied history of herb, over counter medicine or mineral supplement.
- Exercise: volleyball player, playing volleyball 1-2 h./day, 4-5 days/weeks.
- Social alcohol drinking (1-2 times/months), no smoking.

Additional investigation

- FPG: 90 mg/dL, A1C: 5.6 %
- HBsAg: non-reactive, Anti-HCV: negative
- **Upper abdominal ultrasonography** (JAN-2023): The liver shows normal size, shape but diffused increased parenchymal echogenicity. No mass or space occupying lesion is observed: **Impression: fatty liver**

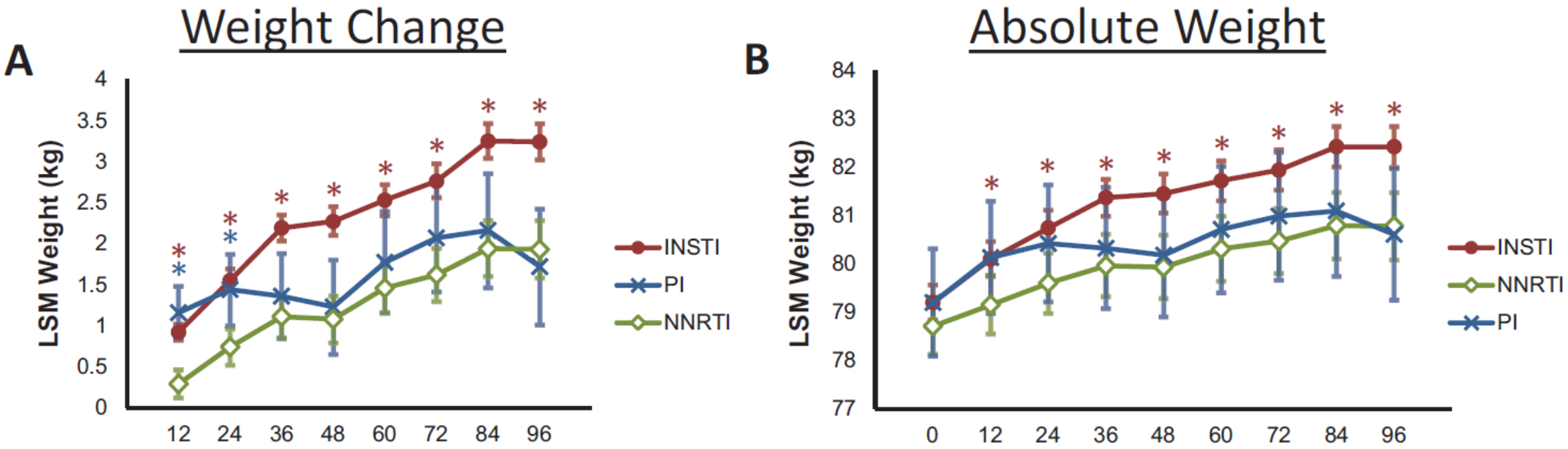
Case 1: What is the most appropriate management?

Problem List

1. **Asymptomatic HIV infection on TDF/FTC/DTG**
2. **Obesity** [BMI: 32.6 kg/m^2, weight gain for 20 %]
3. **Metabolic syndrome**
   - Triglyceride >150 mg/dL, HDL < 40 mg/dL, SBP > 130, DBP >85 mmHg
4. **Nonalcoholic fatty liver disease**
5. **New onset hypertension**

INSTI-containing Regimens and Weight Gain

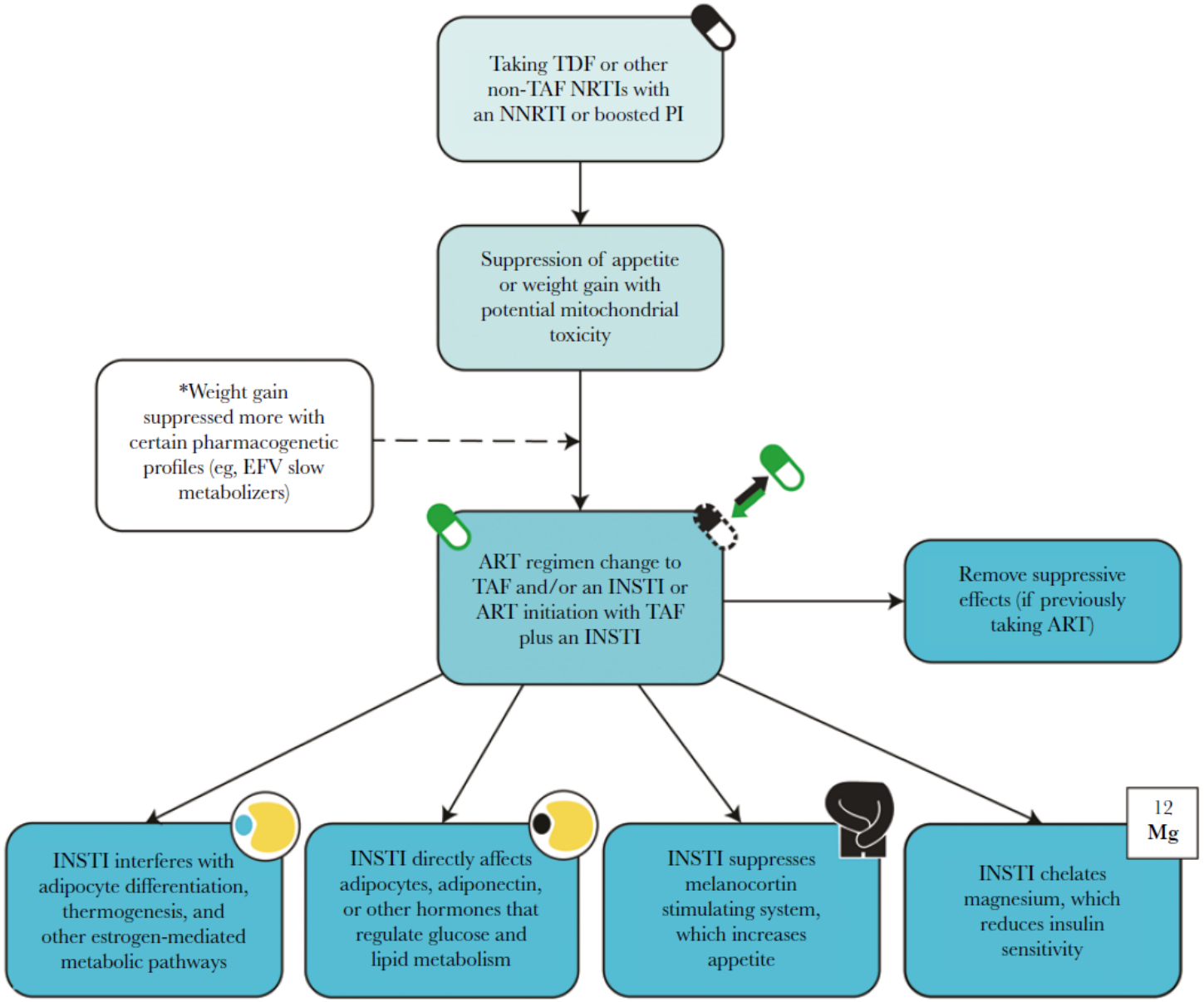
- INSTI-containing regimens associated with **greater** weight gain than NNRTI and PIs, especially when used with TAF
  - DTG = BIC > EVG/c > NNRTI or PIs
- Population at risk : women, Black and Hispanic people, lower baseline weight, lower baseline CD4, higher baseline HIV-1



Weight change and absolute weight in participants initiating antiretroviral therapy.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.
2. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020 Sep 12;71(6):1379-1389.
3. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, Koethe JR, Sterling TR. Greater Weight Gain in Treatment-naive Persons Starting Dolutegravir-based Antiretroviral Therapy. Clin Infect Dis. 2020 ;70(7):1267-1274.

Proposed Mechanisms of TAF- and INSTI-mediated Excess Weight Gain

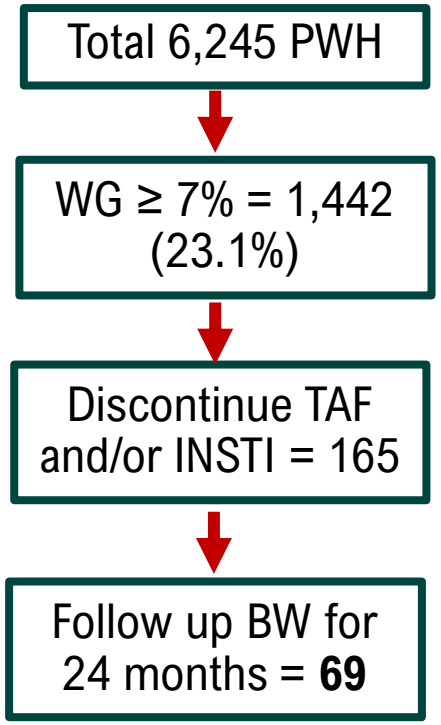


- All proposed mechanisms warrant further study for confirmation, and the explanation may be multifactorial.
- The clinical significance of this weight gain and their impact on cardiovascular diseases, diabetes, and age-related comorbidities among PLWHA are currently unknown.

Wood BR, Huhn GD. Excess Weight Gain With Integrase Inhibitors and Tenofovir Alafenamide: What Is the Mechanism and Does It Matter? Open Forum Infect Dis. 2021;8(12):ofab542.

Is excessive weight gain reversible after discontinue TAF or INSTI?

