ขอเชิญสมาชิกสมาคมโรคเอดส์แห่งประเทศไทย

เข้าร่วมประชุมใหญ่สามัญประจำปี 2567 และฟังบรรยายพิเศษ

ผ่านระบบการประชุมออนไลน์ zoom

วันศุกร์ที่ 22 มีนาคม 2567

12.00-12.05 น. เปิดการประชุม โดย นายกสมาคมโรคเอดส์แห่งประเทศไทย

12.05-12.45 น. บรรยายพิเศษ เรื่อง "A Practical Approach to Transition from TDF to TAF"
รศ. นพ.โอภาส พุทธเจริญ, พญ.อัญชลี อวิหิงสานนท์

12.45.-13.15 น. การประชุมใหญ่สามัญประจำปี 2567
- เลือกตั้งนายกสมาคมโรคเอดส์แห่งประเทศไทย

HIV treatment is a marathon

Start → Maintain viral suppression → **Switch** → Maintain QOL

- New ART agents with **long-term durability**
- New formulations with **enhanced adherence**
- **Affordable**

- **Cure**/Remission strategies

- New ART agents with **new mechanism of action**

- Adherence

- ART initiation in **various settings**
- OI management

- **Treatment failure**
- **Comorbidities**

- Stigmatization
- Sexual health/STIs
- Aging and comorbidities

Beyond undetectable

Start → Maintain viral suppression → Switch → Maintain QOL

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ทำไมต้อง Transition จาก TDF to TAF?

TDF มีผลต่อ BMD > TAF

TDF มีผลต่อ renal biomarkers > TAF

ราคาไม่ต่างจาก TLD

Efficacy : TDF =TAF

Weight Gain:

- **Greater weight gain after ART** initiation with TAF >TDF and ABC.

Lipid Effects:

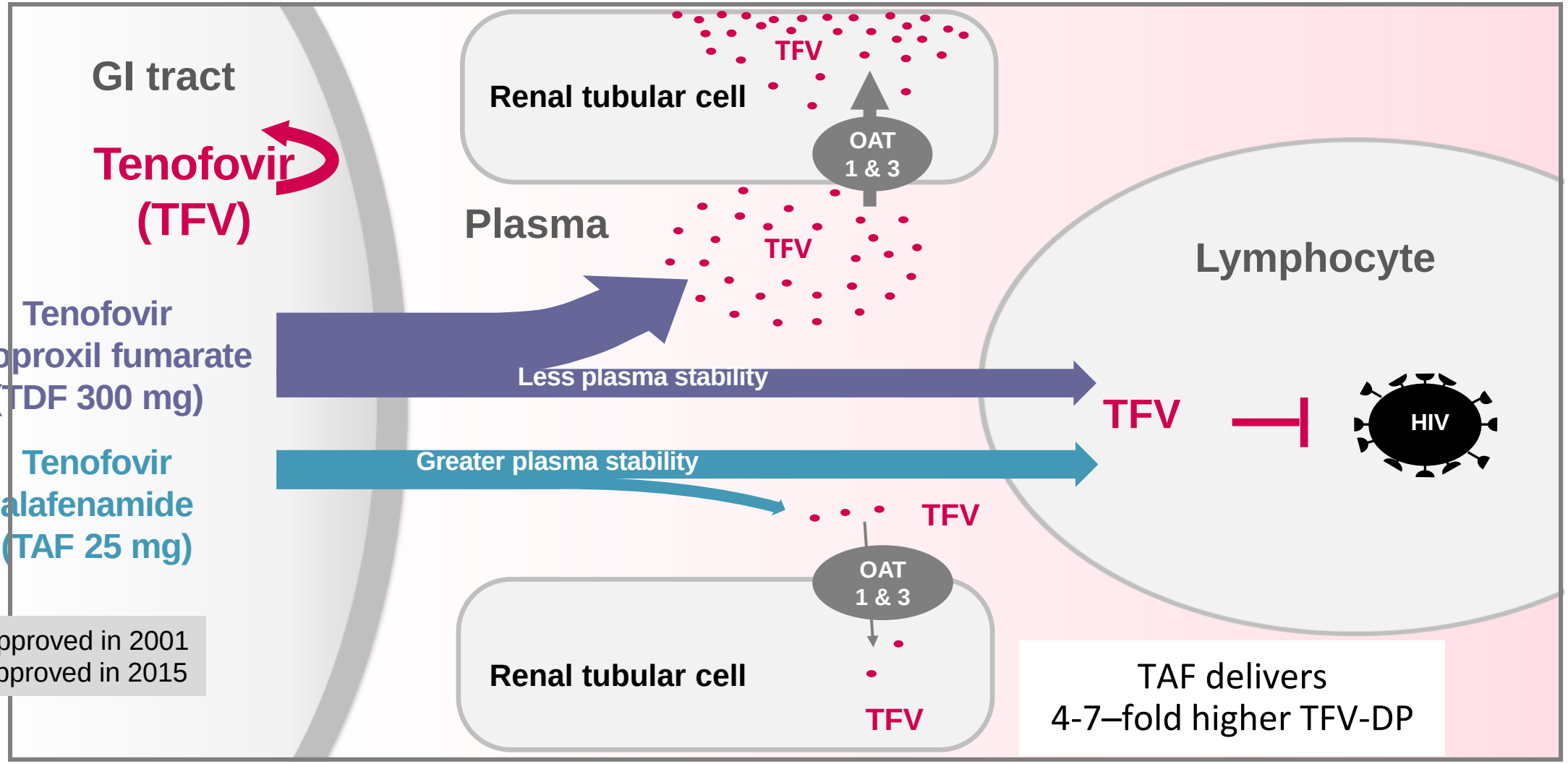
- In RCT in ART-naive and switch studies, levels of LDL, HDL and TG were higher in patients receiving TAF than in patients receiving TDF.
- Total chol to HDL ratios did not differ
- The clinical significance of this finding is not clear.

Lifestyle modification

Individual/personalized medicine

TAF-containing regimens are approved for patients with eGFR ≥30 mL/min

Higher TFV-DP Levels in PBMCs With TAF vs TDF



- TDF approved in 2001
- TAF approved in 2015

TAF results in 80-90% lower TFV plasma levels

OAT: organic anion transporter, TAF: tenofovir alafenamide, TDF: tenofovir disoproxil fumarate, TFV: tenofovir.

1. Sax PE, et al. J Acquir Immune Defic Syndr 2014;67:52-8. 2. Sax PE, et al. Lancet 2015;383:2606-15.3 Ruane. JAIDS. 2013;63:449. Sax. JAIDS. 2014;67:52. Sax. Lancet. 2015;385:2606.

Guideline-Recommended First-line ART Regimens for Most PWH 2024

DHHS[1**]	IAS-USA[2**]	EACS[3]	BHIVA[4]	WHO[5]	Thailand [6]
BIC/FTC/TAF	BIC/FTC/TAF	BIC/FTC/TAF	BIC/FTC/TAF		
DTG + XTC/TXF	DTG + XTC/TXF	DTG + XTC/TXF	DTG + XTC/TXF	DTG + XTC/TDF	**DTG+ XTC/TXF**
DTG/3TC/ABC*		DTC/3TC/ABC*	DTG/3TC/ABC*†		
DTG/3TC‡	DTG/3TC†	DTG/3TC or DTG+XTC‡§	DTG/3TC‡		
		RAL + XTC/TXF			
		DOR/3TC/TDF or DOR + XTC/TXF			

TDF/3TC/DTG：TLD

TAF/FTC/DTG

TAF/FTC + EFV or RPV + DRV/r

*If HLA-B*5701 negative, no HBV. ** If no previous use of LA CAB as PrEP
†If estimated 10-yr risk of CVD <10%.
‡If HIV-1 RNA ≤500,000 c/mL, no HBV, available genotype results.
§Not recommended after PrEP failure.

1. DHHS 2023. 2. Gandhi. JAMA. 2023;329:63. 3. eacsociety.org/guidelines/eacs-guidelines. 4. bhiva.org/HIV-1-treatment-guidelines. 5. who.int/publications/i/item/9789240031593.6 Thailand national HIV guideline 2021/2022

TDF or TAF???

personalized medicine

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

1. NAMSAL ANRS 12313 Study Group. NEJM. 2019;381:816. 2. Venter. Lancet HIV. 2020;7:e666. 3. Arribas. JAIDS. 2017;75:211.
4 Avihingsanon A et al Lancet HIV 2023

1. ARV naïve: Rapid ART/same day ART

DHHS[1]

Recommended Regimens
BIC/FTC/TAF
DTG + XTC/TXF
Boosted **DRV** + XTC/TXF
Regimens Not Recommended
NNRTI-based ART or **DTG/3TC*** (higher rate of transmitted NNRTI and NTRI drug resistance)
ABC-containing regimens until HLA-B*5701 test results received

IAS-USA[2]

Recommended Regimens
BIC/FTC/TAF
DTG + XTC/TXF
Boosted **DRV** + XTC/TXF if starting before genotype results after LA CAB PrEP or with INSTI resistance
Regimens Not Recommended
DTG/3TC* (requires labs before initiation)
ABC-containing regimens

* Thailand/Asia : high prevalence of HBV

1. DHHS ART Guidelines. September 2022. 2. Gandhi. JAMA. 2023;329:63.

2. Recommended Initial ART When HIV Acquired While Receiving oral PrEP

TDF/FTC or TAF/FTC PrEP

- **BIC**/FTC/TAF
- **DTG** + (3TC or FTC) + (TAF or TDF)*

CAB PrEP

- (**DRV**/RTV or **DRV**/COBI) + (3TC or FTC) + (TAF of TDF)

Adjust regimen once results of HIV genotype return

* Thailand guideline

Gandhi. JAMA. 2023;329:63.

3. Initial ART During Pregnancy

Guideline Status	NRTIs	INSTIs	PIs	NNRTIs
Preferred	**3TC/ABC* FTC/TDF (or 3TC + TDF) FTC/TAF (or 3TC + TAF)**	**DTG**	**DRV/RTV†**	
Alternative	3TC/ZDV	RAL†, BIC/F/TAF	ATV/RTV	EFV RPV (PO)‡
Insufficient data to recommend				DOR
Not recommended		EVG/COBI CAB	ATV/COBI DRV/COBI LPV/RTV†	ETR NVP RPV (IM)

*Only if HLA-B*5701 negative.
†Must be used twice daily in pregnancy.
‡Only if pretreatment HIV-1 RNA ≤100,000 c/mL and CD4+ cell count ≥200 cells/mm^3.

DTG+ TAF/FTC vs DTG+TDF/FTC
- Similar efficacy
- TDF has potential renal toxicity
- Fewer adverse birth outcome with TAF/FTC
  (potential fetal bone and early-life growth abnormalities with TDF)
- Weight gain with TAF/FTC

DHHS Perinatal Guidelines. 31 January 2024.

TB/HIV

LTBI/HIV

Rifamycins/TB drug interaction potential

- Induce of
  - Cytochrome P450 (CYP3A4),
  - UDP-glucuronosyltransferases (UGT1A1)
  - P-glycoprotein

→ ARV (eg INSTI, TAF, NNRTIs, PIs, contraceptives, statins, macrolides, methadone

Table 1. Summary of pharmacokinetic and pharmacodynamic parameters of rifamycins.

Drug	C_{max} (mg/mL)	T1/2 (hours)	Protein Binding %	CYP450 Enzyme induction	MIC* mg/mL
Rifampicin	8–24	3–4	80	+++	0.125–0.25
Rifapentine	8–30	13–15	>95	++	0.01–0.05
Rifabutin	0.3–0.9	25–62	85	+	0.03–0.06

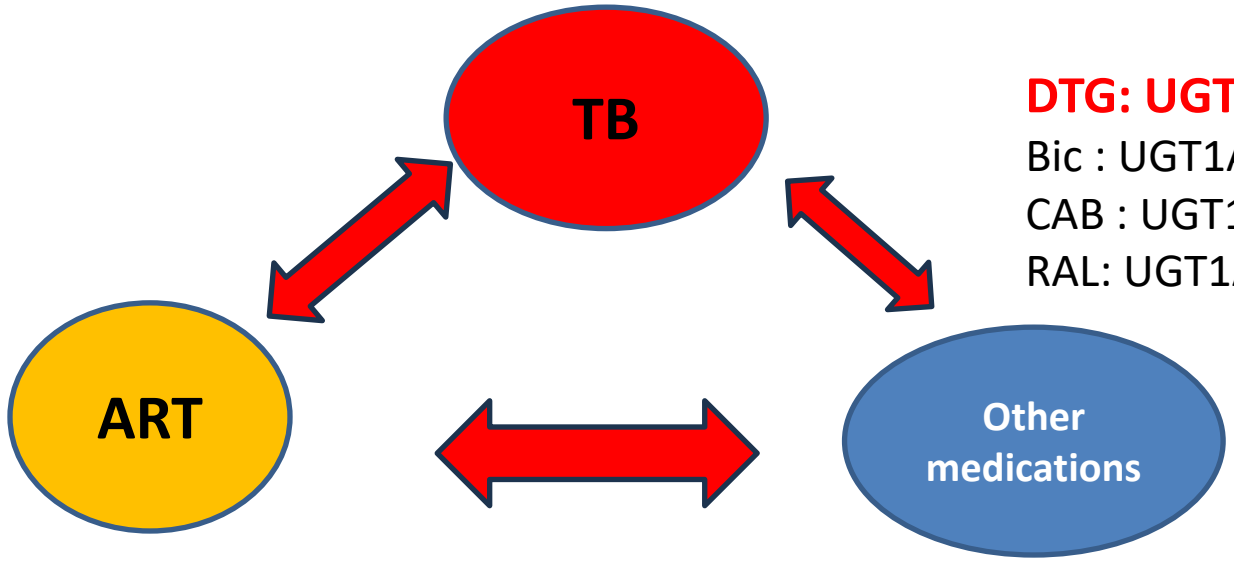
CYP450: cytochrome P450, T1/2: half-life, C_{max}: maximum concentration
*Minimum Inhibitory Concentration for susceptible strains of Mycobacteria.

Potency of CYP3A inducers
Rifampin > Rifapentine > Rifabutin

Rifapentine (RPT) : longer t1/2 than RIF and increased potency
Induction potency 85% of rifampin with daily RPT dosing, less with weekly

Sekaggya-Wiltshire et al 2019 Expert Opinion Drug Metabolism & Tox; 15, 8 p.615-618-341

Significant PK drug-drug interactions between anti TB and ARV



DTG: UGT1A1, CYP 450 3A4 (minor), p-gp

Bic : UGT1A1, CYP 450 3A4 , p-gp

CAB : UGT1A1, p-gp

RAL: UGT1A1

Potency of CYP3A inducers
Rifampicin > Rifapentine > Rifabutin

→

Rifampicin reduces plasma exposure to TAF, NNRTI, INSTIs, PIs, fostemsavir and maraviroc

Sekaggya-Wiltshire et al 2019 Expert Opinion Drug Metabolism & Tox; 15, 8 p.615-618-341

EACS European AIDS Clinical Society

Version 12.0 October 2023

Drug-drug Interactions between AntiTB and ARVs

Anti-tuberculosis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
First line and second line drugs	amikacin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	bedaquiline	↑ b	↑ b	↑	↑	↑62% b	↔	↓18%	↓	↑3%	↔ b	↔ b	↔	↑ c	↔	↔ b	↔	↑	↔	↔	↔
	capreomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ d	↔	↔	↔	↑ E a
	clofazimine	↔	↔	↔	↔	↔	E	↔	↔	↔	E	E	E	↔	E	E	↔	↔	↔	↔	↔
	cycloserine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	delamanid	e	e	e	e	e	↔	↔ f	↔	↔	↔ g	↔ g	↔	h	↔	↔ g	↔	e	↔	↔	↔
	ethambutol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ethionamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	isoniazid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	kanamycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	linezolid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	moxifloxacin	↑ b	↓ b	↔	↓	↓ b	↔	↓	↓	↔	↔ b	↔ b	↔	↔	↔	↔ b	↔	↔	↔	↔	↔
	para-aminosalicylic acid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↑E
	pretomanid	↓ b	↓ b	↓	↓	↓17% b	↔	↓35%	↓	↓	↔ b	↔ b	↔	↔	↔	↔ b	↔	↓	↔	↔	↔
	pyrazinamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	rifabutin	↑ D i	↑ j	↑ D i	↑ j	↑ j	D50% k	↓38% l	D37%	↑17%	D42% m	D30%	n	D #	D38%	D	↔	↑ D i	E19%	D o	↔
	rifampicin	D	D72%	D	D57%	D75% p	D82%	D26% q	D	D58%	D80%	D82%	D r	D82% #	D75%	D	D54% s	D	D40% t	D o	D12%
	rifapentine	D	D	D	D	D	D	D	D	D	D	D	D r	D #	D	D	D u	D	D	D o	↔
	streptomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a

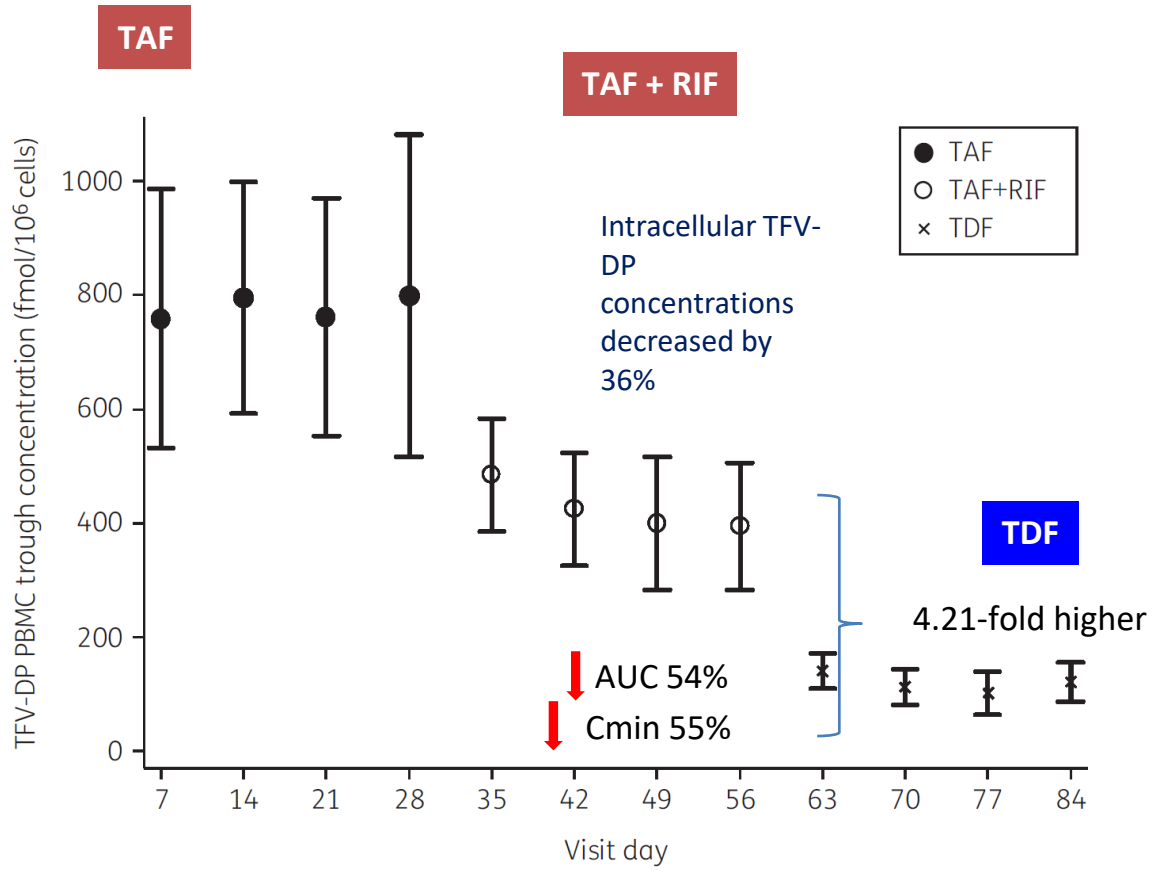
Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/ monitoring or dosage adjustment is unlikely to be required

TAF and rifampicin: Intracellular TFV-DF Levels in 25 healthy volunteers (TAF/FTC25/200)

TAF is a P-gp substrate

TAF **NOT** metabolized via UGT1A1 or CYP3A4)



TAF+RIF : Intracellular TFV-DP concentration reduced 36% but it is still 4 times higher than intracellular TFV-DP concentrations of TDF without RIF

TAF dose adjustments in adults :
Likely not necessary

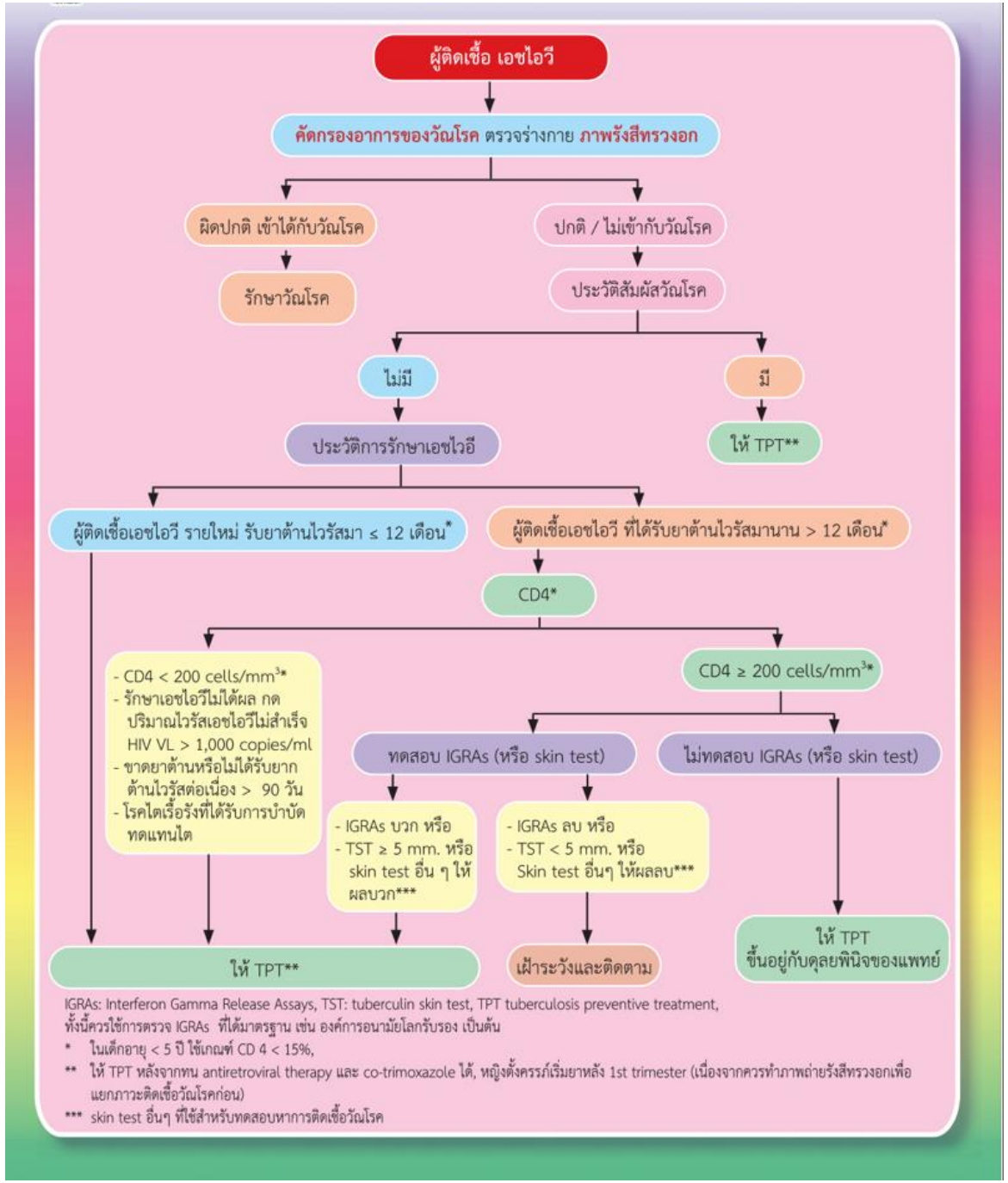
Cerrone et al J Antimicrob Chemother, 2019;74:1670–1678

DHHS 2023, Thai 2023: TAF: do not coadminister unless benefits outweight risk

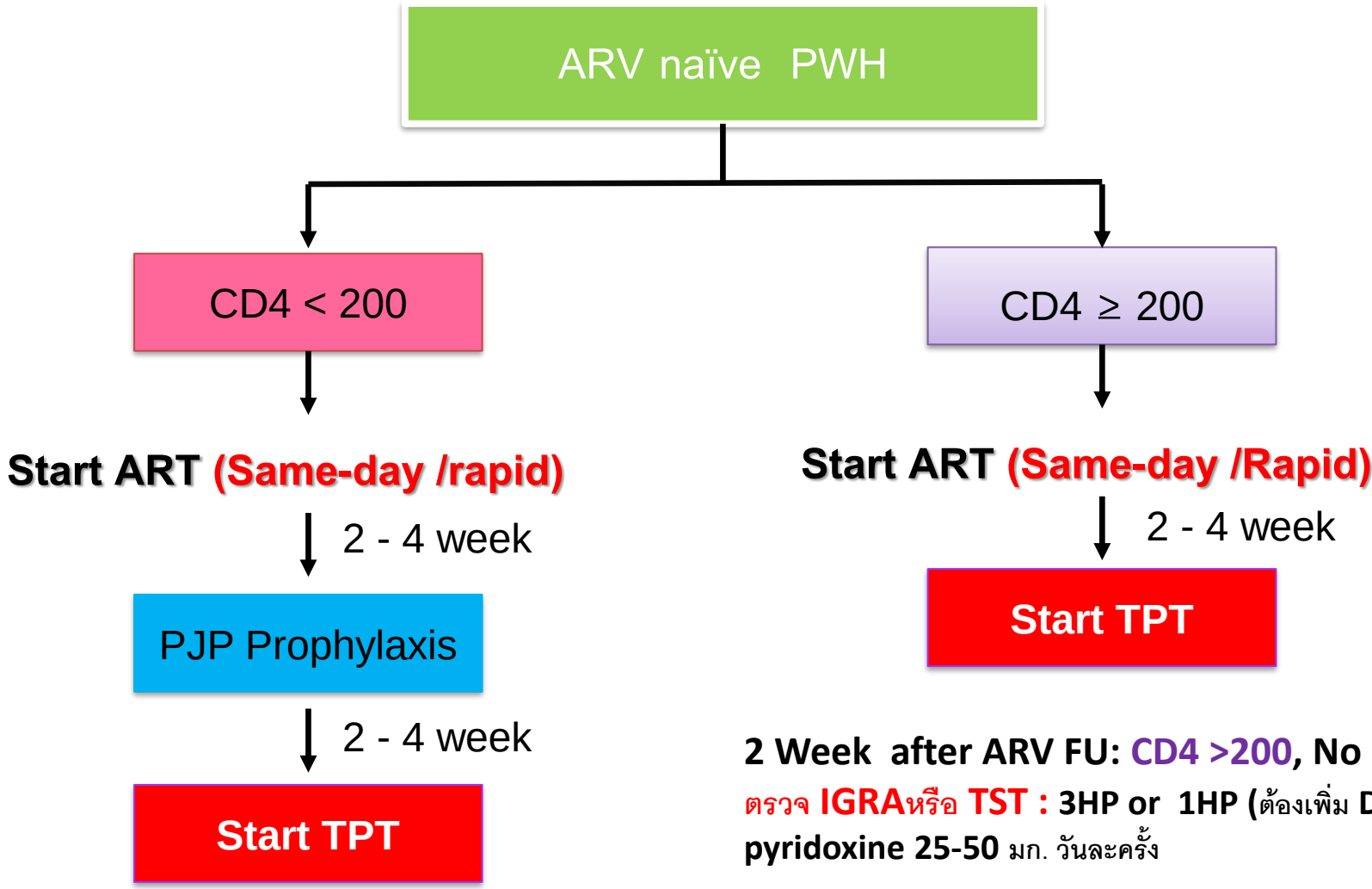
ART in TB/HIV : EACS 2023

Recommended regimens with rifampicin	
TXF/XTC +EFV or TDF/FTC/EFV	**At bed time or 2 hr before dinner**
ABC/3TC+EFV	**HLA-B*5701 negative** **HBsAg negative** **HIV VL< 100,000 c/ml** **At bed time or 2 hr before dinner**
Alternative regimens with rifampicin	
TXF/XTC+ DTG BID **TXF/XTC+RAL BID**	
ABC/3TC+RAL BID	**HLA-B*5701 negative** **HBsAg negative**
Other combinations with rifabutin	
TXF/XTC+DRV/r	With food
ABC/3TC+ DRV/r	HLA-B*5701 negative HBsAg negative HIV VL< 100,000 c/ml With food

แนวทางเวชปฏิบัติการวินิจฉัยและรักษา
วัณโรคระยะแฝง ผู้ติดเชื้อเอชไอวี (++/IV)



ARV naïve or ARV < 12 months: Asymptomatic HIV และไม่มีอาการสงสัยวัณโรค



CBC, CD4
Cr ALT
HBs Ag, HCV Ab
Syphilis Ab
CXR

CD4 <100
Serum Crypto Ag
•Urine LAM
•CRP (if available)

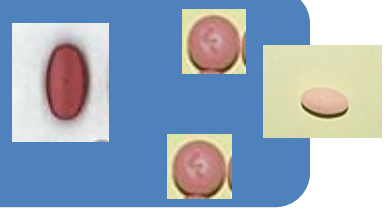
2 Week after ARV FU: CD4 >200, No S/E of ART: เริ่ม **TPT** ไม่ต้องตรวจ **IGRAหรือ TST : 3HP or 1HP (**ต้องเพิ่ม **DTG** เป็น **BID) pyridoxine 25-50** มก. วันละครั้ง

TPT regimen among PLHIV in Thailand: 2023

1 HP:
EFV: no dose adjustment
DTG 50 mg BID
Avoid boosted PI, NVP, RPV

Prefer : 1HP

INH 300 mg+ RPT 450-600mg dailyx4 weeks (+B6)



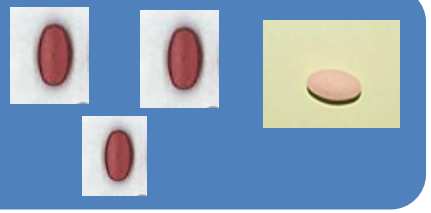
BW<35 kg, RPT 300mg
BW 35-45 kg, RPT 450 mg
BW > 45 kg, RPT 600 mg

Completion rate 97% (1HP) vs 90% (9H), p<0.001 (BRIEF study)

Prefer

INH 15 mg/Kg (max 900)

INH 900 mg+ RPT 900 mg weekly x12 weeks (+B6)



BW ≥ 50 kg, RPT 900mg
BW 32-49.9 kg, RPT 750 mg
BW > 60 kg, INH 900 mg

3HP
EFV, DTG : no dose adjustment
Avoid boosted PI, RPV, NVP

Completion rates 82% (3HP) vs 69% (9H)