- Dutch ATHENA Cohort; total 6,245 PWH
- Inclusion criteria: PWH with ≥7% weight gain (WG) within 24 months after switch to TAF and/or INSTI + VL suppressed
- Exclusion criteria: PWH with comorbidities/co-medication known to be associated with WG



Body wight	Stopping only TAF (n=21)	Stopping only INSTI (n=37)	Stopping TAF+INSTI (n=11)
Mean WG before stopping ART(kg)	+ 3.20	+ 5.98	+ 5.84
Mean weight reduction 24 months after stopping ART(kg)	- 1.48	- 2.73	- 7.95

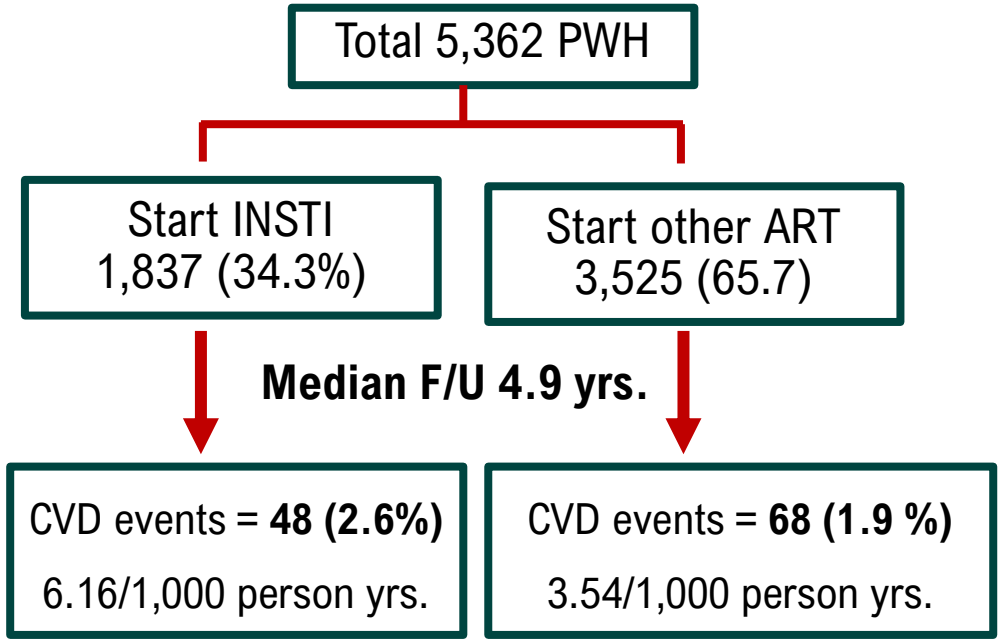
800 PWH continued TAF and/or INSTI after ≥7% WG, the adjusted mean weight change at 24 months = **-0.77** kg

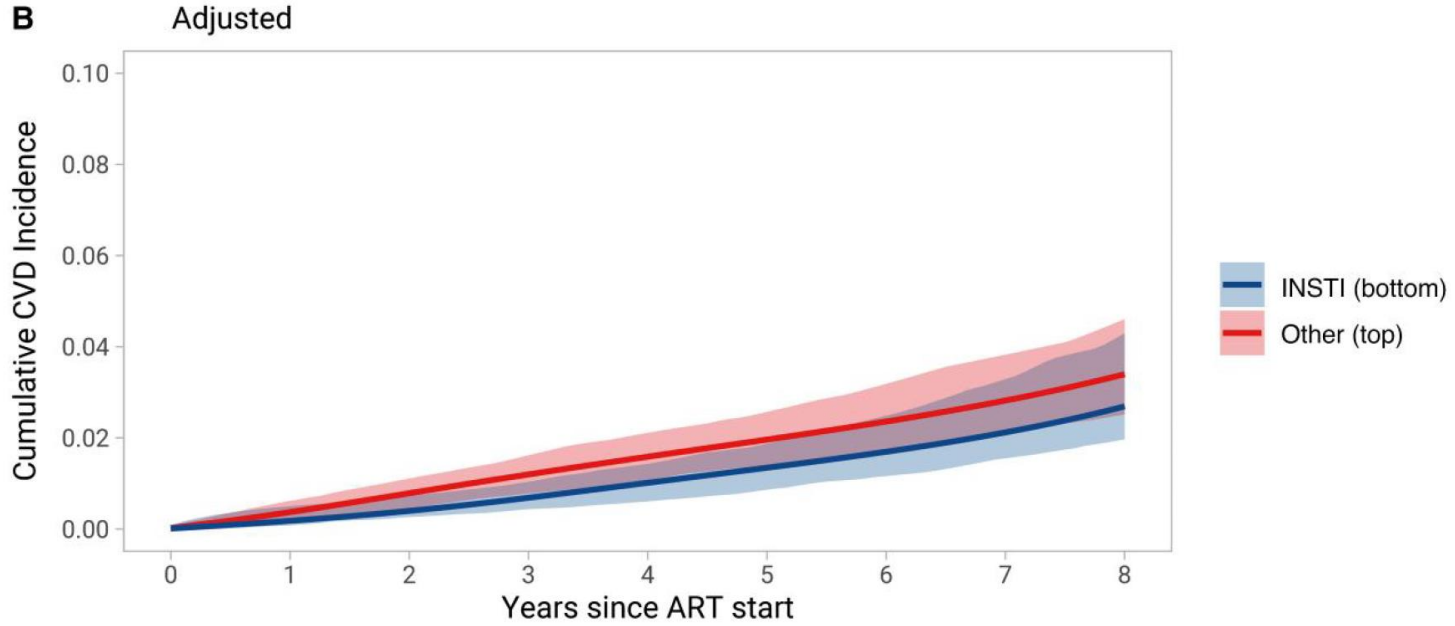
Conclusion: TAF and/or INSTI-associated WG of ≥7% appears to be only partly reversible after discontinuing TAF and/or INSTI

Verburgh ML, Wit F., Anders Boyd A., Reiss P., Van der Valk M. Reversibility of TAF- and/or INSTI-associated weight gain. Oral presentation, 30th Conference on Retroviruses and Opportunistic Infections, Seattle, Washington; Feb 19-22, 2023

Is INSTI-based ART increased cardiovascular disease event?

- ART-naïve Swiss HIV Cohort Study participants after May 2008
- **Primary outcome**: first of CVD event (MI, stroke, or invasive cardiovascular procedure) compare INSTI vs. other regimens.
- Adjusted multiple confounders covariate e.g., comorbidities, sex, age, personal and family history of CVD.





Cumulative incidence of cardiovascular disease (CVD) events after starting antiretroviral therapy

Conclusions: We found **no difference** in short- or long-term risk for CVD events between treatment-naïve people with HIV who started INSTI-based ART and those on other ART.

Surial B, Chammartin F, Damas J, Calmy A, Haerry D, Stöckle M, Schmid P, Bernasconi E, Fux CA, Tarr P, Günthard HF, Wandeler G, Rauch A; Swiss HIV Cohort Study. Impact of integrase inhibitors on cardiovascular disease events in people with HIV starting antiretroviral therapy. Clin Infect Dis. 2023 :ciad286.

Case 1: A young Thai male with weight gain

Management

- Initiated atorvastatin(40) 1-tab oral pc od and amlodipine (10) 1-tab oral pc od
- Monitor BW and metabolic profiles
- Continue TDF/FTC/DTG
- **Follow up visit (JUN-2023)**
  - BW: 95 kg, Height: 175 cm. [BMI: 31.15 kg/m^2], BP 120/85 mmHg
  - Lipid profile: Triglyceride 350 mg/dL, LDL < 81.8 mg/dL, HDL < 45 mg/dL
  - LFT: ASL: 58 IU/L, ALT: 127 IU/L

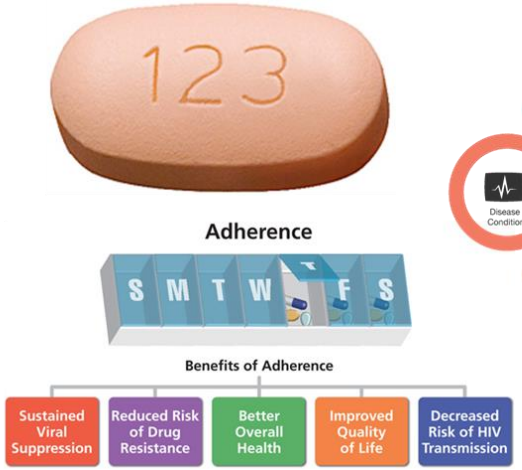
Case 1: Summary and Key points

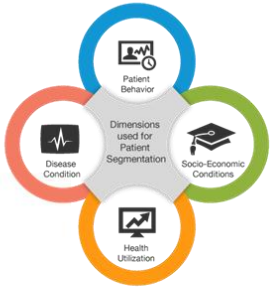
- INSTI-containing regimens associated with **greater** weight gain especially when used with TAF
  - [**DTG = BIC** > EVG/c > NNRTI or PIs]
- Risk factors: women, ↓ baseline weight, ↓ baseline CD4, ↑ baseline HIV-1
- TAF and/or INSTI-associated weight gain were partly reversible after discontinuing.
- To date, no difference in short- or long-term risk for CVD events between treatment-naïve people with HIV who started INSTI-based ART vs. other ART.
- **Management**
  - Close monitoring body weight and occurrence of weight related disease.
  - Multidisciplinary approach is suggested for proper management.
  - More data are required on which switch strategies should be adopted.

Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. Geneva: World Health Organization; 2022.

Case 2

A middle-aged Thai male with increased serum creatine





Case 2: A middle-aged Thai male with increased serum creatine

Case 45 yrs., male, government officer, live in Bangkok

- **Occupation**: government officer, **Health scheme**: civil servant medical benefit
- **First diagnosis**: Asymptomatic HIV infection (2015)
- **Physical examination**: unremarkable, BW: 70 kg, Height: 174 cm [BMI: 23.1 kg/m^2]
- **Initial laboratory assessment**

- Anti-HIV: reactive
- CD4+ T cell: 279 cell/μL (10.2%)
- LFT: ASL: 25 IU/L, ALT: 27 IU/L
- HBsAg: non-reactive, Anti-HBS: positive
- Anti-HCV: negative
- RPR : non-reactive, TPHA: negative
- Cr.: 1 mg/dL (eGFR: 95 mL/min/1.73 m^2)

- **Start TDF+3TC + EFV 1 tab oral at 21.00**

Case 2: A middle-aged Thai male with increased serum creatine

Date	Treatment	CD4+ T cell (%) [cell/µL]	HIV-1 VL [copies/mL]
MAR-2015	- Asymptomatic HIV infection: TDF+3TC+EFV at 21.00	279 (10.2)	NA
AUG-2015	- Asymptomatic HIV infection: TDF+3TC+EFV at 21.00	342 (12.8)	<20
JUL-2017	- Asymptomatic HIV infection: switch to STR: TDF/FTC/EFV at 21.00	445 (19.3)	<20
AUG-2018	- Asymptomatic HIV infection: TDF/FTC/EFV at 21.00	506 (20.1)	<20
JUL-2019	- Asymptomatic HIV infection: TDF/FTC/EFV at 21.00	512 (23.1)	<20
2019-2021	- Asymptomatic HIV infection: TDF/FTC/EFV at 21.00	488-484 (27-28)	<20
JUN-2022	- Switch to TDF/FTC/DTG at 21.00	437(27.3)	<20

Adherence: Good (>95%)

Case 2: A middle-aged Thai male with increased serum creatine

Date	Treatment	HIV-1 VL [copies/mL]	BW [kg]/ BMI [kg/m^2]	Creatinine [mg/dL]	BUN [mg/dL]	eGFR* [mL/min/1.73 m^2]
AUG-2015	TDF/FTC/EFV	<20	72/23.8	1	12	92
JUL-2017	TDF/FTC/EFV	<20	73/24.1	1.1	11	84
AUG-2018	TDF/FTC/EFV	<20	71/23.5	1.1	16.4	84
JUL-2019	TDF/FTC/EFV	<20	70/23.1	1	13.3	92
2019-2021	TDF/FTC/EFV	<20	72/23.8	1-1.1	12.3-15.8	84-92
JUN-2022	TDF/FTC/DTG	<20	**73/24.1**	**1**	**11.6**	**92**
DEC-2022	TDF/FTC/DTG	NA	**78/25.8**	**1.37**	**14.5**	**67**

*eGFR calculation by Cockcroft-Gault Equation

Case 2: A middle-aged Thai male with increased serum creatine

Additional history

- He was doing well, denied history of herb, over counter medicine or mineral supplement
- Exercise: jogging, 30 – 60 min/day, 3-4 days/weeks
- Social alcohol drinking (4-5 times/months), no smoking

Additional investigation

Serum electrolyte

Sodium (mEq/L)	141
Potassium (mEq/L)	4
Chloride (mEq/L)	105
Bicarbonate (mEq/L)	21
Phosphate (mEq/L)	3.07

Urinalysis

Sp.gr.	pH	Leukocyte	Nitrite	Glucose	Ketone	Uro billinogen	Billirubin	Blood	WBC	RBC
1.015	7	negative	negative	negative	negative	negative	negative	negative	0-1	0-1

Case 2: What is the most appropriate management?

Problem List

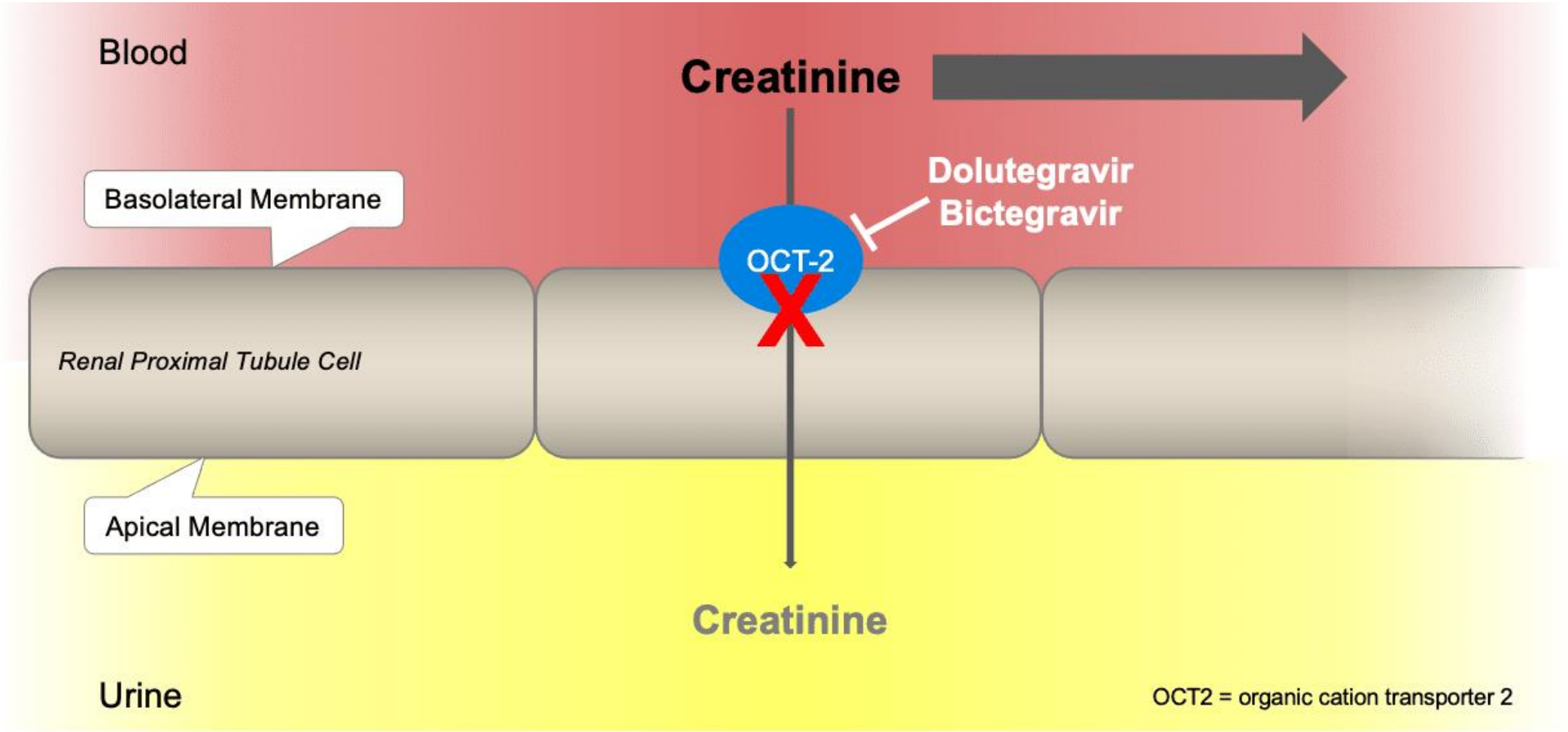
1. **Asymptomatic HIV infection on TDF/FTC/DTG**

2. **Increased serum creatinine** (1 →1.37 mg/dL)

    - **Acute kidney injury?**

INSTI-containing ART and Renal Adverse Effect

DTG and BIC decreases tubular secretion of creatinine without affecting glomerular function