Alternative : 9H

INH 300 mg +B6 dailyx9 months

RPT + INH
300 mg/300 mg
Film-coated

3 HP : 3 pills/weeklyx12 weeks = 14.25 USD

RPT 300 mg

1 HP : 1 pill of RPT/INH + 1pill RPT /day, daily x 28 days= 18.98 USD

MedAcess, Unitaid, GDF, CHAI
RPT/INH: Macleods, Lupin, RPT 300 : Lupin

All PLWH receive ART < 12 months. " Treat without Test" : ↓ cost of test (IGRA), most benefit of TPT (↓ death, ↓ TB, easy ART management

TLD:3-6months (+TPT) → TAF/FTC/DTG

อายุ > 2 ปี ที่รับประทานยาเม็ดได้

HIV and HBV co-infection 2024

TAF> TDF : Age > 60, CrCl < 60 cc/min, osteoporosis, history of fragility fracture, hemodialysis/peritoneal dialysis

Contraindication for TDF or TAF

backbone
- **TAF/FTC**
- **TDF/FTC**
- **TDF+3TC**

+

DTG or Bictegravir

DRV/r

EFV or RPV

TDF/3TC/DTG：TLD

TAF/FTC/DTG

Intolerant or HIV resistance to TDF or TAF

Backbone =Non-TDF or non-TAF regimen
- **ABC+3TC**
- **AZT+3TC**

+ **entecavir for HBV treatment**

+ **DTG or Bictegravir or DRV/r**

Avoid 3TC monotherapy for HBV due to YMDD mutation 20% per year in HIV/HBV

- ↑ Risk of HBV reactivation and liver failure)[1,2] if TDF or TAF + FTC or 3TC discontinuation
- LFT 6-12 mo, HBV DNA q 12 mo, HBsAg q 12 mo
- HCC surveillance: U/S upper abdomen +/- AFP every 6-12 months for all cirrhosis, male > 40 yrs, females > 50 yrs, Family history of HCC in first-degree relative

long-acting cabotegravir and RPV, dual therapy (DTG+3TC, DTG+RPV) is not recommended

1. DHHS guideline 2024; 2. Dore GJ, AIDS 2010; 24: 857–65.;3 EASL CPG HBV. J Hepatol 2017;67:370–98

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	GZR/EBR	SOF/LDV	SOF/VEL	SOF/VEL/VOX	SOF + DCV
ATV + (RTV or COBI)	X	X	✓*	✓*	X	Decrease DCV dose (30 mg)
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*†	✓
LPV + RTV	X	X	✓*	✓*	X	✓
EFV, NVP, ETR	X	X	✓*	X	X	Increase DCV dose (90mg)
RPV, doravirine	✓	✓	✓*	✓	✓	✓
DTG, Bictegravir/TAF/FTC	✓	✓	✓*	✓	✓	✓
RAL	✓	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	X	X	✓*	✓*†	Decrease DCV dose
EVG/COBI/FTC/TAF	✓†	X	✓	✓	✓†	Decrease DCV dose
3TC/ABC	✓	✓	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓*	✓* (increased TFV Cmax 44-46%, AUC 40%)	✓*	✓

*Monitor for tenofovir toxicity if used with TDF.

†No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline 2020

Liverpool HEP Interactions - HEP Drug Interactions

https://www.hep-druginteractions.org/prescribing-resources

HCV/HIV without cirrhosis

APRI > 1.5/FIB-4 > 3.25 = cirrhosis

Exclude Advanced Fibrosis/Cirrhosis
(No biopsy required)

≥ 4-wk adjustment before starting HCV DAAs to ensure ART is tolerated and effective

Risk for Hepatitis B Virus Reactivation

Screen for drug-drug interaction
HBsAg testing

Pangenotypic Therapy
GLE/PIB 8 weeks or SOF/VEL 12 weeks

TDF/FTC/EFV

Minimal Monitoring (A5360)
(No HCV-related laboratory monitoring required)

Assess for Cure→ SVR12 (HCV RNA/HCV core Ag at 12 weeks or longer, after HCV treatment completion
Risk Reduction

TDF/FTC or
TAF/FTC+rilpivirine
or
TDF/3TC/DTG,
TAF/FTC/DTG or
TAF/FTC/Bictegravir

≥1 mo before SOF/VEL

START treatment

SOF/Vel 1 tab
OD with food

adherence

3 months treatment

12 weeks

≥ 3 months HCV RNA

≥12 weeks :HCV RNA: Cure

reinfection

AASLD/IDSA guideline 2024, Solomon SS et al Lancet Gastroenterol Hepatol. 2022 Jan 10:S2468-1253(21)00397-6

TLD : TDF/3TC/DTG

Reasons to Consider Regimen Optimization in Setting of Viral Suppression

- **S**implification: reduce pill burden and/or dosing frequency;
  - **S**witch to long-acting injectable regimen to relieve pill fatigue, decrease potential stigma or disclosure concerns associated with daily oral medications
- **T**olerability: enhance tolerability and/or decrease short- or long-term toxicity
- **I**nteractions: prevent or mitigate drug–drug interactions
- **F**ood/fluid requirements: eliminate food or fluid requirements
- **F**ertility: allow for optimal use of ART during pregnancy or in cases where pregnancy may occur
- **Cost**: reduce costs

ARV experienced with HIV RNA < 50 copies/ml

Emerging co-morbidities in HIV

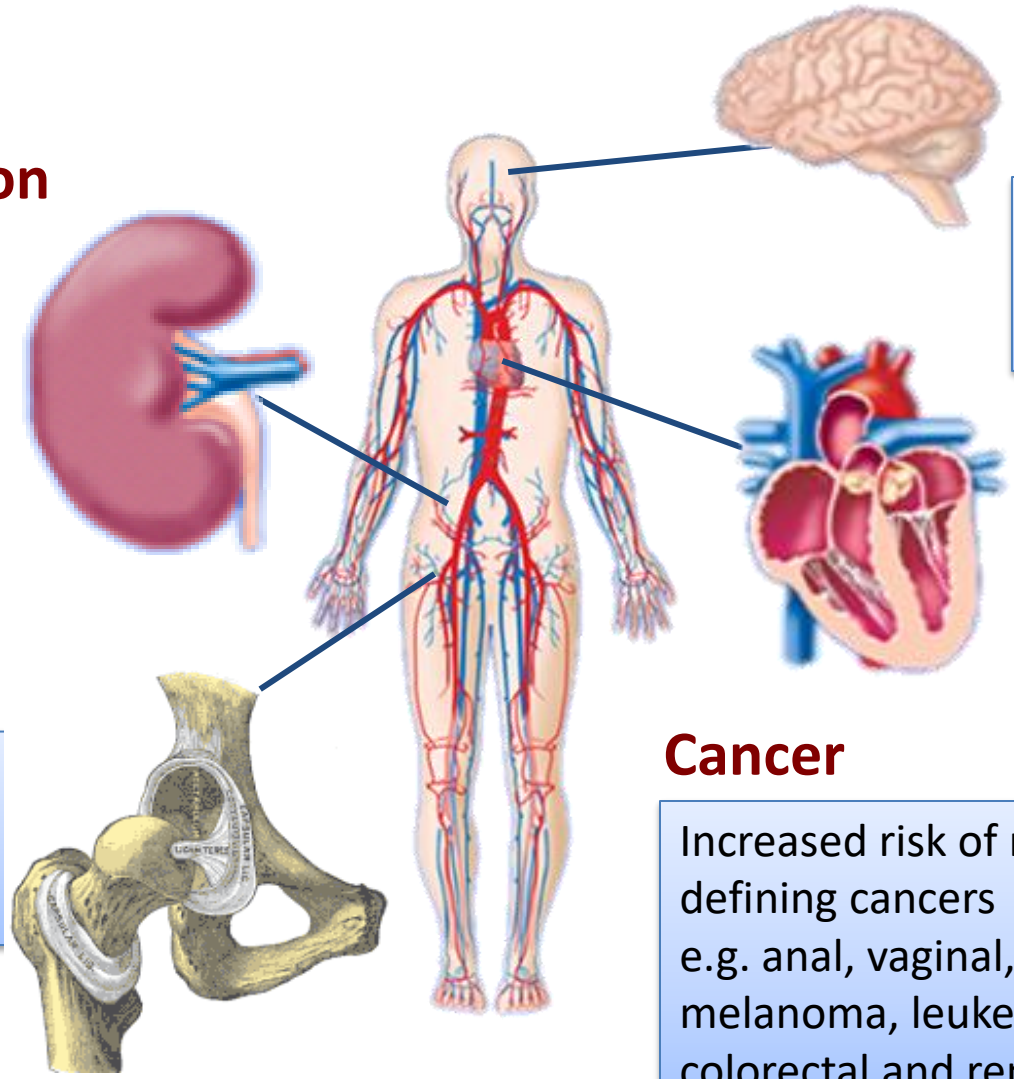
Aging population

Renal dysfunction

30% of HIV+ patients have abnormal kidney function[1]

Reduced bone mineral density

Increased prevalence **63%** of HIV+ patients[2]



Neurocognitive dysfunction

Impairment present in **≥50%** HIV+ patients[3]

Cardiovascular disease

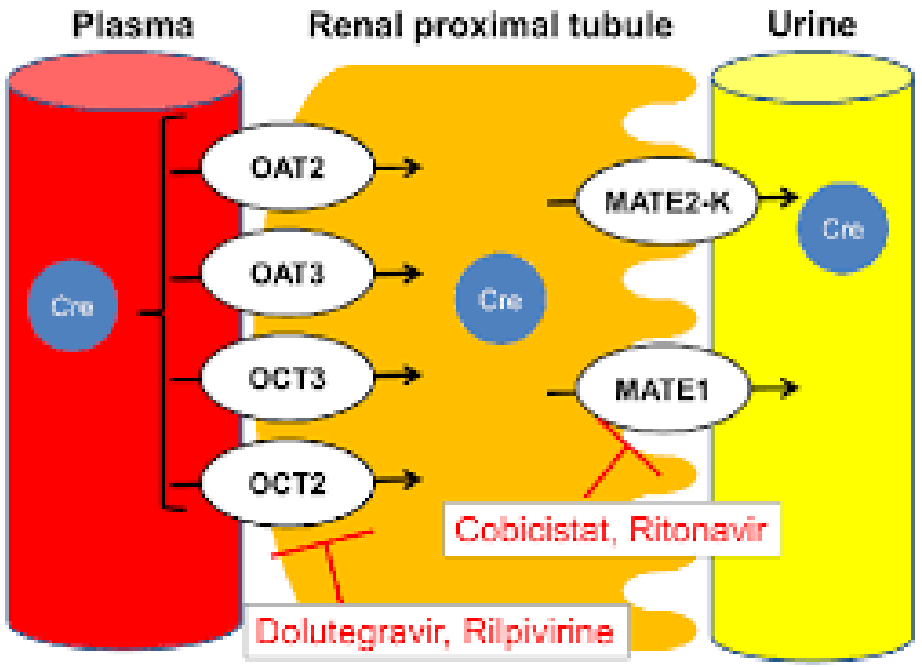
75% increase in risk of acute MI[4]

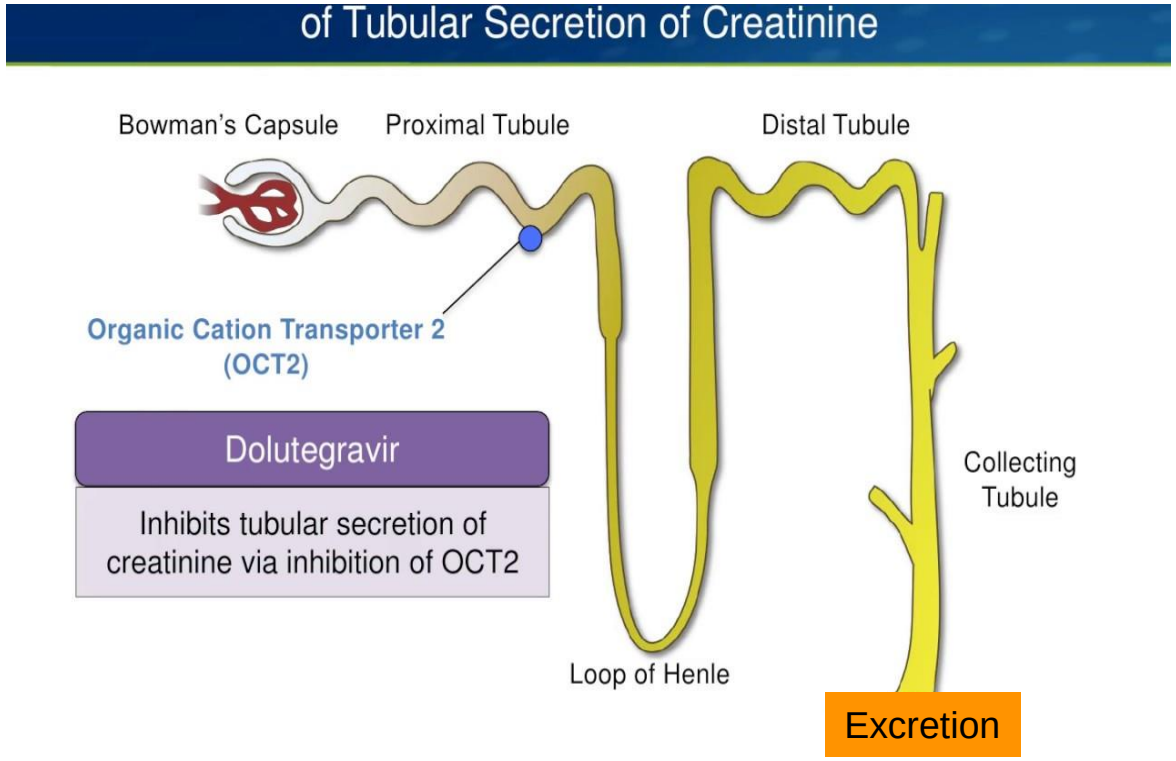
Cancer

Increased risk of non-AIDS-defining cancers
e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal[5]

Gupta SK et al. Clin Infect Dis 2005;40:1559–1585. ,Brown TT et al. J Clin Endocrinol Metab 2004;89(3):1200–1206, Clifford DB. Top HIV Med 2008;16(2):94–98
Triant VA et al. J Clin Endocrinol Metab 2007;92:2506–2512, Patel P et al. Ann Intern Med 2008;148:728–736

Dolutegravir and Kidney





DTG may increase SCr levels by 10–14%. However, its effects are reversible and nonpathological

Scr ⇧ < 0.4 mg/dl

DTG increases the SCr levels initially but remains stable throughout the treatment

Scr rise related to DTG?