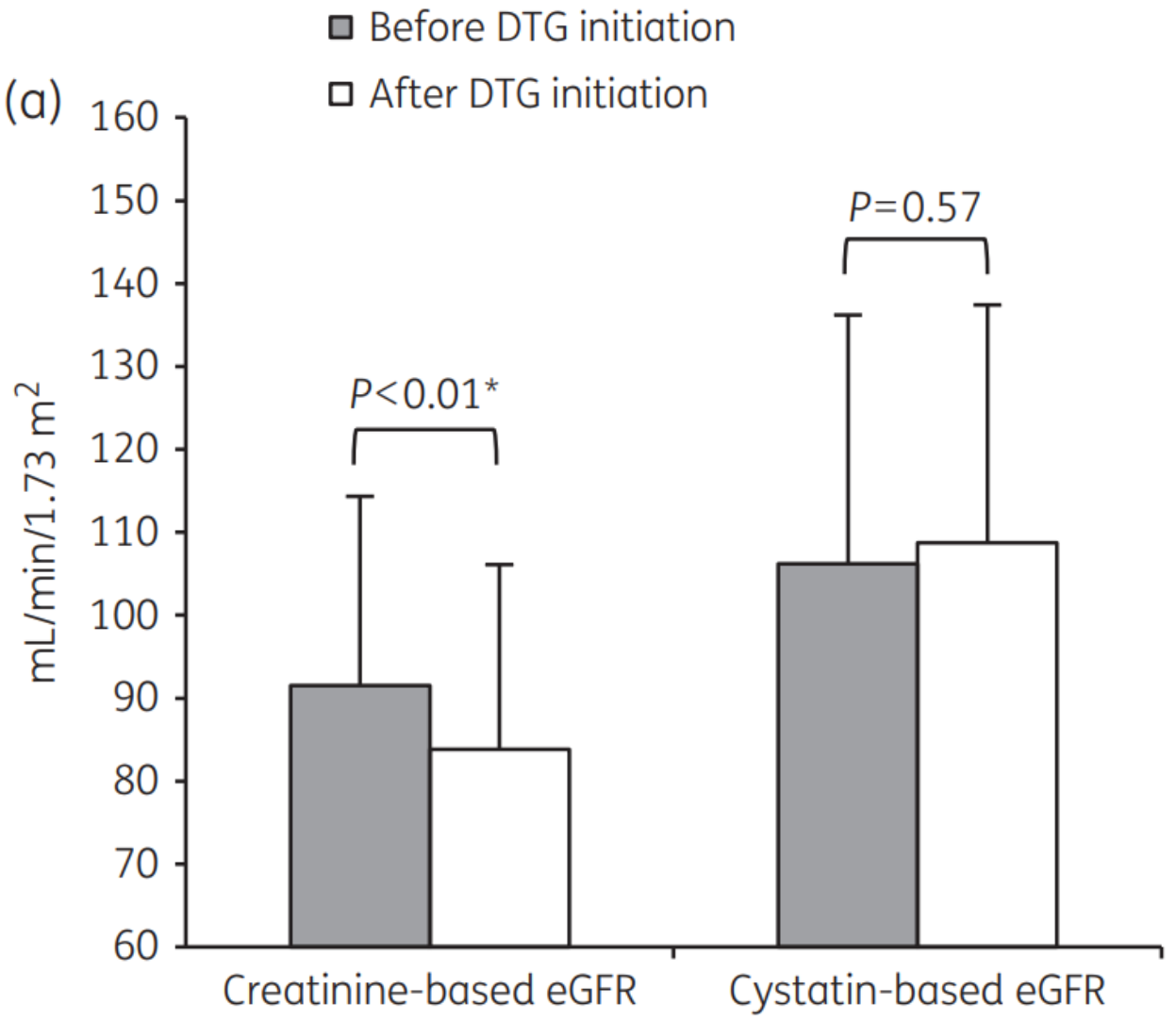


1. Adverse Effects of Antiretroviral Medications [Internet]. National HIV Curriculum. 2023 [cited 14/08/2023]. Available from: https://www.hiv.uw.edu/go/antiretroviral-therapy/adverse-effects/core-concept.
2. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors. Curr Treat Options Infect Dis. 2019;11(4):372-387.

Plasma cystatin C as a marker for eGFR assessment in HIV- infected patients treated with DTG-based ART

- 44 PWH who received DTG [6 ART naïve & 38 ART switching] performed both serum creatinine and cystatin C.
- **Primary outcome:** evaluate the changes in creatinine- and cystatin C-based eGFR before and after DTG initiation.
  - eGFR calculation: CKD-EPI$_{creat}$ and CKD-EPI$_{cyst}$
  - Mediant time of DTG exposure: 41 days

Conclusions: Creatinine values increased after DTG initiation, whereas **no change** was observed for cystatin C values.



Variation in plasma creatinine- and cystatin-based eGFR after DTG initiation

Palich R, Tubiana R, Abdi B, Mestari F, Guiguet M, Imbert-Bismut F, Katlama C, Bonnefont-Rousselot D, Isnard-Bagnis C. Plasma cystatin C as a marker for estimated glomerular filtration rate assessment in HIV-1-infected patients treated with dolutegravir-based ART. J Antimicrob Chemother. 2018; 73(7):1935-1939.

INSTI-containing ART and Increased Serum Creatinine

- DTG, EVG/c and BIC **decreases tubular secretion of creatinine** without affecting glomerular function.

- Serum creatinine are observed raising typically within the first **4** weeks of DTG or BIC therapy
  - Median increase of **0.10 - 0.2** mg/dL after 48 weeks

- Patients with a confirmed increase in serum creatinine **>0.4 mg/dL** from baseline should be monitored closely and evaluated for evidence of TDF-related proximal renal tubulopathy. [based on ECV/c recommendation]

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.

Case 2: A middle-aged Thai male with increased serum creatine

Management

- Continue TDF/FTC/DTG, inform and reassure the patient.
- Investigation: urine glucose: 1 mg/dL, urine potassium: 8 mg/dL, urine phosphate: 11.3 mg/dL [$FePO_4$: 12.8%]
- Ultrasonography of KUB (JUN-2023): normal size and shape of both kidneys, normal cortex and medulla

Date	Treatment	HIV-1 VL [copies/mL]	BW [kg]/ BMI [kg/m^2]	Creatinine [mg/dL]	BUN [mg/dL]	EGFR* [mL/min/1.73 m^2]
JUN-2022	TDF/FTC/DTG	<20	73/24.1	1	11.6	**92**
DEC-2022	TDF/FTC/DTG	NA	78/25.8	**1.37**	**14.5**	**67**
JUN-2023	TDF/FTC/DTG	<20	75/24.8	**1.28**	**12.7**	**77**

*eGFR calculation by Cockcroft-Gault Equation

Case 2: Summary and Key points

- DTG , EVG/c and BIC **decreases tubular secretion of creatinine** without affecting glomerular function.

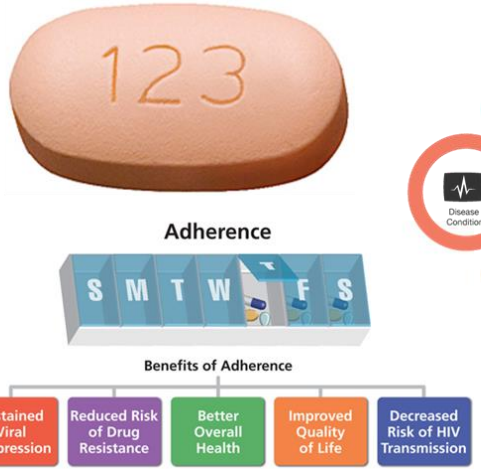
- Patients with a confirmed increase in serum creatinine **> 0.4** mg/dL after initiated INSTI should be caution and intensive investigation to confirmed AKI from any cause.

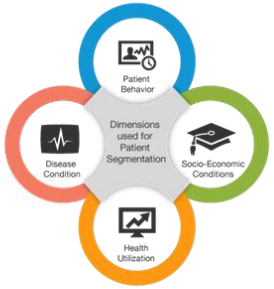
- All INSTIs can lead to mild increases in creatinine levels, usually without clinical significance, but caution is needed in patients with **low eGFR**, when using other nephrotoxic drugs, e.g., TDF.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.
2. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors. Curr Treat Options Infect Dis. 2019;11(4):372-387.

Case 3

A middle-aged Thai male with poor controlled T2DM





Case 3: A middle-aged Thai male with poor controlled T2DM

Case 58 yrs., male, government officer, live in Bangkok

- **Occupation**: government officer, **Health scheme**: civil servant medical benefit
- **First diagnosis**: Asymptomatic HIV infection (2008)
- **Physical examination**: unremarkable, BW: 83.6 kg, Height: 172 cm [BMI: 28.3 kg/m^2]
- **Initial laboratory assessment**

- Anti-HIV: reactive
- CD4+ T cell: 138 cell/µL (9.1%)
- LFT: ASL: 34 IU/L, ALT: 44 IU/L
- HBsAg: non-reactive, Anti-HBS: positive
- Anti-HCV: negative
- FPG: 112 mg/dL
- RPR : non-reactive, TPHA: negative
- Cr.: 0.8 mg/dL (eGFR: 95 mL/min/1.73 m^2)

- **Start AZT+3TC 1 tab oral at 8.00, 20.00 + EFV 1 tab oral at 20.00**

Case 3: A middle-aged Thai male with poor controlled T2DM

Date	Treatment	CD4+ T cell (%) [cell/μL]	HIV-1 VL [copies/mL]
SEP-2008	- Asymptomatic HIV infection: AZT+3TC+EFV - TMP/SMX prophylaxis	138(9.1)	NA
MAY-2009	- Asymptomatic HIV infection: AZT+3TC+EFV	270 (11)	<20
2010-2016	- Asymptomatic HIV infection: AZT+3TC+EFV	340-497 (13-26)	<20
SEP-2016	- Asymptomatic HIV infection: switch to STR TDF/FTC/EFV at 20.00	557(26)	<20
2017-2021	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00	538 - 587 (27)	<20
OCT-2022	- Asymptomatic HIV infection: TDF/FTC/EFV at 22.00 - Patient ask for change to INSTI-based regimen - No drug adverse effect from TDF/FTC/EFV	547 (30%)	<20

Adherence: Good (>95%)

Case 3: A middle-aged Thai male with poor controlled T2DM

Date	T2DM Treatment	BW [kg]/ BMI [kg/m^2]	BP [mmHg]	FPG [mg/dL]	Hb A1C [%]	LDL/HDL [mg/dL]
FEB-2011	Metformin 850 mg/day	83.6/ 28.3	130/90	208	7.8	160/55
JAN-2012	Metformin 1,700 mg/day Glipizide 5 mg/day	88/ 29.8	130/90	140-160	6.5-7.9	130/44
2013-2019	Metformin 2,450 mg/day Glipizide 20 mg/day	90/ 30.5	140/90	158-180	6.9-7.6	70-117/40-45
2020-2022	Metformin 2,450 mg/day Glipizide 20 mg/day Pioglitazone 15 mg/day	96/ 32.5	150/90	143-185	7.5-10	70-90/40-45
OCT-2022	Metformin 2,000 mg/day Vildagliptin 100 mg/day Gliclazide 60 mg/day	97/ 32.8	140/80	170	7.7	83/45

No diabetic retinopathy, no others macro or microvascular complication of diabetes

Case 3: A middle-aged Thai male with poor controlled T2DM

Additional history

- **Others underlying disease;** essential hypertension and dyslipidemia
- He was doing well, sedentary lifestyle, denied history of herb, over counter medicine or mineral supplement
- Exercise: not routine, social alcohol drinking (3-4 times/months), no smoking

Additional investigation

Sodium (mEq/L)	138
Potassium (mEq/L)	4.4
Chloride (mEq/L)	103
Bicarbonate (mEq/L)	21
BUN (mg/dL)	14.9
Creatinine (mg/dL)	1.06
eGFR (ml/min/1.73m^2)	77.5

Urinalysis

Sp.gr.	pH	Leukocyte	Nitrite	Glucose	Ketone	Uro billinogen	Billirubin	Blood	WBC	RBC
1.016	5	negative	negative	trace	negative	negative	negative	negative	0-1	0-1

Urine microalbumin: 4 mg/dL [< 29 mg/dL]

Case 3: Can we switch ART to TDF/FTC/DTG?

Problem List

1. **Asymptomatic HIV infection on TDF/FTC/EFV**
2. **Poor controlled T2DM**
3. **Obesity** [BMI: 32.8 kg/m^2]
4. **Essential hypertension**
5. **Dyslipidemia**

Current medications

- TDF/FTC/EFV 1 tab at 20.00
- Metformin/vildagliptin (50/1,000) 1-tab oral pc bid
- Amlodipine/valsartan (10/160) 1-tab oral pc od
- Gliclazide MR (60) 1-tab oral ac od
- Simvastatin (20) 1-tab oral pc od

INSTI-containing ART Associated Drug Interaction [1]

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Polyvalent Cation (e.g., Ca, Mg, Al, Fe, Zn)	DTG, BIC	Concentrations of PO INSTIs are decreased	Administer polyvalent cation containing drugs at least **2 h. before** or **6 h. after** DTG.
Rifampin	DTG	DTG AUC ↓ 54%	Use DTG 50 mg twice daily (instead of DTG 50 mg OD)
	BIC	BIC AUC ↓ 75%	Contraindicated
Metformin	DTG	Metformin AUC ↑ 79%	- Start metformin at the lowest dose and titrate based on glycemic control. (**≤ 1,000** mg/day) - Monitor for adverse events of metformin.
	BIC	Metformin AUC ↑ 39%	Monitor for adverse events of metformin.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.

INSTI-containing ART Associated Drug Interaction [2]

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Dexamethasone (systemic)	DTG	↔ DTG	No dose adjustment needed
	BIC	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV
Carbamazepine	DTG	DTG AUC ↓ 49%	Use DTG 50 mg twice daily (instead of DTG 50 mg OD)
	BIC	↓ BIC possible	Do not co-administer

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.

DTG and Metformin Drug Interaction

- DTG decreases the renal clearance of metformin (MFM) by inhibiting organic cation transporters in renal tubular cells.
- Co-administration of dolutegravir 50 mg q 24 h. increased MFM area under the curve(AUC) by 79% and C_{max} by 66% in healthy subject.
- The clinical significance of these interactions is unclear.
- **Real life experience**: multicenter, retrospective case series evaluating 19 PWH concurrently prescribed DTG and MFM. [36.8% of PWH received MFM >1,000 mg/day]
- Efficacy: 72% had stable or decreased HbA_1C values
- Adverse effect
  - 68% increased serum Cr. (median 0.3 mg/dL), 16% had GI distress, 16% had hypoglycemic symptoms
  - 21% had adverse drug reactions resulted in MFM dose reduction and/or discontinuation

1. Song IH, Zong J, Borland J, Jerva F, Wynne B, Zamek-Gliszczynski MJ, Humphreys JE, Bowers GD, Choukour M. The Effect of Dolutegravir on the Pharmacokinetics of Metformin in Healthy Subjects. J Acquir Immune Defic Syndr. 2016;72(4):400-7.
2. Masich A, Badowski ME, Liedtke MD, Fulco PP. Evaluation of the concurrent use of dolutegravir and metformin in human immunodeficiency virus-infected patients. Int J STD AIDS. 2017; 28(12):1229-1233.

Case 3: A middle-aged Thai male with poor controlled T2DM

Management

- Continue TDF/FTC/EFV
- Diabetic controlled; diet counselling, encourage exercise and weight reduction

Date	T2DM Treatment	BW [kg]/ BMI [kg/m^2]	BP [mmHg]	FPG [mg/dL]	Hb A1C [%]	LDL/HDL [mg/dL]
OCT-2022	Metformin 2,000 mg/day Vildagliptin 100 mg/day Gliclazide 60 mg/day	97/ 32.8	140/80	170	7.7	83/45
JUN-2023	Metformin 2,000 mg/day Vildagliptin 100 mg/day Gliclazide 60 mg/day	97/ 32.8	130/80	172	7.7	76/46

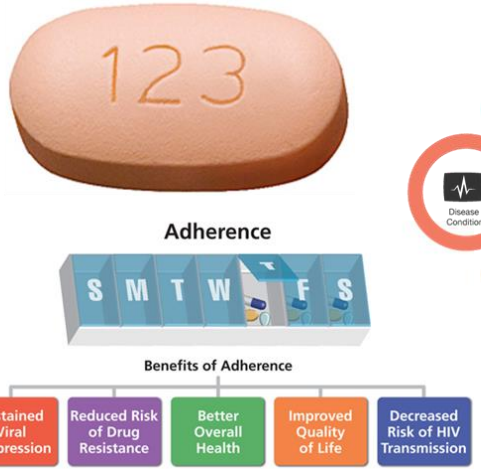
Case 3: Summary and Key points

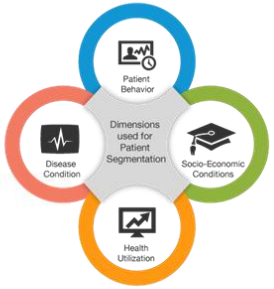
- Metformin had a significant increase in metformin levels when co-administered with DTG.
- This should prompt clinicians to closely monitor MFM adverse reaction especially **lactic acidosis** symptoms.
- Guidelines suggest limiting the total daily dose of metformin to **1,000** mg.
- Further understanding of these pathways, and the clinical significance of this drug interaction mechanism is needed.

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.
2. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors. Curr Treat Options Infect Dis. 2019;11(4):372-387.

Case 4

A young Thai female with first trimester pregnant





Case 4: A young Thai female with first trimester pregnant

Case 19-year-old female, unemployed, live in Bangkok

- **Consultation for HIV treatment from ANC clinic**
- She was pregnant (G1P0) with GA 9 weeks.
- She had unprotected SI with multiple sexual partner since she was 15.
- She had a small tattoo on her back which tattooing by her husband.
- **Past history**: no history of significance medical or surgical illness.
- **Alcohol & smoking**: social alcohol drinking (2-4 times/months), no smoking
- **Occupation**: unemployed, **Education**: secondary school, **Health scheme**: universal coverage
- **Couple**: husband (truck driver), 27-year-old, Anti-HIV: non-reactive, current smoking 10 pack-year

Case 4: A young Thai female with first trimester pregnant

Hb (g/L)	12.6
Hct (%)	38
Wbc (/ul)	8,400
Pmn (%)	57
Lymp (%)	29.3
Mono (%)	11.6
Eo (%)	0
Baso (%)	0
Plt (/ul)	333,000
MCV (fl)	80.2
RDW (%)	14
MPV (fl)	7.6
MCH (pg)	26.5
MCHC (g/dl)	33.1

Initial laboratory assessment

- Anti-HIV: reactive
- CD4+ T cell: 214 cell/μL (9%)
- HIV VL: 203,000 copies/mL
- HBsAg: non-reactive, Anti-HBS: positive
- Anti-HCV: negative
- RPR : non-reactive, TPHA: negative
- Creatinine: 0.5 mg/dL [eGFR 137 mL/min/1.73 m^2]
- AST/ALT: 17/17 IU/L
- Urinalysis: trace proteinuria

Case 4: Can we start TDF/3TC/DTG?

Problem List

1. **Asymptomatic HIV infection**
   - CD4+ T cell: 214 cell/μL (9%), HIV-1 VL: 203,000 copies/mL
2. **First trimester pregnancy**
   - G1P0, GA 9 weeks

Current medications [start prior 2 weeks]

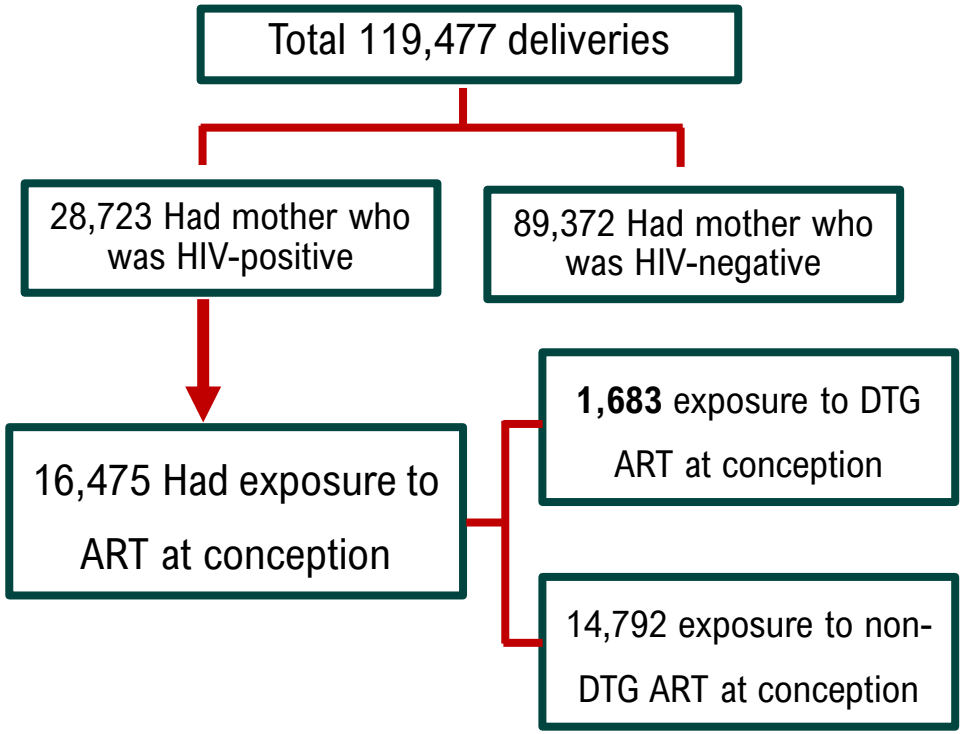
- Folic acid (5) 1-tab oral pc od morning
- Ferrous fumarate (200) 1-tab oral pc od morning