- Rise in Cr <30umol/L (0.339 mg/dl)
- Occurred within the 1st-3rd month of initiating DTG
- Did not progress after the 1-3 months

Yes

Scr rise <20umol/L (0.226 mg/dl)

- Likely DTG related
- Leave on current regimen
- Continue routine monitoring

Scr rise <20-30umol/L (0.0226-0.339 mg/dl)

- Likely DTG related
- Leave on current regimen
- Check Scr in 1 month

Creatinine rise should have plateaued (no further significant increase)
If not: 1 work up for renal disease
2 if eGFR<50ml/min/1.73m2, stop TDF and switch to ABC/3TC/DTG, TAF/FTC/DTG or dual therapy (if VL < 50 c/ml, no HBV, no history 3TC resistance (DTG+3TC or NNRTI resistance (DTG+ RPV)

No

Requires work up for possible renal disease
if eGFR<50ml/min/1.73m2, stop TDF and switch to ABC/3TC/DTG, TAF/FTC/DTG or dual therapy (if VL < 50 c/ml, no HBV, no history 3TC resistance (DTG+3TC or NNRTI resistance (DTG+ RPV)

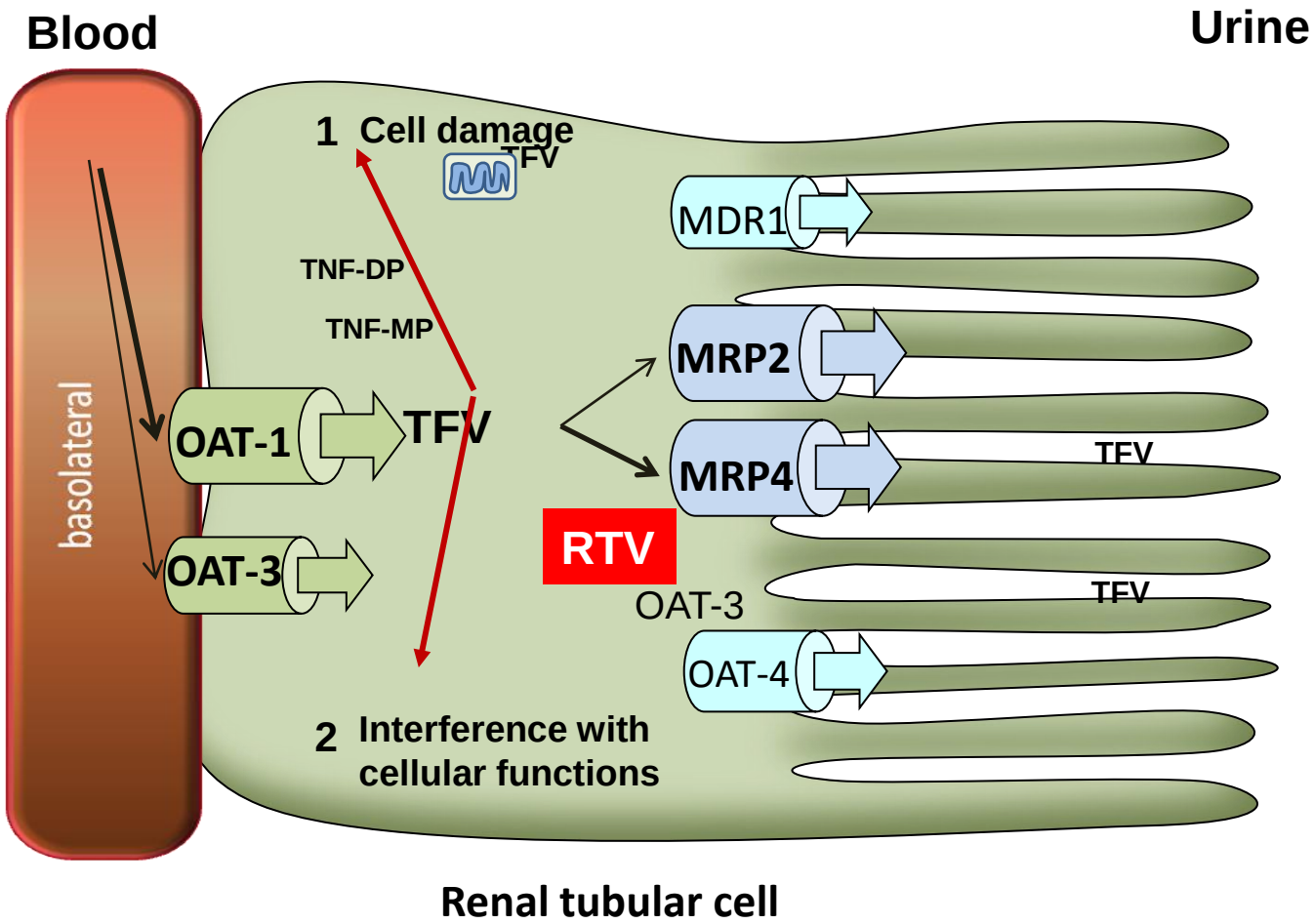
Modified from Southen Afirican HIV guideline

TDF and the Kidneys

- TDF induced nephrotoxicity is reported in ~ 15% of patients treated for > 2 years[1]
  - Include Fanconi syndrome, progresive decline in renal function, tubulopathy, acute tubular necrsis
- For every year of exposure to TDF, risk of proteinuria, decline in kidney function and development of CKD increases by 34, 11, and 33%[2]
- Studies demonstrate stopping TDF does not always reverse the kidney injury and recovery may be significantly delayed
  - Discontinued TDF at eGFR<60 ml/min/1.73m2, increased the odd of incomplete recovery 13 fold[3]
- TDF is eliminated mostly through free glomerular filtration but 20-30% is secreted by the proximal tubules via OAT1 and OAT3
  - TDF accummulates within proximal tubules resulting in mitochondrial injury and depletion[4-7]

1Quinn Int J STD AIDS 2010; 2 Scherzer AIDS 2012; 3 Jose S J Infect Dis 2014; 210: 363-373; 4 Kohler Lab Invest 2009; 5 Kohler Lab Invest 2011; 6 Zhao X Scientific reports 2017;7 Matthew H AIDS 2022

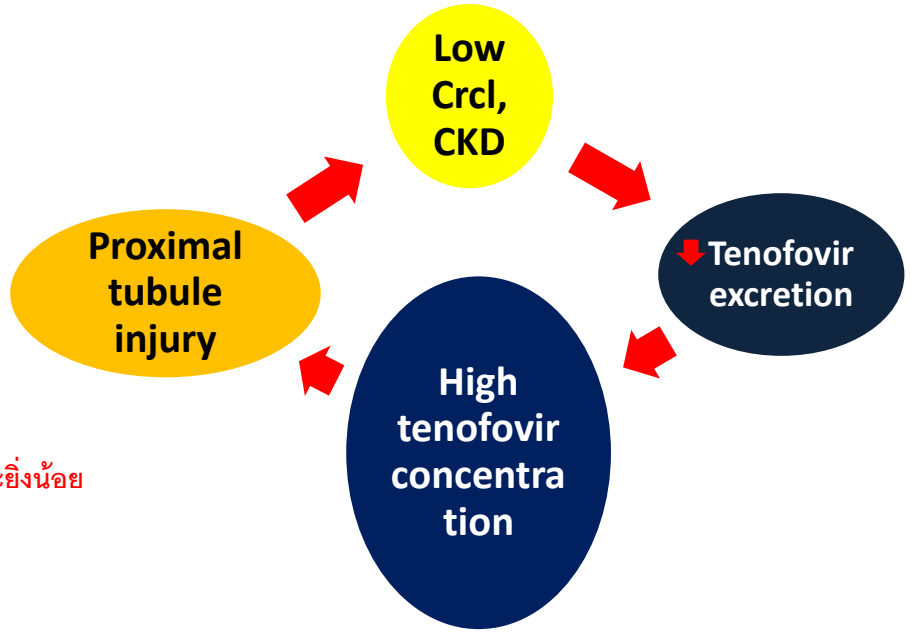
Kidney Tubular Dysfunction in HIV Patients Treated with TDF



Tenofovir renal clearance decreaed 17.5%

Table I. Single-dose tenofovir disoproxil fumarate pharmacokinetic parameters in subjects with varying degre

Parameter	Renal study			
	normal function (n = 3)	mild impairment (n = 10)	moderate impairment (n = 8)	severe impairment (n = 11)
C_{max} (ng/mL)	346 (300–360)	325 (261–426)	403 (153–566)	528 (381–1030)
AUC_{∞} (ng • h/mL)	2060 (2020–2480)	2910 (1530–4580)	5400 (2530–10 300)	17 500 (5820–30 200)
$t_{1/2}$ (h)	18.3 (16.9–18.4)	18.2 (15.4–32.6)	21.1 (17.8–28.3)	25.2 (19.5–40.0)
CL_R (mL/min)	246 (209–275)	167 (128–214)	92.3 (67.2–153)	32.0 (10.6–109)
CL_{CR} (mL/min)[c]	86.5 (82.5–101)	64.2 (51.7–79.8)	33.8 (31.9–42.7)	18.6 (12.3–27.8)



Renal function ต่ำ การขับออกของ**TDF** จะยิ่งน้อย ระดับยา **TDF** ยิ่งสูงขึ้น และทำให้ **nephrotoxicity** มากขึ้น

Rodríguez-Nóvoa et al. (2009) *Clin Infect Dis.* **48** (11):e108-16.
Slide Courtsey: A Owen, Univeristy of Liverpool, UK

Kiser et al 2009 Clin. Pharm Therapy

Incidence and Risk Factors of Tenofovir Disoproxil FumarateInduced Nephrotoxicity and Renal Function Recovery, a Hospital Case-Control Study

Infection & Chemoteraphy

Aim

Incidence and risk factors for nephrotoxicity in HIV-infected patients receiving tenofovir disoproxil fumarate (TDF) regimens.

Methods

พุทธชินราช/นครพิงค์

2012-2018

Retrospective cohort study (3,214 TDF-treated patients)

Outcome : Renal dysfunction
eGFR decline of greater than 25%
proximal renal tubulopathy (PRT)

Result

Incidence

Renal dysfunction 11.76%

Proximal renal tubulopathy 15.20%

Risk factors: Renal dysfunction

Older age (Odds ratio [OR] = 2.851)

Smoking (OR = 1.972)

TDF use for more than 3 years (OR = 1.928)

Risk factors: PRT

TMP/SMX (OR = 4.727)

NSAIDs (OR = 4.313)

Elderly (OR = 3.357)

Recovery of renal function

12.96%

Recovery of PRT

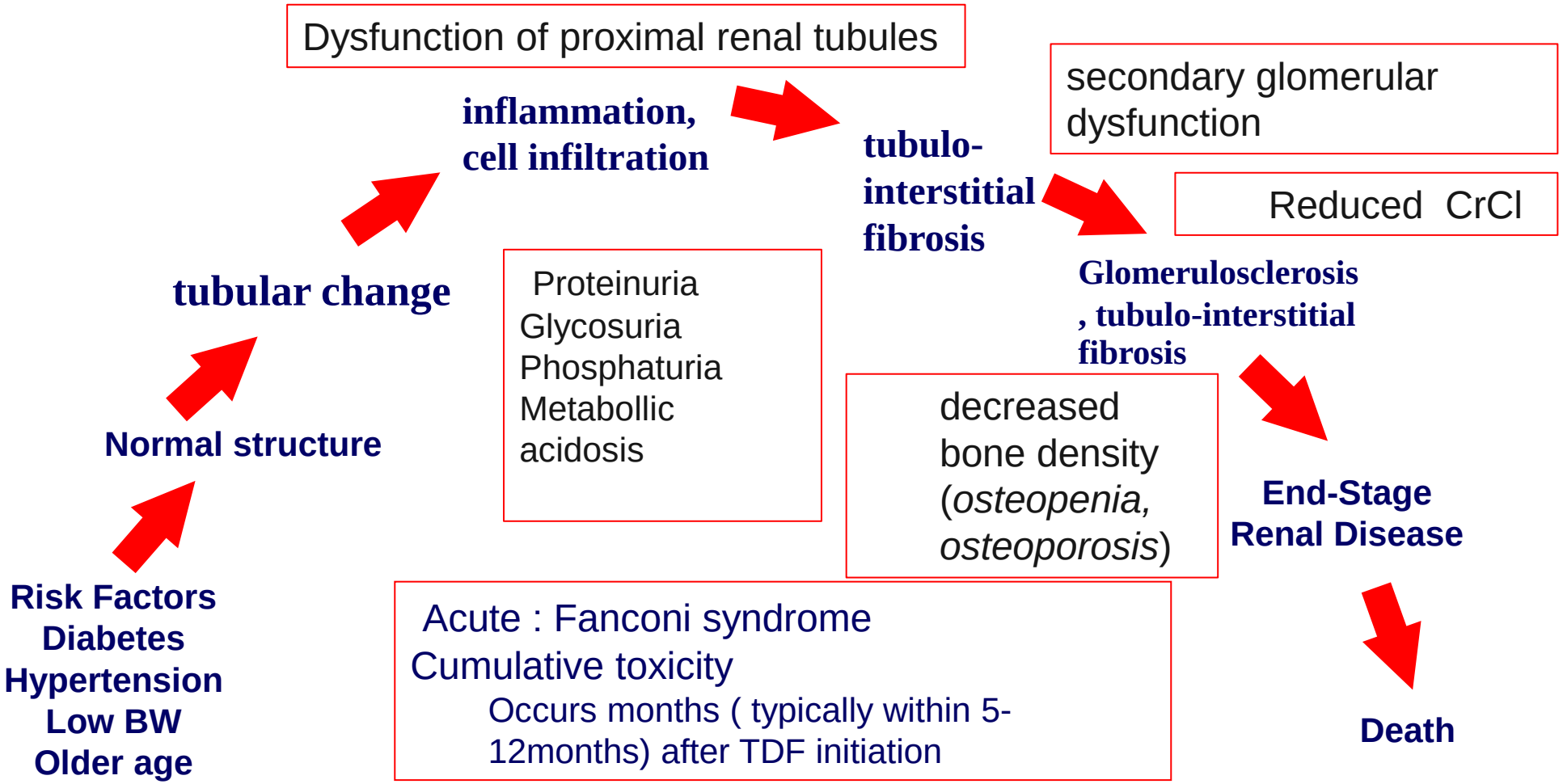
33.33%

Conclusion

Twelve percent and 15 percent of patients receiving TDF developed renal dysfunction and PRT, respectively. Age, TMP/SMX, NSAIDs, and long-term TDF exposure were independent risk factors for TDF-induced nephrotoxicity. Thirteen and thirty-three percent of patients with renal dysfunction and PRT recovered from their conditions, respectively. The discontinuation of TDF at an eGFR greater than 60 mL/min/1.73 m^2 was advantageous for the recovery of renal function and PRT.

Srisopa S et al Infect Chemother 2023 Jun;55(2):226-236

Tenofovir nephrotoxicity : Morbidity and Mortality Along the Renal Continuum



Izzedine et al. AIDS 2004; 18: 1074-6. Gupta. AIDS Patients Care STDS 2008; 22: 99-103Cooper et al. Nephron Clin Prac 2011; 118: c262-8

Chronic Kidney Disease Classification

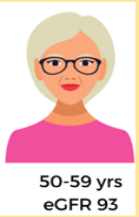
Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60-89*
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	< 15 or dialysis

* May be normal for age

Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m^2 for ≥ 3 months

Gupta SK, et al. *Clin Infect Dis*. 2005;40:1559-1585.

kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm

Month	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	≥ 70 yrs
0	109.0	99.0	87.2	78.3	69.3	61.1
6	104.5	93.6	86.9	79.1	72.9	60.3
12	103.4	91.9	84.3	77.2	70.5	55.6
General population	 20-29 yrs eGFR 116	 30-39 yrs eGFR 107	 40-49 yrs eGFR 99	 50-59 yrs eGFR 93	 60-69 yrs eGFR 85	 70+ yrs eGFR 75

Kidney damage : UP/C >500 mg/g or UA/C 300 mg/g

Kidney disease: diagnosis and management

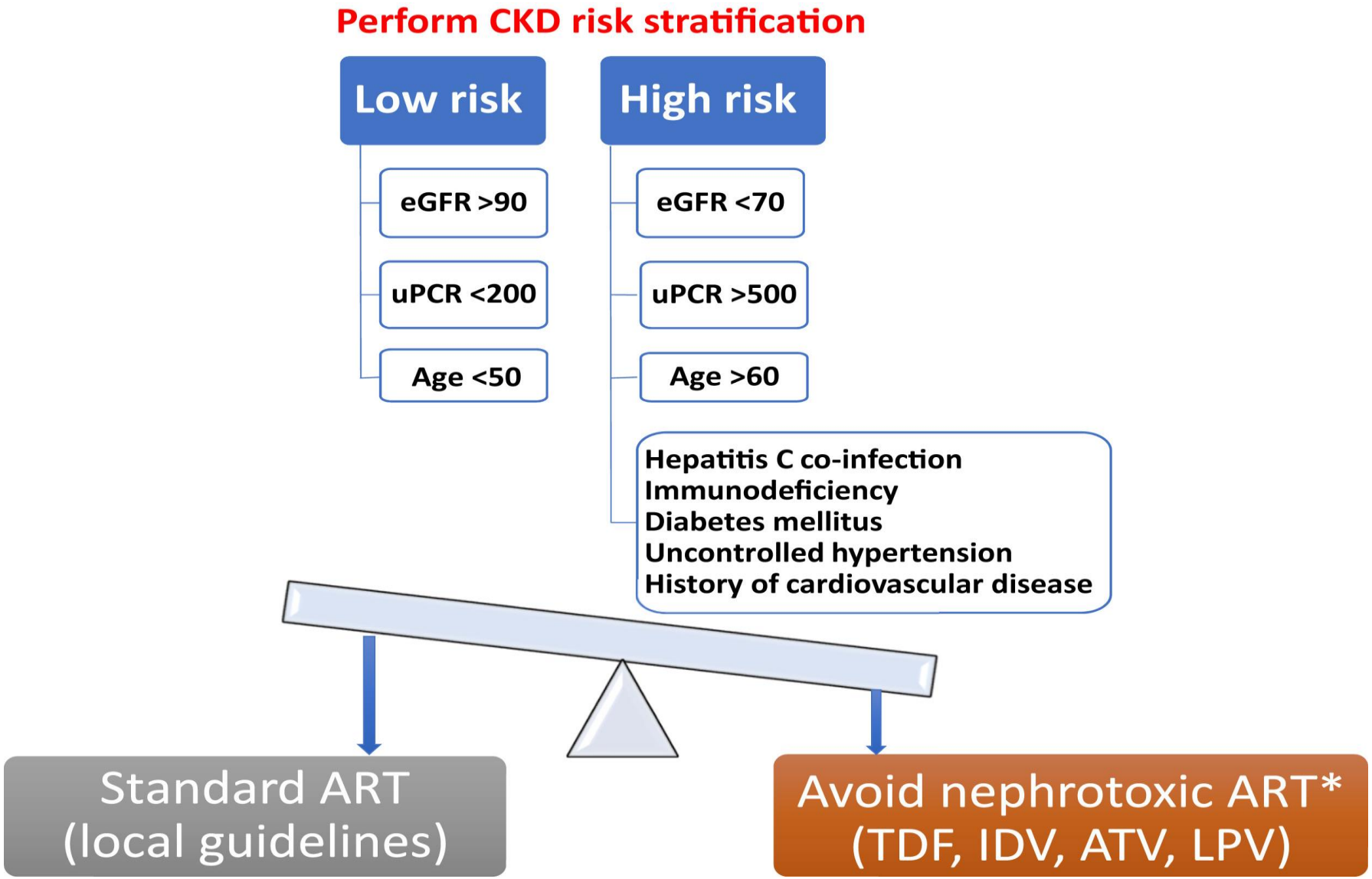
			eGFR		
			≥60 ml/min	**30-59 ml/min Or >60 ml/min, but accelerated decline of eGFR***	**≤30 ml/min**
Proteinuria / microhematuria	UPCR <0.15 mg/mg (< 150 mg/g) or UACR <30 mg/g		Regular Follow-up		
	UP/C 0.15-0.5 mg/mg (150-500 mg/g) or UA/C 30-300 mg/g	- hematuria	•Check risk factors for CKD and nephrotoxic medication including ART •Discontinue or adjust drug dosages where appropriate		•Discontinue or adjust drug dosages where appropriate
		+ hematuria	•Perform renal ultrasound •If hematuria present with any level of proteinuria refer to nephrologist •Refer to nephrologist if new CKD or progressive decline in eGFR		•Perform renal ultrasound •Refer to nephrologist
	UP/C >500mg/g or UA/C >300 mg/g				

eGFR by CKD-EPI

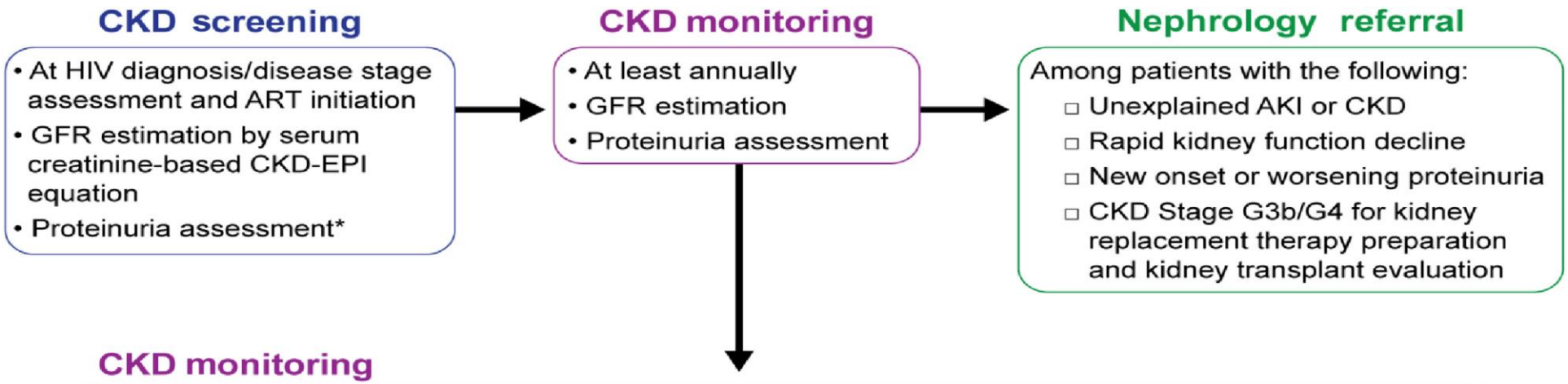
Urine protein > 500 mg/day

* Confirmed eGFR decline from baseline or decrease in eGFRof 5 ml/min per year for ≥ 3 consecutive years

Modified from EACS 2023



Kidney International 2018 93545-559DOI: (10.1016/j.kint.2017.11.007)



CKD monitoring

Low CKD risk	• Yearly during follow-up (if clinically stable and virologically suppressed)** • Before and 1 month after ART modification • GFR estimation • Proteinuria assessment
High CKD risk	• Twice yearly during follow-up (if clinically stable and virologically suppressed)** • Before and 1 month after ART modification • GFR estimation • Proteinuria assessment
On TDF plus ritonavir or cobicistat	• Twice yearly during follow-up (if clinically stable; more frequently if eGFR decline or marked hypophosphatemia is present) • GFR estimation • Proteinuria assessment • Serum phosphorus • Urinalysis • Fractional excretion of phosphate and urinary low-molecular weight protein in those suspected to have developed proximal tubulopathy
Established CKD	• Follow KDIGO guidelines for monitoring

Kidney International 2018 93545-559DOI: (10.1016/j.kint.2017.11.007)

Recommendations for management of CKD risk factors in HIV-positive individuals

Hypertension	
Nonproteinuric	•Target systolic blood pressure **≤140 mm Hg**
Proteinuric	•Target systolic blood pressure **≤130 mm Hg** •Preferred antihypertensive: ACE inhibitors or angiotensin receptor blockers
Diabetes mellitus	•Target hemoglobin A1c ~7%
Hepatitis B virus co-infection	•Treat per existing guidelines •TAF may be used in patients with eGFR ≥ 30 ml/min per 1.73 m^2 •Where TAF is unavailable or in patients with eGFR < 30 ml/min per 1.73 m^2, dose-adjusted TDF or entecavir may be considered.
Hepatitis C virus co-infection	•Treatment per existing guidelines •In patients with HCV genotypes 1 and 4 and CKD G4-5, ribavirin-free grazoprevir/elbasvir or glecaprevir/pibrentasvir regimens may be effective •In patients with genotypes 2, 3, 5, and 6 and CKD G4-5, the pan-genotypic glecaprevir/pibrentasvir regimen can be used; **sofosbuvir-based regimens can be used in patients with any genotype, but should be avoided or dose adjusted in patients with eGFR < 30 ml/min per 1.73 m^2.** the combination of ledipasvir and sofosbuvir with TDF should be avoided.

Kidney International 2018 93545-559DOI: (10.1016/j.kint.2017.11.007)

Management of nephropathy in HIV-positive patients

Prevention of progressive renal disease	Comment
1. Antiretroviral therapy	Start ART immediately where HIV-associated nephropathy (HIVAN) or HIV immune complex disease strongly suspected. Renal biopsy to confirm histological diagnosis recommended **Consider discontinuing or replacing TDF by non tenofovir drug or by TAF if** • UP/C 15-50 mg/mmol • eGFR > 60 ml/min, but decrease in eGFR by 5 mL/min per year for > 3 consecutive years • Co-morbidities with a high risk of CKD (ie DM, HT) • BW < 60 kg • Use of a PI/b as a third agent **Discontinuing or replacing TDF by non tenofovir drug or by TAF if** ❖ UP/C >50 mg/mmol ❖ eGFR <60 ml/min ❖ Nephrotoxic comedication ❖ Previous TDF toxicity (proximal renal tubulopathy
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: a) Hypertension, and/or b) Proteinuria	Monitor eGFR and K+ level closely on starting treatment or increasing dose a) Blood pressure target; <130/80 mmHg
3. General measures: a) Avoid nephrotoxic drugs b) Life style measures (smoking, weight, diet) c) Treat dyslipidaemia and diabetes d) Adjust drug dosages where necessary	CKD and proteinuria are independent risk factors for CVD

There are limited data on use of TAF with low eGFR, particularly eGFR ≤ 10 mL/min

Weight gain

Disclosures

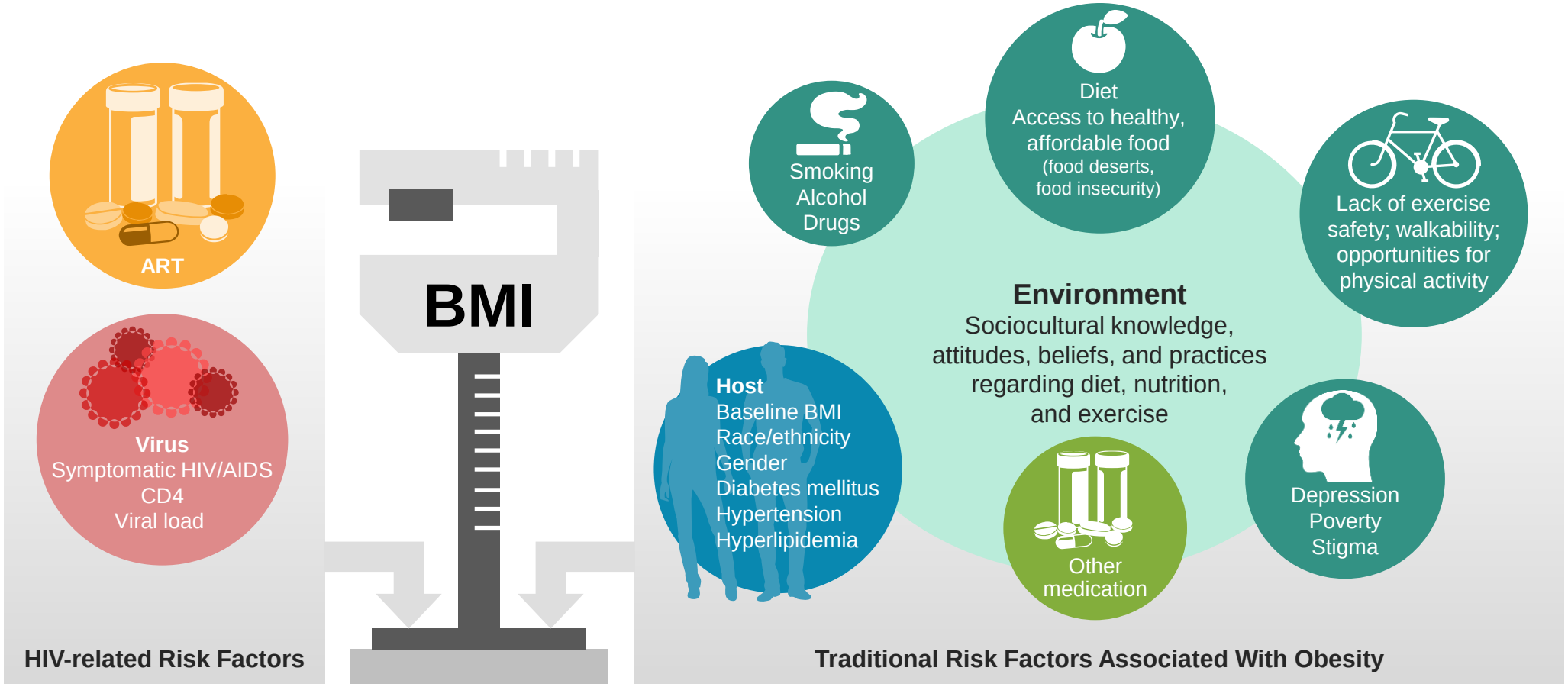
Opass Putcharoen, MD. MSc.

- Non-CME/CE services from Gilead Sciences, BMS, Merck, Mylan Healthcare, ViiV, GSK, Siam Pharmaceutical and Q Bioscience
- Advisory board: Pfizer, Celltrion, Abbott Laboratory, and Zuellig Pharma

Disclaimer

This presentation is based on my personal opinions and not related with my current position or organization

Weight Gain in PLWH Is a Multifactorial Process Driven by the Interplay Among Virus, ART, and Traditional Risk Factors[1-17]



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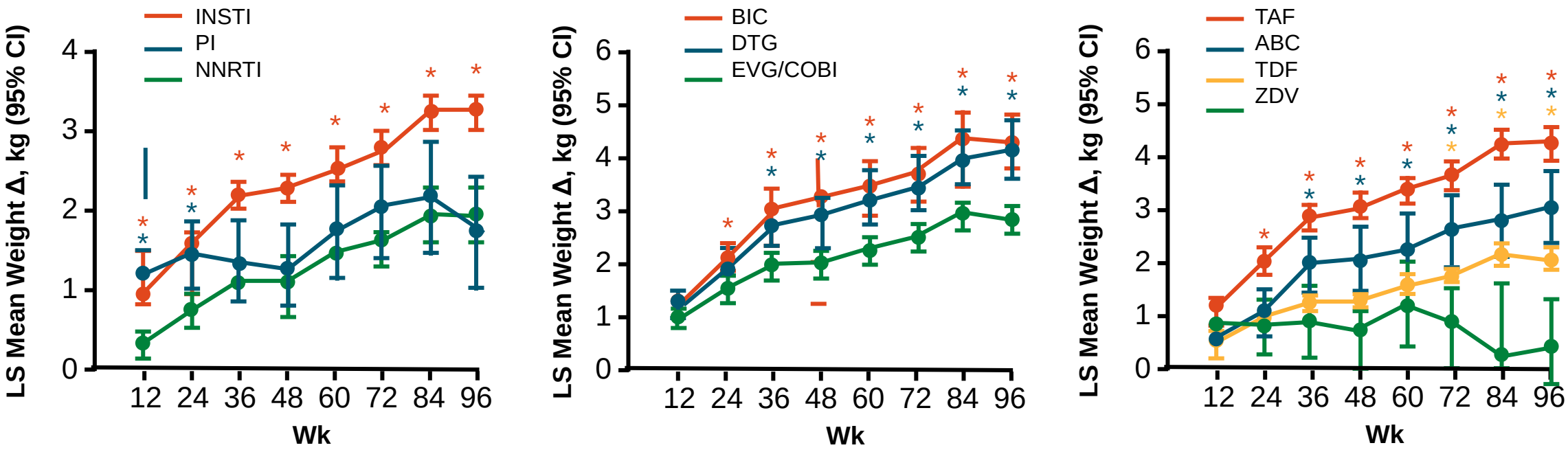
13. Lake J, et al. CROI 2019. Seattle, WA. Poster 669.
14. McComsey G, et al. CROI 2019. Seattle, WA. Poster 671.
15. Pallela F, et al. CROI 2019. Seattle, WA. Poster 674.
16. Kerchberger A, et al. CROI 2019. Seattle, WA. Poster 672.
17. O'Halloran J. CROI 2019. Seattle, WA. Oral TD-08.