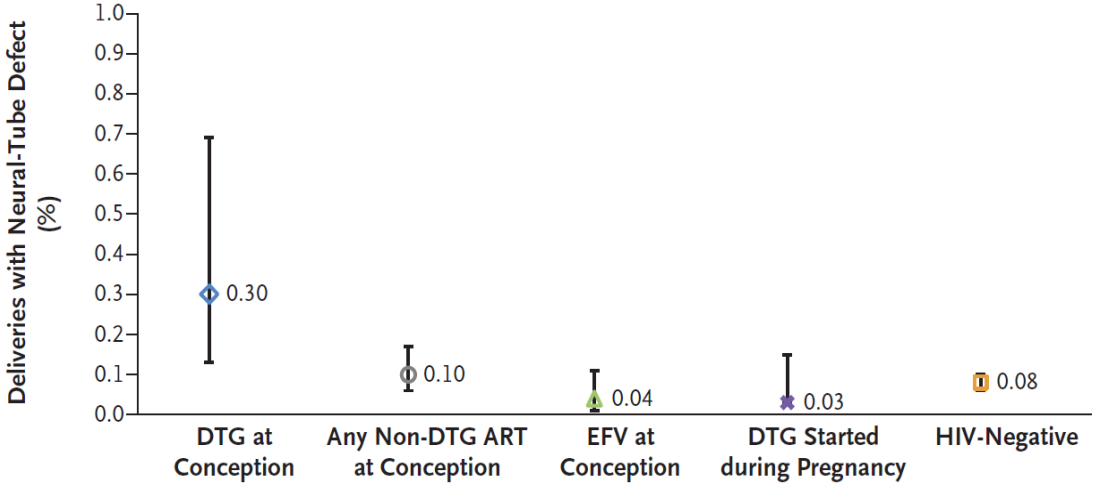
Case 4: A young Thai female with first trimester pregnant

Date	Treatment	GA (wks.)	CD4+ T cell (%) [cell/μL]	HIV-1 VL [copies/mL]
DEC-2022	- Asymptomatic HIV infection: start TDF/FTC/DTG at 20.00 - Pregnancy: folic and ferrous supplement	9	214 (9)	203,000
JAN-2023	- Asymptomatic HIV infection: TDF/FTC/DTG at 20.00 - Good adherence (>95%), no adverse drug reaction - Pregnancy: folic and ferrous supplement	13	NA	NA
MAR-2023	- Asymptomatic HIV infection: TDF/FTC/DTG at 20.00 - Good adherence (>95%), no adverse drug reaction - Pregnancy: folic and ferrous supplement	24	350 (12)	87
MAY-2023	- Asymptomatic HIV infection: TDF/FTC/DTG at 20.00 - Good adherence (>95%), no adverse drug reaction - Pregnancy: folic and ferrous supplement	33	NA	<20

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana (The Tsepamo Study)

- Birth-outcomes surveillance at hospitals throughout Botswana during **AUG 2014 - MAR 2019**
- **Methodology**: surface examinations and photograph of all liveborn and stillborn infants by midwives.
- **Primary outcomes**: evaluated the signal for neural tube defects with follow-up of additional births.





	DTG at Conception	Any Non-DTG ART at Conception	EFV at Conception	DTG Started during Pregnancy	HIV-Negative
No. of Neural-Tube Defects	5	15	3	1	70
No. of Exposures	1683	14,792	7959	3840	89,372
Percent with Defect (95% CI)	0.30 (0.13–0.69)	0.10 (0.06–0.17)	0.04 (0.01–0.11)	0.03 (0.00–0.15)	0.08 (0.06–0.10)
Difference in Prevalence (95% CI) — Percentage Points	Reference	0.20 (0.01–0.59)	0.26 (0.07–0.66)	0.27 (0.06–0.67)	0.22 (0.05–0.62)

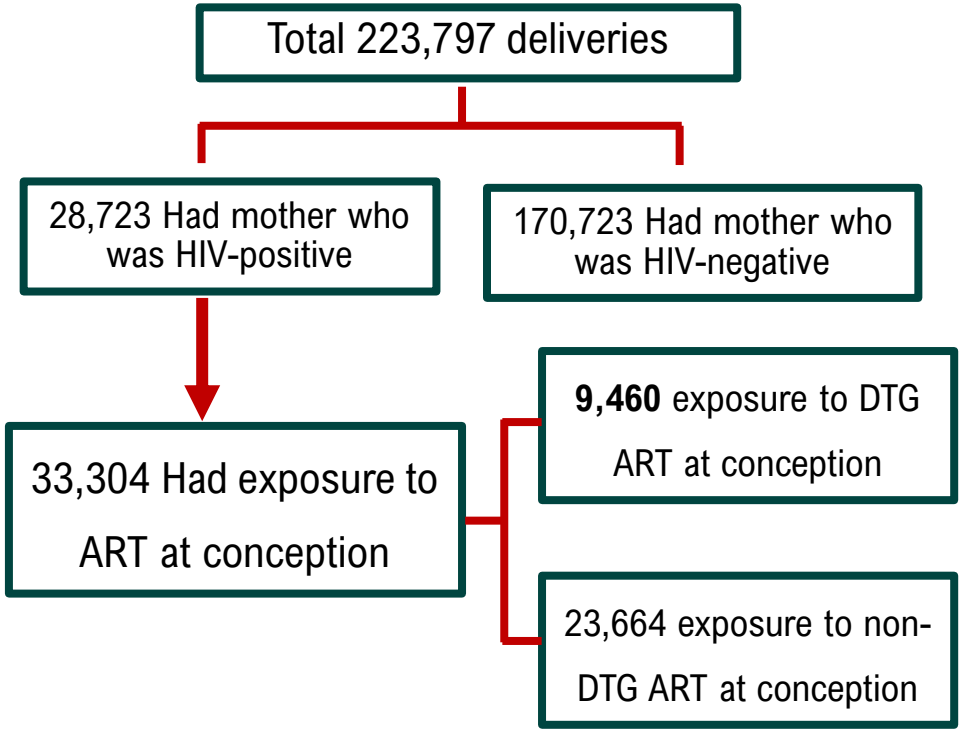
Neural-Tube Defects According to Maternal ART and HIV Infection Status, AUG 2014-MAR 2019

Conclusions: The prevalence of neural-tube defects was slightly higher in association with dolutegravir exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries).

Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, Davey S, Mabuta J, Mmalane M, Gaolathe T, Essex M, Lockman S, Makhema J, Shapiro RL. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019;381(9):827-840.

Update on Neural Tube Defects with Antiretroviral Exposure in the Tsepamo Study, Botswana

- Birth-outcomes surveillance at hospitals throughout Botswana extended duration during **AUG 2014 - MAR 2022**
- **Methodology**: surface examinations and photograph of all liveborn and stillborn infants by midwives
- **Primary outcomes**: evaluated the signal for neural tube defects with follow-up of additional births.



Prevalence Difference of Neural Tube Defects by ARV and HIV Exposure Categories

Exposure vs. Comparison group	Prevalence (%)	Prevalence Difference(%) (95% CI)
DTG vs. Non-DTG at conception	0.11 vs. 0.11	0.00 (-0.07, 0.10)
DTG vs. EFV at conception	0.11 vs. 0.08	0.03 (-0.05, 0.12)
DTG at conception vs. DTG started in pregnancy	0.11 vs. 0.06	0.04 (-0.06, 0.14)
DTG at conception vs. Women without HIV	0.11 vs. 0.06	0.04 (-0.01, 0.13)

Conclusions: The prevalence of NTDs among infants born to women on DTG at conception has declined slightly to 0.11% and does **not substantially differ** from other exposure groups.

These data support existing WHO guidelines that recommend DTG as first-line for use in all adults, regardless of reproductive potential.

Zash R. Holmes L.B., Diseko M., Jacobson D., et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. Presented at: AIDS 2022; 2022. Montreal, Canada. Available at: https://programme.aids2022.org/Abstract/Abstract/?abstractid=12759.