Infographic developed by Gilead Sciences, with data supported by the following references:

Weight Gain Following ART Initiation by ARV Class and ARV Drug



*Color-coded to match respective comparators, denoting *P* ≤.05 vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

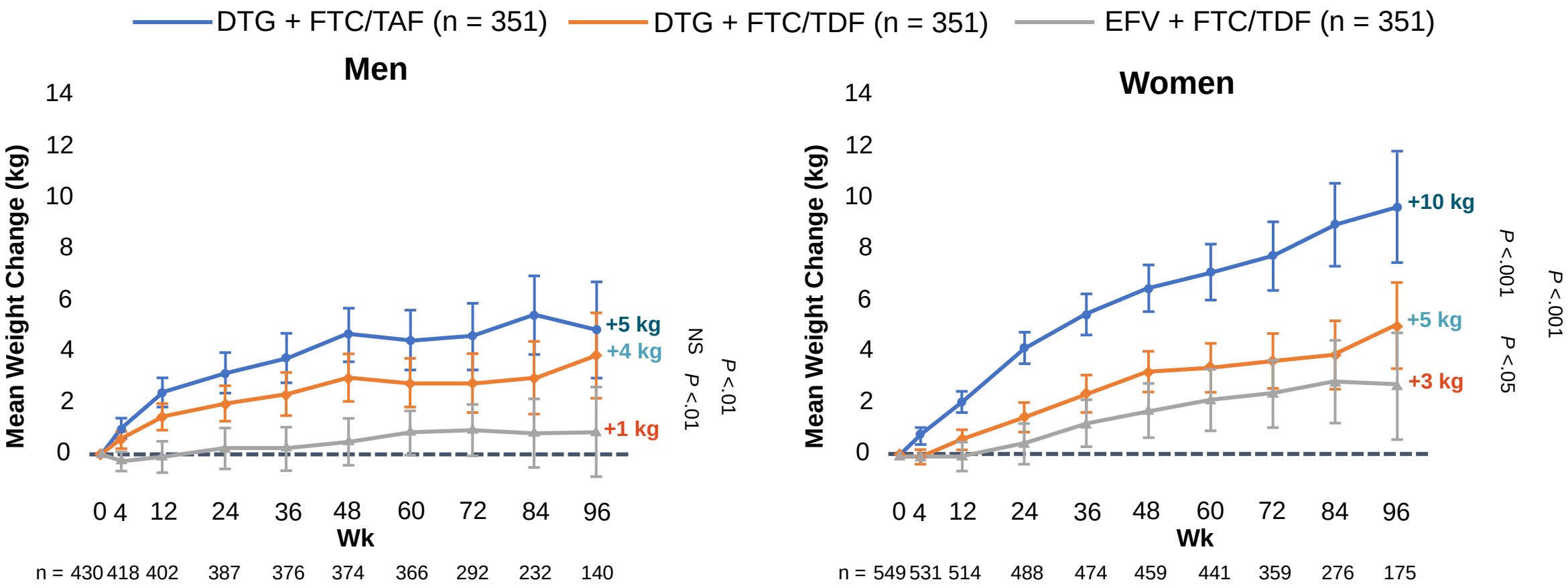
DTG, BIC,TAF cause more weight gain than others

Slide credit: CCO

Clin Infect Dis. 2020;71:1379.

ADVANCE: Mean Change in Weight by Sex at Wk 96

- Significantly greater weight increase with **DTG** vs **EFV**, with **TAF** vs **TDF** at Wk 96; plateauing in weight gain after Wk 48 observed in men but not in women



Slide credit: CCO

Hill. IAS 2019. Abstr MOAX0102LB. Venter. Lancet HIV. 2020;7:e666.

Change in body weight and risk of hypertension after switching from efavirenz to dolutegravir in adults living with HIV: evidence from routine care in Johannesburg, South Africa

Alana T. Brennan,[a,b,c,*] Cornelius Nattey,[a] Emma M. Kileel,[b,c] Sydney Rosen,[a,b] Mhairi Maskew,[a] Andrew C. Stokes,[b] Matthew P. Fox,[a,b,c,e] and Willem D. F. Venter[d,e]

[a]Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[b]Department of Global Health, Boston University School of Public Health, Boston, MA, USA
[c]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[d]Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

- Mean change in weight (1.78 kg; 95% confidence interval (CI):1.04,2.52 kg)
- 14.2 %-point increase (95% CI: 10.6,17.7) in the risk of hypertension

EClinicalMedicine. 2023 Feb 6:57:101836.

RESEARCH ARTICLE

Body weight and blood pressure changes on dolutegravir-, efavirenz- or atazanavir-based antiretroviral therapy in Zimbabwe: a longitudinal study

Tinei Shamu[1,2,3,§], Matthias Egger[2,4,5], Tinashe Mudzviti[1,6], Cleophas Chimbetete[1], Justen Manasa[7] and Nanina Anderegg[2,4]

[§]**Corresponding author**: Tinei Shamu, Newlands Clinic, 56 Enterprise Road, Newlands, Harare, Zimbabwe. (tineis@newlandsclinic.org.zw)

Prevalence of high blood pressure among PLHIV receiving DTG-based ART increased from around 5%at baseline to over 20% at 24 months, with no change in PLHIV receiving EFV- or ATV/r-based ART.

Journal of the International AIDS Society 2024, 27:e26216

Weight gain after antiretroviral therapy initiation and subsequent risk of metabolic and cardiovascular disease

Bares et al., 2023 | *Clinical Infectious Diseases*

IDSA
Infectious Diseases Society of America

Weight gain following initiation of antiretroviral therapy (ART) is common. We assessed the impact of changes in weight in the year following ART initiation with subsequent cardiometabolic disease among AIDS Clinical Trials Group (ACTG) participants.

Participants (n=2624) were primarily male (81%) and non-White (60%). Mean weight gain from 0-48 weeks was 3.6 kg (SD 7.3); 130 participants developed DM; 360 metabolic syndrome; 424 any cardiometabolic event; 28 any cardiovascular event.

In adjusted models, per 1kg increase in weight from weeks 0-48:

- Total cholesterol increased by 0.63 mg/dL (95% CI 0.38, 089)

- LDL increased by 0.39 mg/dL (0.19, 0.59)

Summary Table

Adjusted Cox Proportional Hazard Models of Weight Change at Week 48 and Subsequent Clinical Events Among Participants with >10% Weight Gain

Clinical Event	HR (95% CI)
Diabetes Mellitus (N=130)	2.01 (1.30, 3.08)
Metabolic Syndrome (N=360)	2.02 (1.55, 2.62)
Cardiometabolic Event (N=424)	1.54 (1.22, 1.95)
CV Event (N=28)	0.60 (0.22, 1.67)

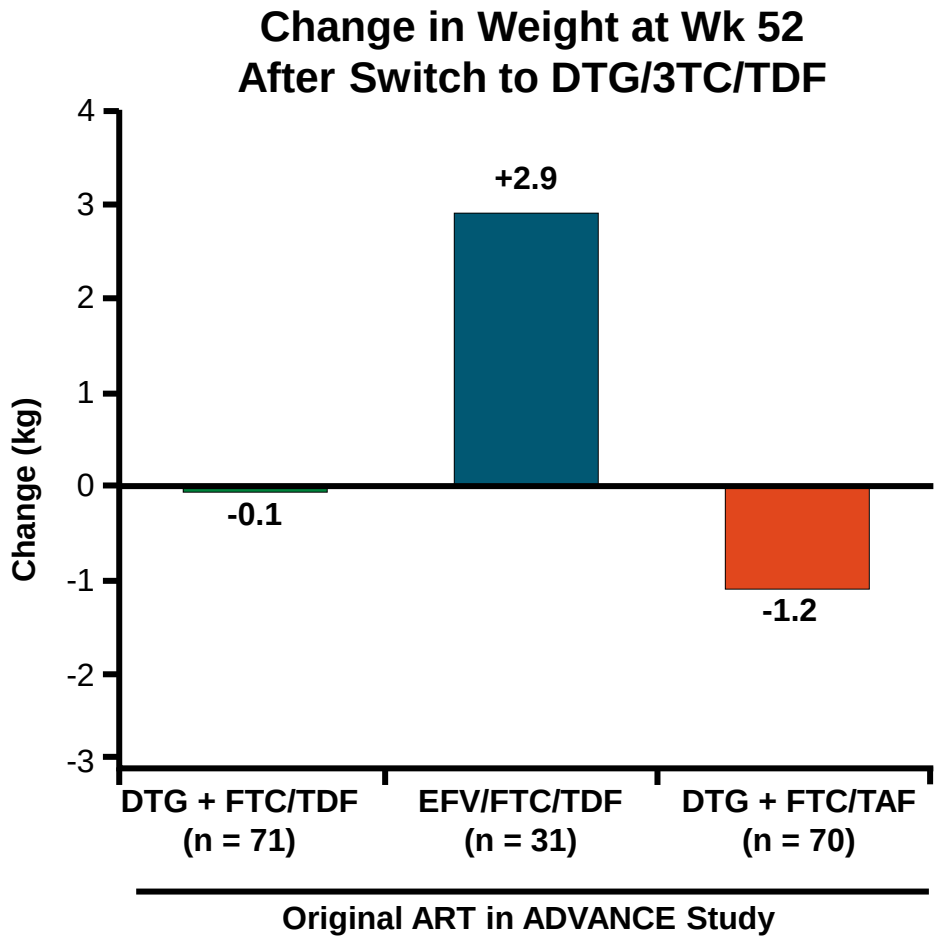
Weight and body composition changes in the first year following ART initiation are associated with contemporaneous changes in metabolic parameters and subsequent cardiometabolic disease.

Participants who lost more than 5% of their baseline weight had a lower risk of incident metabolic syndrome HR 0.67, 95% CI (0.42, 1.07)

Clin Infect Dis. 2024 Feb 17;78(2):395-401.

CHARACTERISE Study: Weight Changes After Switching to DTG/3TC/TDF

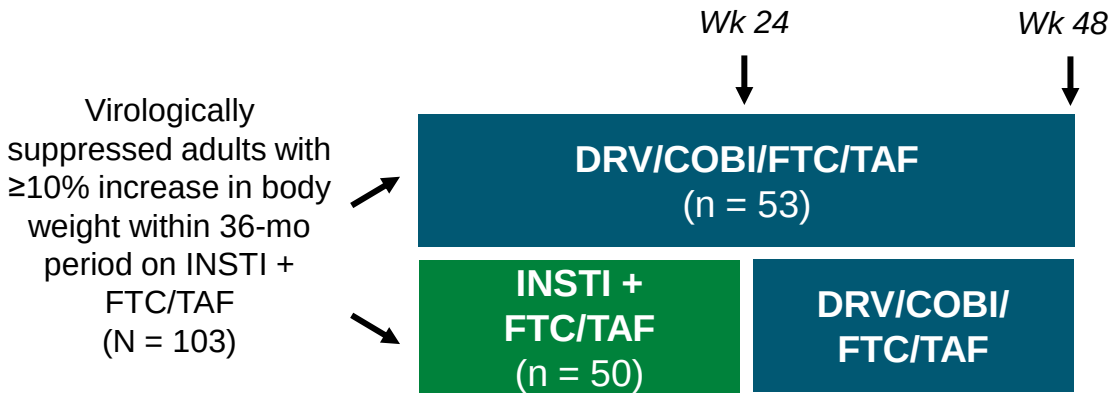
- 52-wk follow-up for patients who had previously been in ADVANCE study (n = 172)
  - Switched from **DTG + FTC/TDF, EFV/FTC/TDF, DTG + FTC/TAF**
  - HIV RNA <50 c/mL prior to switch (98%)
- After switch to **DTG/3TC/TDF**
  - **Weight loss** if switched from **DTG + FTC/TAF**
  - **Weight gain** if switched from **EFV/FTC/TDF**



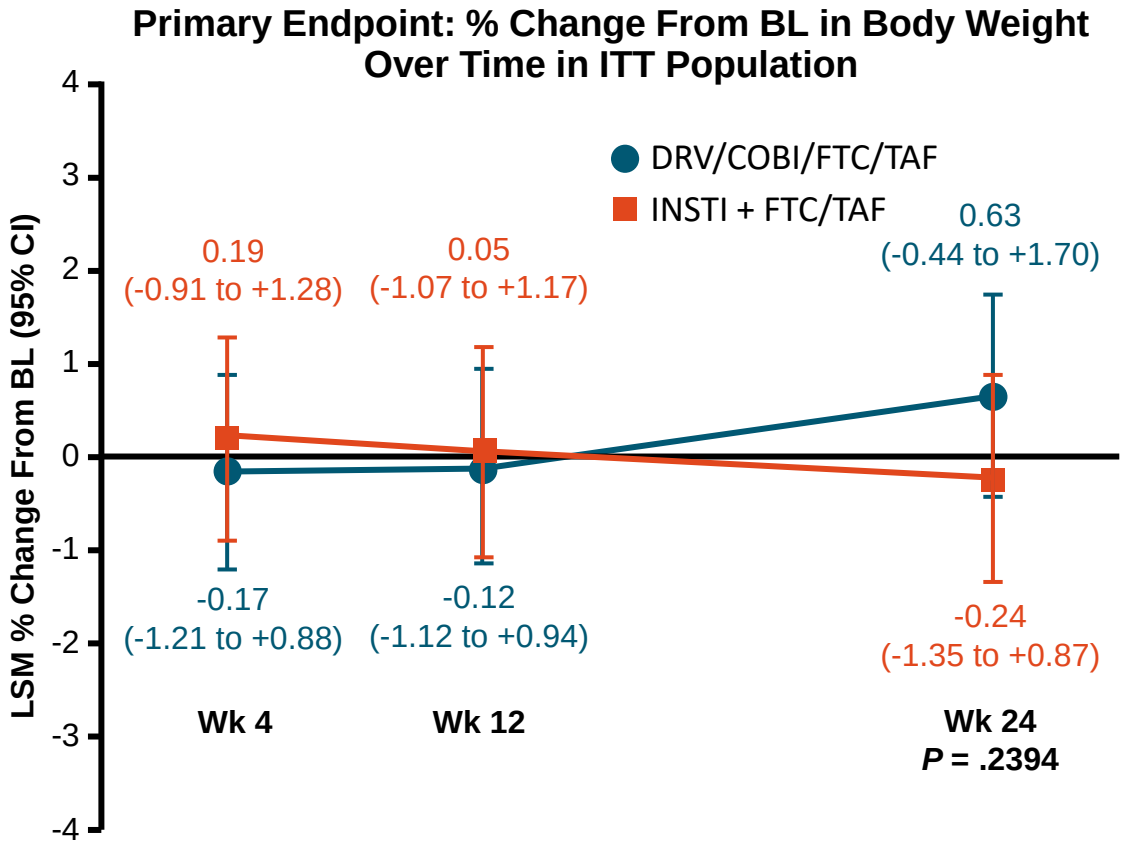
Bosch. Clin Infect Dis. 2023;76:1492.

DEFINE: Switch to PI-Based ART Following Weight Gain on INSTI-Based ART

- Prospective, randomized, open-label, active-controlled phase IV trial

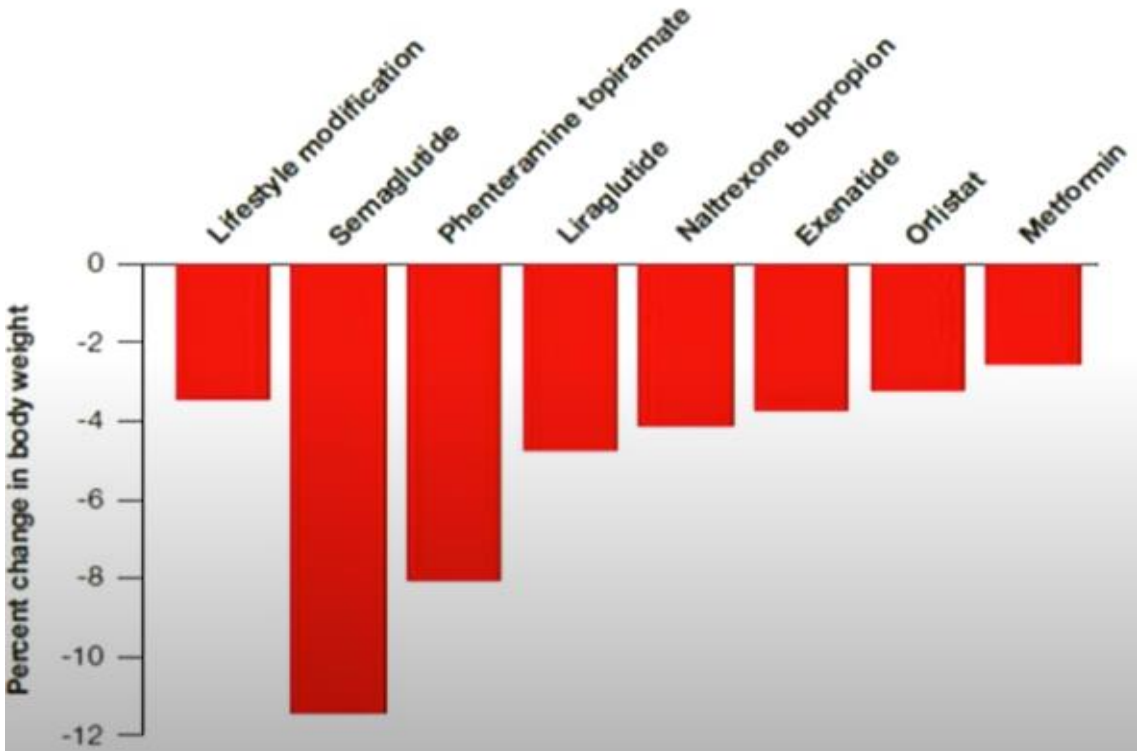


- **No significant difference in weight change** between arms from baseline to Wk 24
  - Changes in body weight were consistent among key subgroups (eg, BMI ≥ 30 kg/m^2, sex, race)



Short. IAS 2023. Abstr OALBB0502.

Pharmacologic weight loss

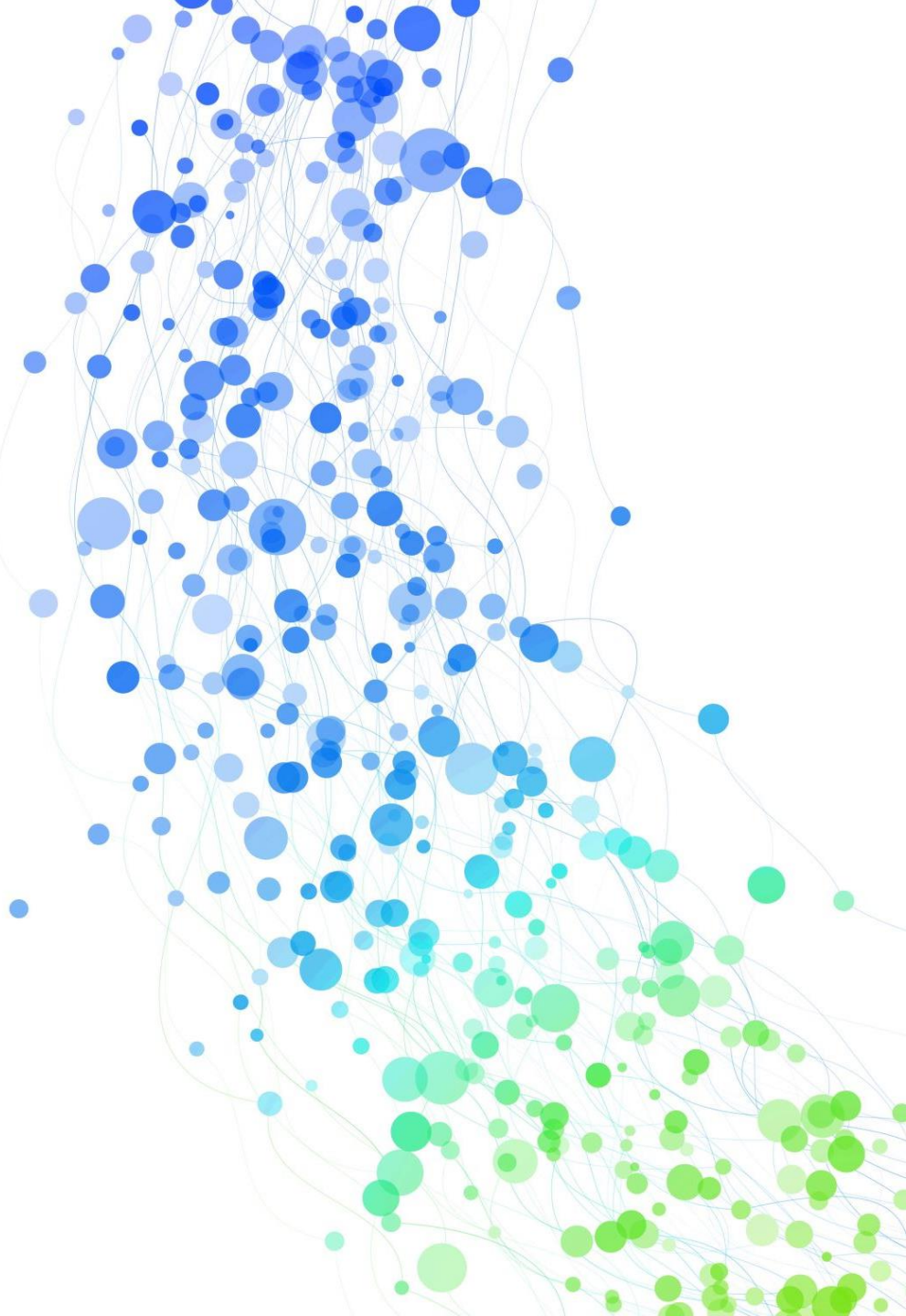


Lancet. 2022 Jan 15;399(10321):259-269

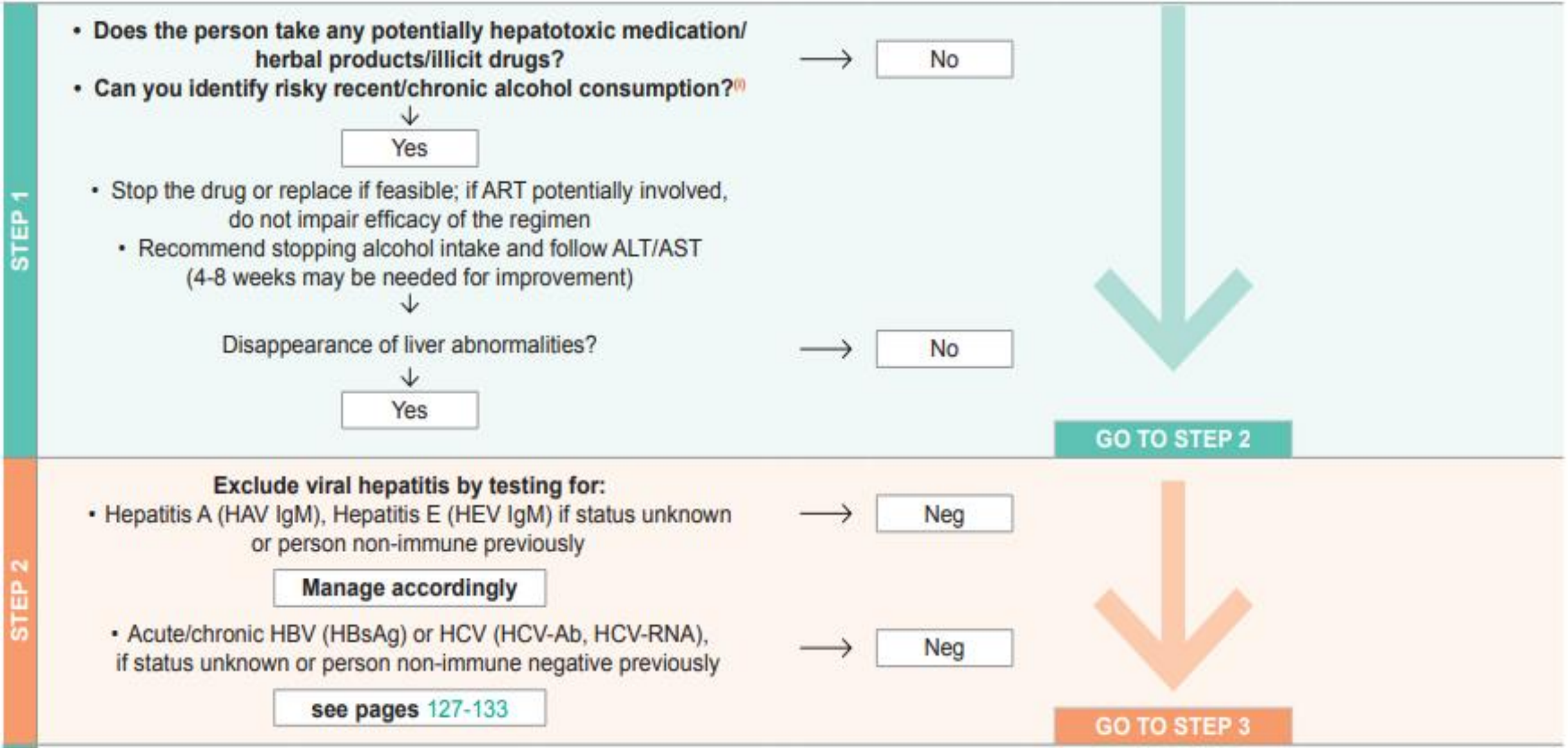
Weight gain in PWH

Contributing factors	▪ **Older age** ▪ Sedentary lifestyle ▪ Altered sleep pattern ▪ Intake of excess or poor-quality calories (e.g., saturated fats, processed sugars) ▪ Excess alcohol consumption ▪ Some medications (e.g., psychotropic drugs, steroids, anti-diabetic drugs) ▪ Endocrine disorders (e.g., GH deficiency, hypothyroidism, Cushing's syndrome, hypogonadism
Impact of ART	▪ Initiation of ART increases weight as part of a return-to-health phenomenon ▪ INSTI and TAF may induce greater weight gain than other ARVs´ ▪ **Switching from INSTI and/or TAF may have a small weight loss effect in <u>overweight/obese people</u> with HIV**
Aim of intervention	Emphasize the importance of behavior goals rather than weight loss goals **An objective of 5 - 10% weight loss may have benefits on:** ↑ 5% HDL cholesterol ↓ 5 mmHg systolic and diastolic BP in hypertension ↓ 0.5% (decrease 2.55 mmol/mol) HbA1c in DM Improving sleep apnea

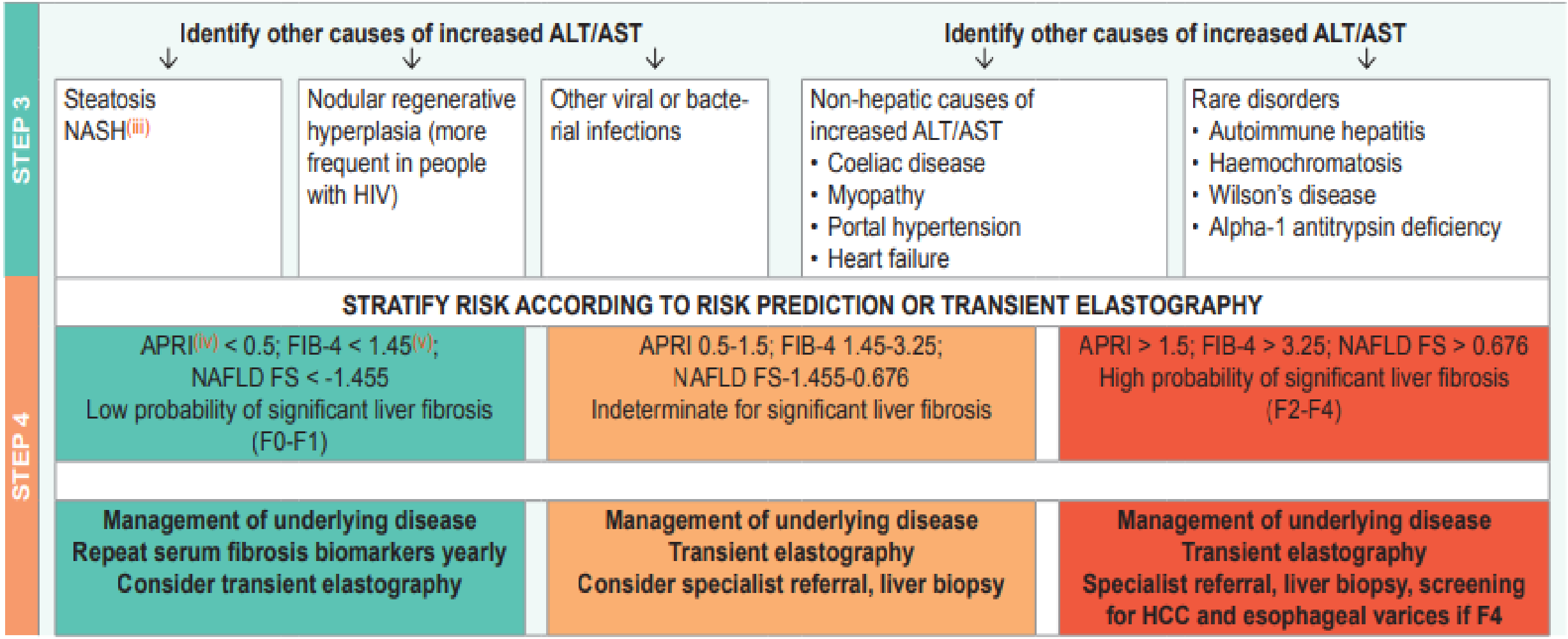
Transaminitis in PWH on ART



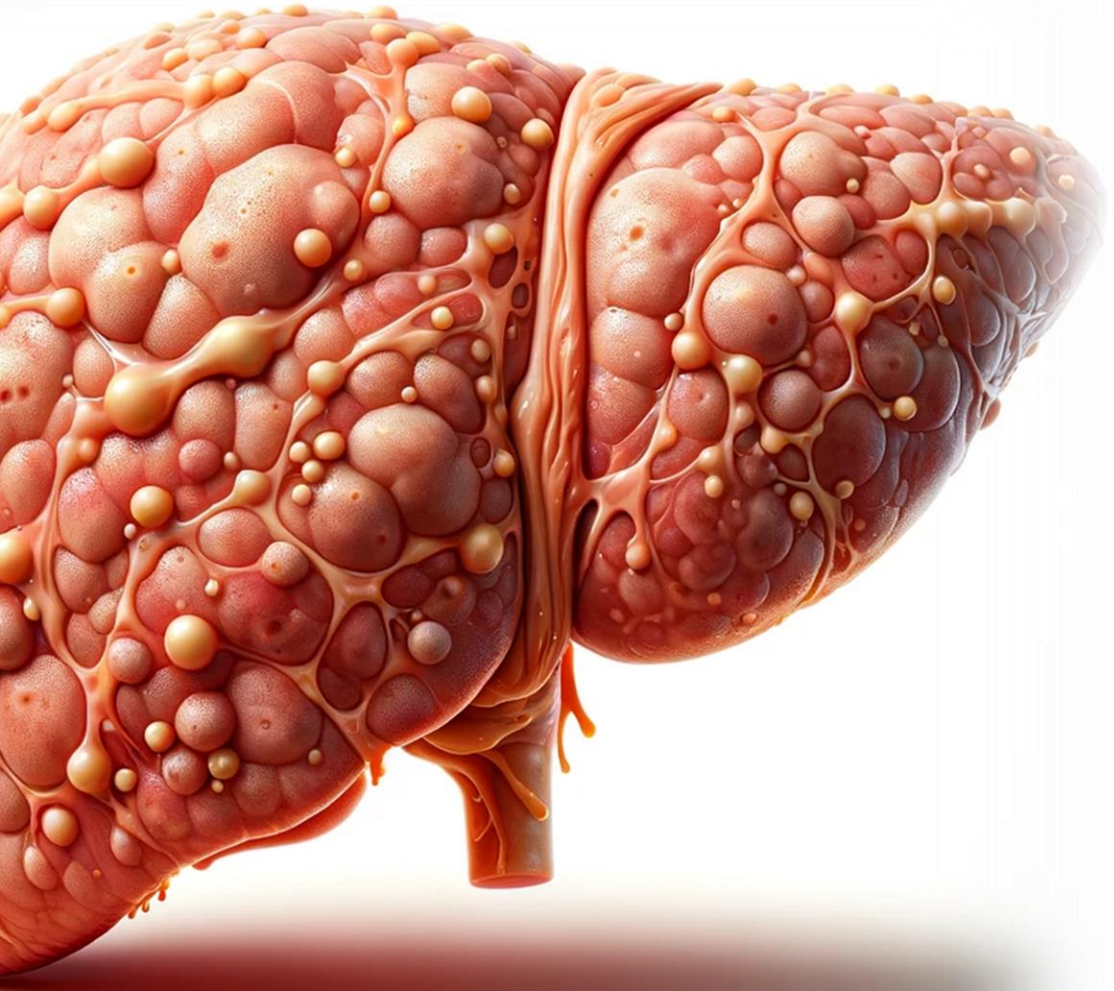
Work-up and Management of Persons with Increased ALT/AST