Current Guidelines Recommendation for ART Initiation in Pregnant Women

Guidelines	Recommendation	Comments
DHHS 2023	- Preferred regimen: ABC/3TC/DTG, TXF/XTC/DTG, TXF/XTC/DRV/r	- Preferred DRV/r regimen for initial treatment in people with early HIV infection and a history of CAB exposure for PrEP.] - First-trimester exposure to DTG has not been associated with increased risk of congenital anomalies, including neural tube defects.
EACS 2022	- Preferred regimen: ABC/3TC/DTG, TXF/XTC/DTG, TXF/XTC/RAL, TXF/XTC/DRV/r	- DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy. - TAF/FTC not recommended in first 14 weeks of pregnancy.
WHO 2021	- Preferred regimen: NRTI backbone + DTG	- Benefit of DTG out weight risk
Thailand 2021-2022	- Preferred regimen: TXF/XTC/DTG	- Benefit of DTG out weight risk - Recommended concurrent folic supplement and perform fetal ultrasonography at GA 18-20 weeks.

1. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Department of Health and Human Services
2. Guidelines for the management of people living with HIV in Europe. 2022. Available at https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2022.pdf
3. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021.
4. Ruxrungtham K, Chokephaibulkit K, Chetchotisakd P, Chariyalertsak S, Kiertburanakul S, Putacharoen O, et al. Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022. Nonthaburi: Division of AIDS and STIs, Department of Disease Control; 2022.

Case 4: A young Thai female with first trimester pregnant

Fetal ultrasonography [FEB-2023]

- GA 20 weeks, female, no fetal anomaly

Perinatal care

- In labor: GA 38 weeks, Vaginal delivery

Her infant

- A healthy girl, APGAR; 9, 10, birth weight; 2,830 gm.

Case 4: Summary and Key points

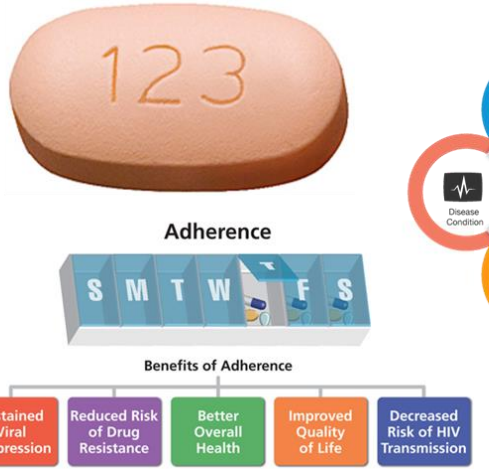
- The prevalence of neural tube defects among infants born to women on DTG at conception does not substantially differ from other ART exposure groups.

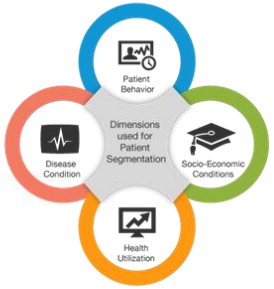
- Current evidence supported use of DTG among childbearing age and pregnant women.

- All current guidelines suggest use of DTG-containing regimen ART among childbearing age and pregnant women.

Case 5

An elderly Thai male with HIV virologic failure





Case 5: An elderly Thai male with HIV virologic failure

Case 75 yrs., male, retired, live in Bangkok

- **Occupation**: retired (previous government employee), **Health scheme**: universal coverage
- **First diagnosis**: AIDS with Pneumocystis pneumonia(2002; age 54-year-old)
- **Initial laboratory assessment** (2002)

- Anti-HIV: reactive
- CD4+ T cell: 183 cell/μL (10%)
- HBsAg: non-reactive, Anti-HBS: negative
- Anti-HCV: negative
- RPR : non-reactive, TPHA: negative
- Cr.: 0.9 mg/dL (eGFR: 95 mL/min/1.73 m^2)

- **Start d4T/3TC/NVP** (GPOvir S-30) **1 tab oral at 8.00, 20.00 (2002)**

Case 5: An elderly Thai male with HIV virologic failure

Date	Treatment [1]	CD4+ T cell (%) [cell/μL]	HIV-1 VL [copies/mL]
2002	- AIDS: start d4T/3TC/NVP (GPOvir S-30) 1 tab oral at 8.00, 20.00	183 (10)	NA
2002-2015	- HIV infection: d4T/3TC/NVP (GPOvir S-30)	255-344 (13-18)	<20
DEC-2016	- HIV infection: d4T/3TC/NVP (GPOvir S-30) - Virologic failure - HIV-1 drug resistant genotype: NRTI; M184V, NNRTI; G190A - Switch ART to AZT+TDF+LPV/r at 8.00, 20.00	143 (6.9)	14,700
MAY-2017	- HIV infection: AZT+TDF+LPV/r	414 (12.3)	<20
2018 - 2021	- HIV infection: AZT+TDF+LPV/r	238 -249 (11-12)	30 - 80

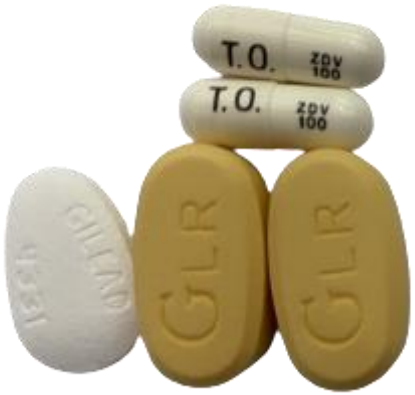
Case 5: An elderly Thai male with HIV virologic failure

Date	Treatment [2]	CD4+ T cell (%) [cell/μL]	HIV-1 VL [copies/mL]
NOV-2021	- HIV infection: AZT+TDF+LPV/r - Enhance adherence counselling	213 (12)	766
NOV-2022	- HIV infection: AZT+TDF+LPV/r - Enhance adherence counselling	249 (12)	896
APR-2023	- HIV infection: AZT+TDF+LPV/r - Virologic failure - HIV-1 drug resistant genotype: - NRTI; D67N - NNRTI; none - PIs: M46I, I47V, L76V, I84V	143 (6.9)	2,840

Case 5: An elderly Thai male with HIV virologic failure

Additional history

- Others underlying disease; none
- He was doing well, denied history of herb, over counter medicine or mineral supplement
- Adherence: 60-70%, usually forgot to take medicine and 1-2 h. late, complaint about pill burden.
- Lack of care giver; his wife pass away 2 years ago.
- Mild cognitive impairment
    - [Thai Mental State Examination score = 21]



Physical examinations: unremarkable

- BP; 135/70 mmHg, BW 44 kg., Height 160 cm [BMI 17 kg/m^2]

Case 5: An elderly Thai male with HIV virologic failure

Additional investigation

Hb (g/L)	12.6
Hct (%)	38
Wbc (/ul)	8,400
Pmn (%)	57
Lymp (%)	29.3
Mono (%)	11.6
Eo (%)	0
Baso (%)	0
Plt (/ul)	333,000
MCV (fl)	80.2
RDW (%)	14
MPV (fl)	7.6
MCH (pg)	26.5
MCHC (g/dl)	33.1

Sodium (mEq/L)	137
Potassium (mEq/L)	4.35
Chloride (mEq/L)	103
Bicarbonate (mEq/L)	22
Phosphate (mg/dL)	3.5
BUN (mg/dL)	13.5
Creatinine (mg/dL)	1.02
eGFR (ml/min/1.73m^2)	71

FPG (mg/dL)	100
Cholesterol (mg/dL)	145
Triglyceride (mg/dL)	108
HDL (mg/dL)	53
LDL (mg/dL)	81
Albumin (g/dL)	4.29
AST (U/L)	44
ALT (U/L)	21

Sp.gr.	pH	Leukocyte	Nitrite	Glucose	Ketone	Uro billinogen	Billirubin	Blood	WBC	RBC
1.015	7	negative	negative	negative	negative	negative	negative	negative	0-1	0-1

Urinalysis

Case 5: Can we switch ART to TDF/FTC/DTG?

Problem List

1. **Acquired drug resistance HIV infection**

   • CD4+ T cell: 143 cell/μL (6.9%), HIV-1 VL: 2,840 copies/mL

2. **Elderly with mild cognitive impairment and lack of care giver**

Current medications

- Zidovudine (100) 2-tab oral at 08.00, 20.00
- Lopinavir/ritonavir (200/50) 2-tab oral at 08.00, 20.00
- TDF (300) 1-tab oral at 08.00

Case 5: An elderly Thai male with HIV virologic failure

Cumulative HIV-1 drug resistant genotype

- **NRTI**: D67N, M184V
- **NNRTI**: G190A
- **PIs**: M46I, I47V, L76V, I84V
- **INSTI**: none

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Intermediate Resistance
etravirine (ETR)	Potential Low-Level Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Low-Level Resistance

Protease Inhibitors	
atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Intermediate Resistance
lopinavir/r (LPV/r)	High-Level Resistance

Mutational analysis using HIVdb Program: Mutations Analysis (Stanford University HIV Drug resistance Database)

Principle of ART Selection in Multi-class Antiretroviral Treatment Failure

- Evaluation of virologic failure should include an assessment of
  - ART adherence, drug–drug and drug–food interactions, drug tolerability, **factors contribute virologic failure**.
  - HIV-RNA level and CD4 T lymphocyte (CD4) cell count trends over time.
  - ART history, and prior and current drug-resistance test results.
  - History of co-infection especially hepatitis B.
- Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen or within **4** weeks of treatment discontinuation.
- A new regimen can include two fully active ARV drugs if at least one with a high resistance barrier is included (e.g., DTG or DRV/r)
- Adding a single ARV drug to a virologically failing regimen is **not recommended.**

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.
2. Ruxrungtham K, Chokephaibulkit K, Chetchotisakd P, Chariyalertsak S, Kiertburanakul S, Putacharoen O, et al. Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022. Nonthaburi: Division of AIDS and STIs, Department of Disease Control; 2022.

Principle of ART Selection in Multi-class Antiretroviral Treatment Failure

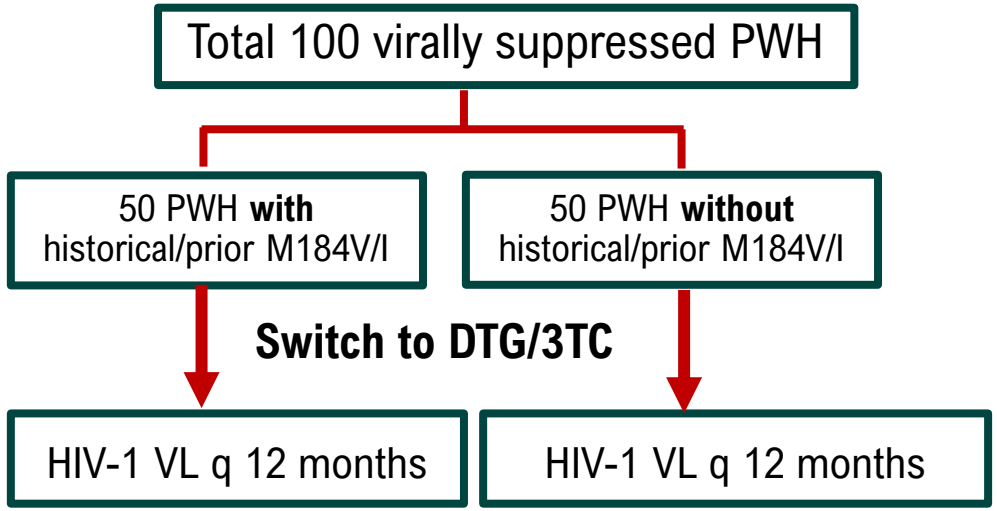
Failure regimen	Predicted mutation	Recommended new ART
NNRTI + NRTIs	NNRTIs RAMs	- Same NRTIs + DTG
	NNRTIs RAMs + M184V/I	- 2 active NRTIs + DTG
	NNRTIs RAMs + NRTIs RAMs (multiple)	- Boosted PIs + DTG
Boosted PIs + NRTIs	NRTIs RAMs (without PIs RAMs)	- 2 active NRTIs + DTG or boosted PIs - RPV + DTG
	NRTIs RAMs + PIs RAMS	- 2 active NRTIs + boosted PIs or DTG - Expert consultation
NRTIs + RAL	M184V/I + integrase inhibitor resistance mutation	- Expert consultation
DTG + NRTIs	NRTIs RAMs	- 2 active NRTIs + DTG - Boosted PIs + DTG - 2 active NRTIs + boosted PIs - RPV + DTG

RAMs; resistance–associated mutations

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Updated MAY 2023.
2. Ruxrungtham K, Chokephaibulkit K, Chetchotisakd P, Chariyalertsak S, Kiertburanakul S, Putacharoen O, et al. Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2021/2022. Nonthaburi: Division of AIDS and STIs, Department of Disease Control; 2022.

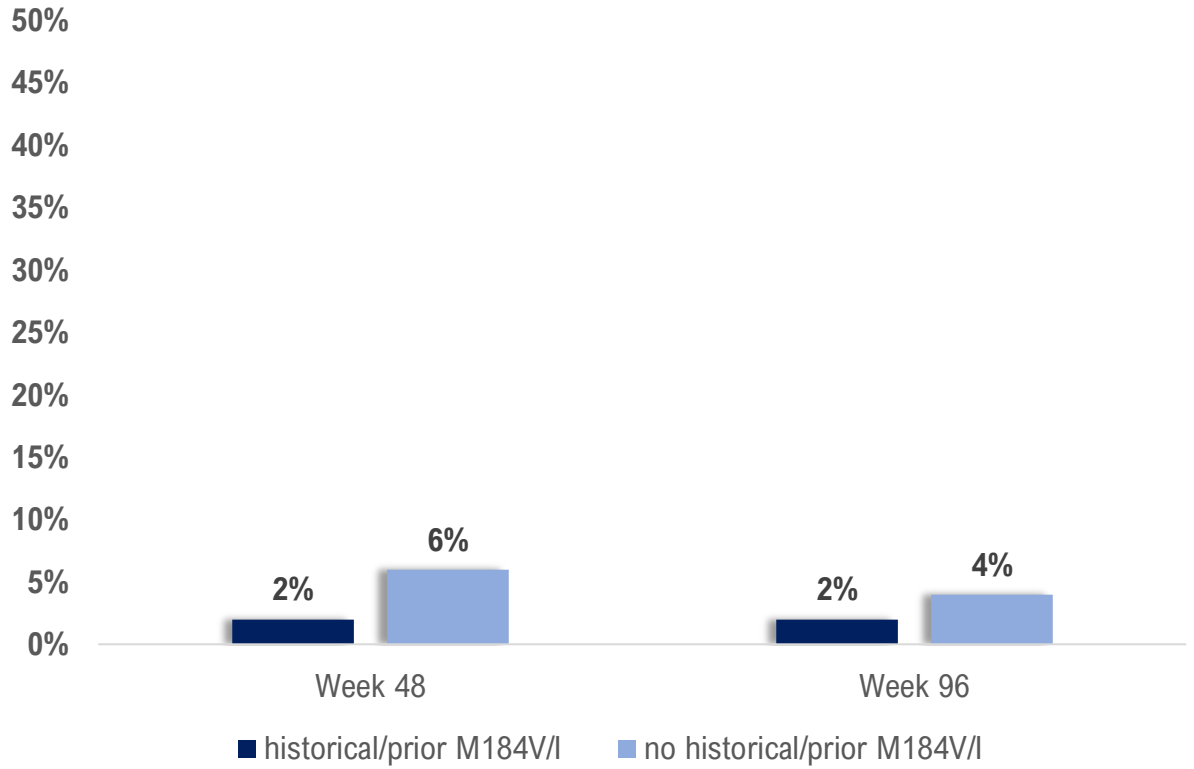
Prior M184V/I and multiple prior virological failures have no impact on the efficacy of switching HIV+ adults to DTG/3TC through 96Wks in SOLAR-3D

- Prospective, open-label, comparative 96-week study, enrolled form May 2019-April 2020 in US.
- Primary outcome: HIV-1 VL ≥ 50 copies/mL at 48, and 96 weeks



Baseline Proviral DNA NGS demonstrated M184V/I was no longer present in 64.4% of those with prior M184V/I

Primary virologic outcome: HIV-1 VL ≥ 50 copies/mL at 48, and 96 weeks



Conclusion: Through 96 weeks, SOLAR-3D, confirms prior history/current presence of M184V/I does not impact the efficacy of DTG/3TC switching in virologically suppressed PWH.

G. Blick, E. Cerreta, G. Mancini, A. Cosenza, L. Fang.Prior M184V/I and multiple prior virological failures have no impact on the efficacy of switching HIV+ adults to DTG/3TC through 96Wks in SOLAR-3D. oral presentation, 12th IAS Conference on HIV Science, Brisbane, Australia; July 23-26, 2023

Case 5: An elderly Thai male with HIV virologic failure

Management

- Switch ART to TDF/3TC/DTG at 20.00
- Enhance adherence counselling

- **Follow-up visit at JUN-2023**
  - He was doing well, no adverse drug reaction
  - Adherence 90%
  - Plan follow up HIV-1 VL next visit

Case 5: Summary and Key points

- Drug-resistance testing is recommended in persons with virologic failure and HIV RNA >1,000 copies/mL.

- Carefully review ART history, and prior and current drug-resistance test results.

- A new regimen can include two fully active ARV drugs if at least one with a high resistance barrier is included (e.g., DTG or DRV/r)

- It is important to consider the factors contribute virologic failure before designing new ART regimen.
  - If possible, should be consider well-tolerated and adherence-friendly regimens.

Q & A

Thank You


HIV TREATMENT
as PREVENTION
A HIGHLY EFFECTIVE STRATEGY TO PREVENT THE SEXUAL TRANSMISSION OF HIV
People living with HIV who take
HIV medication daily
as prescribed
and get and keep an
undetectable viral load
have effectively no risk of
sexually transmitting HIV
to their HIV-negative partners
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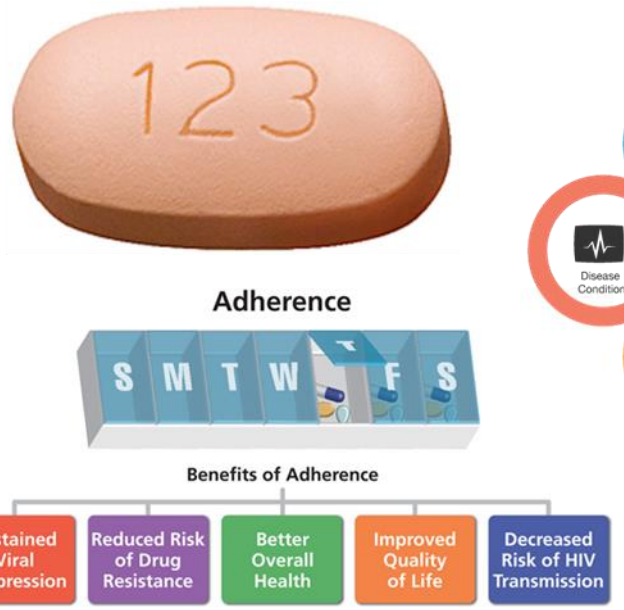
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Adherence
S M T W F S
Benefits of Adherence
Sustained Viral Suppression
Reduced Risk of Drug Resistance
Better Overall Health
Improved Quality of Life
Decreased Risk of HIV Transmission


Patient Behavior
Disease Condition
Dimensions used for Patient Segmentation
Socio-Economic Conditions
Health Utilization