Work-up and Management of Persons with Increased ALT/AST



Fatty liver



Steatotic liver disease

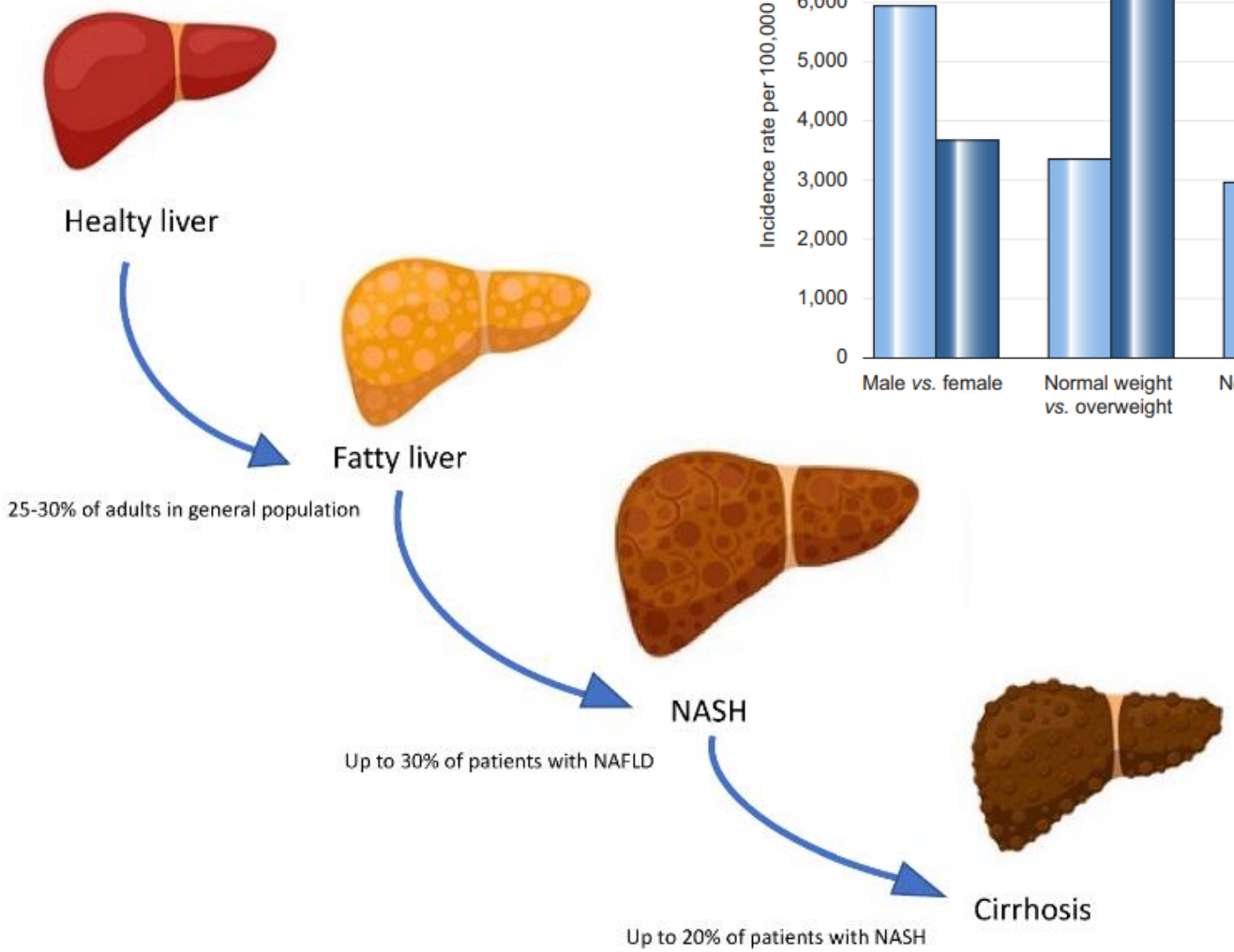
- Metabolic dysfunction-associated steatotic liver disease (MASLD) or NAFLD
- MASLD with metabolic dysfunction-associated steatohepatitis (MASH)
- MASH cirrhosis
- Metabolic dysfunction- and alcohol-associated liver disease (MetALD)

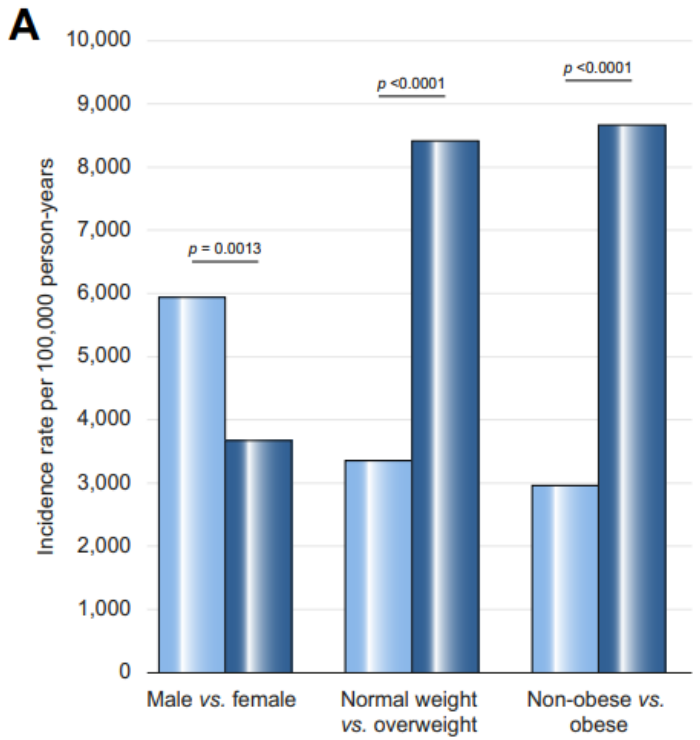
Risk factor and associated conditions

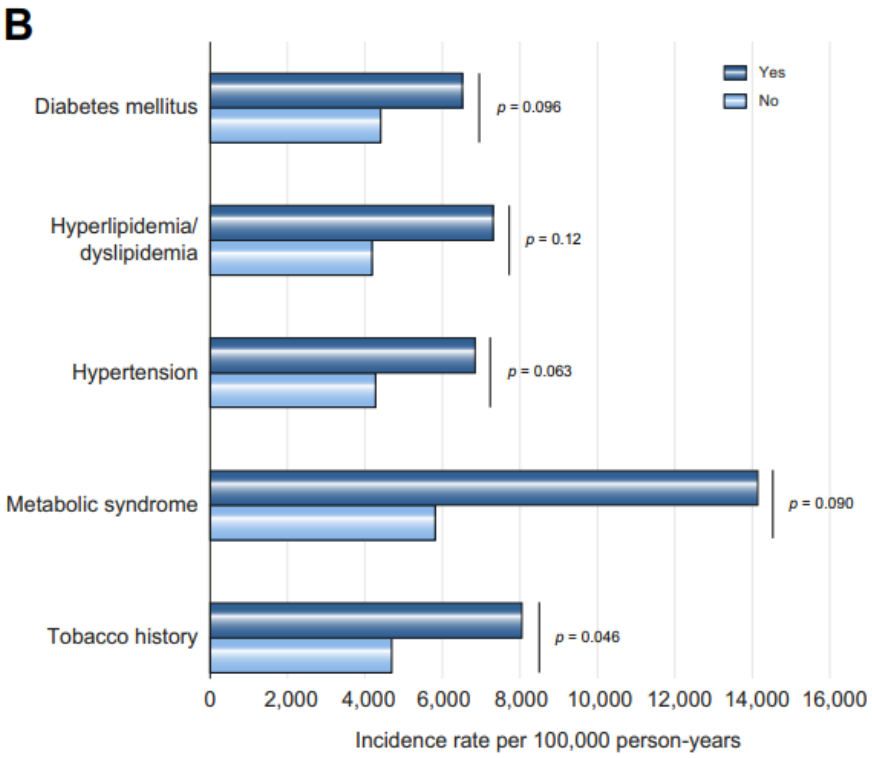
- Obesity (BMI ≥ 23 kg/m2 in Asian populations)
- Hypertension
- Dyslipedemia
- Type 2 DM

* If ≥ one metabolic factor have an increased risk for progression to MASH

NAFLD incidence is increasing with a current estimate of 4,613 new cases per 100,000 person-years.







J Hepatol. 2023;79(2):287-295.

Data are based on the following works:

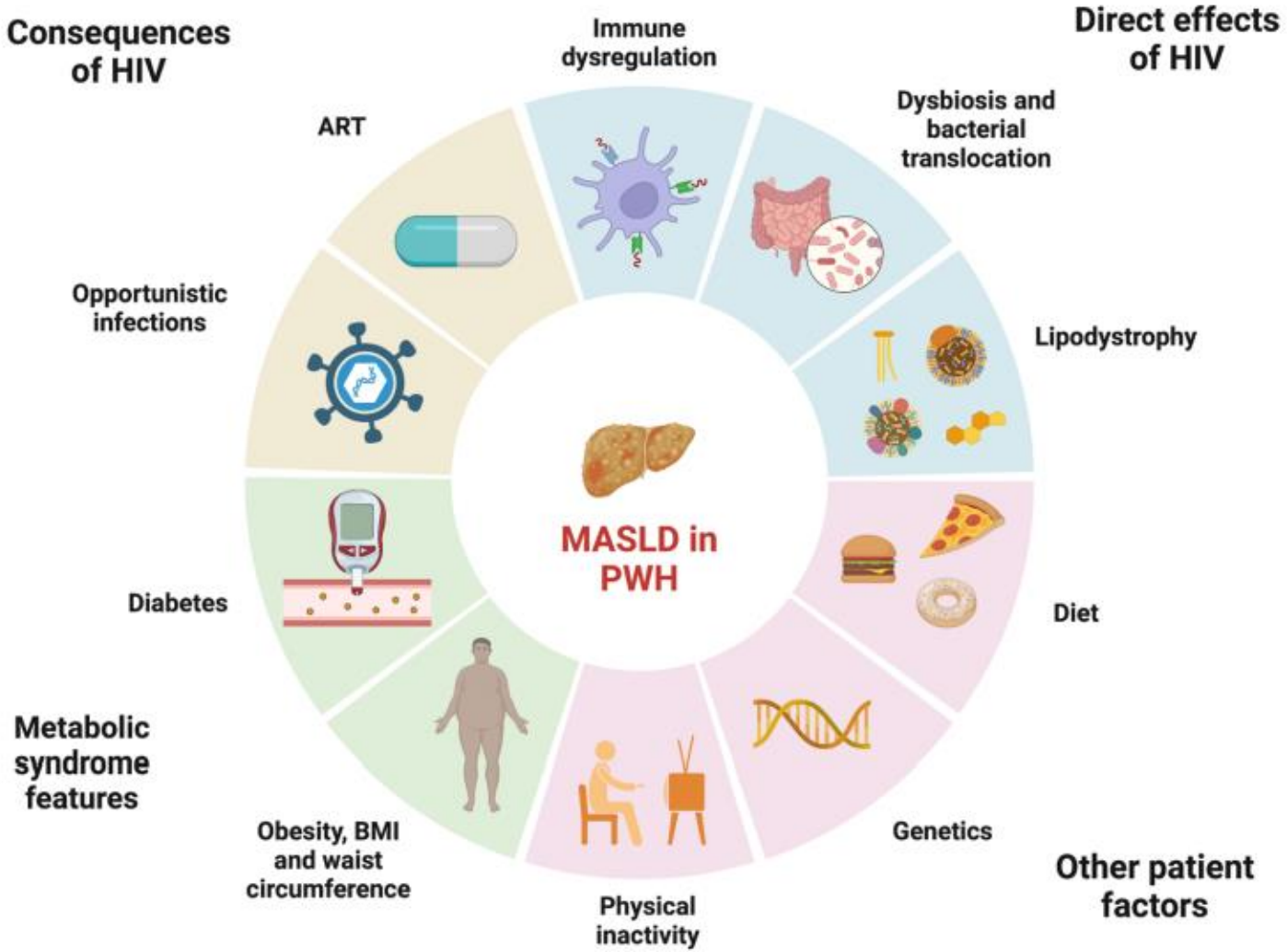
- Younossi ZM et al. Hepatology 2016;64:73-84.
- Rinella ME. JAMA 2015;313:2263-2273.
- Drew L. Nature. 2017;550:S102-S103

Prevalence of MASLD in PWH

Authors and year	Population	N	MASLD definition	MASLD prevalence	MASH definition	MASH prevalence	Fibrosis ≥F2	Advanced Fibrosis (F3-F4)
Gawrieh et al. 2023 [13•]	PWH	342	Ultrasound CAP ≥ 263 dB/m	49% 51%	–	–	17%	6%
Kalligeros et al. 2023 [15•]	PWH meta-analysis	8,230	Imaging	33.9%	Biopsy	49% of MASLD	12%	–
Chew et al. 2023 [11]	PWH	662	2 consecutive ↑ ALT	35%	–	–	–	–
Lemoine et al. 2023 [16•]	PWH with: Met syndrome ↑ALT/AST Lipodystrophy	402	MRI-PDFF	64%	–	–	–	11.3% of MASLD
Michel et al. 2022 [44]	PWH	282	CAP ≥ 275 dB/m	27%	FAST > 0.35	10%	7%	–
Price et al. 2022 [14]	Female PWH	1,543	CAP ≥ 248 dB/m	48%	–	–	24%	–
Riebensahm et al. 2022 [12]	PWH	416	CAP ≥ 248 dB/m	43%	–	–	5.2%	–

Current HIV/AIDS Reports2023;20:405–418

Pathogenesis of MASLD in PWH



Current HIV/AIDS Reports2023;20:405–418

EACS European AIDS Clinical Society

Consideration of ARV drugs

- Consider use of metabolic neutral ART regimens in individuals at risk of or with NAFLD (e.g. risk of weight gain induced by INSTI or TAF)

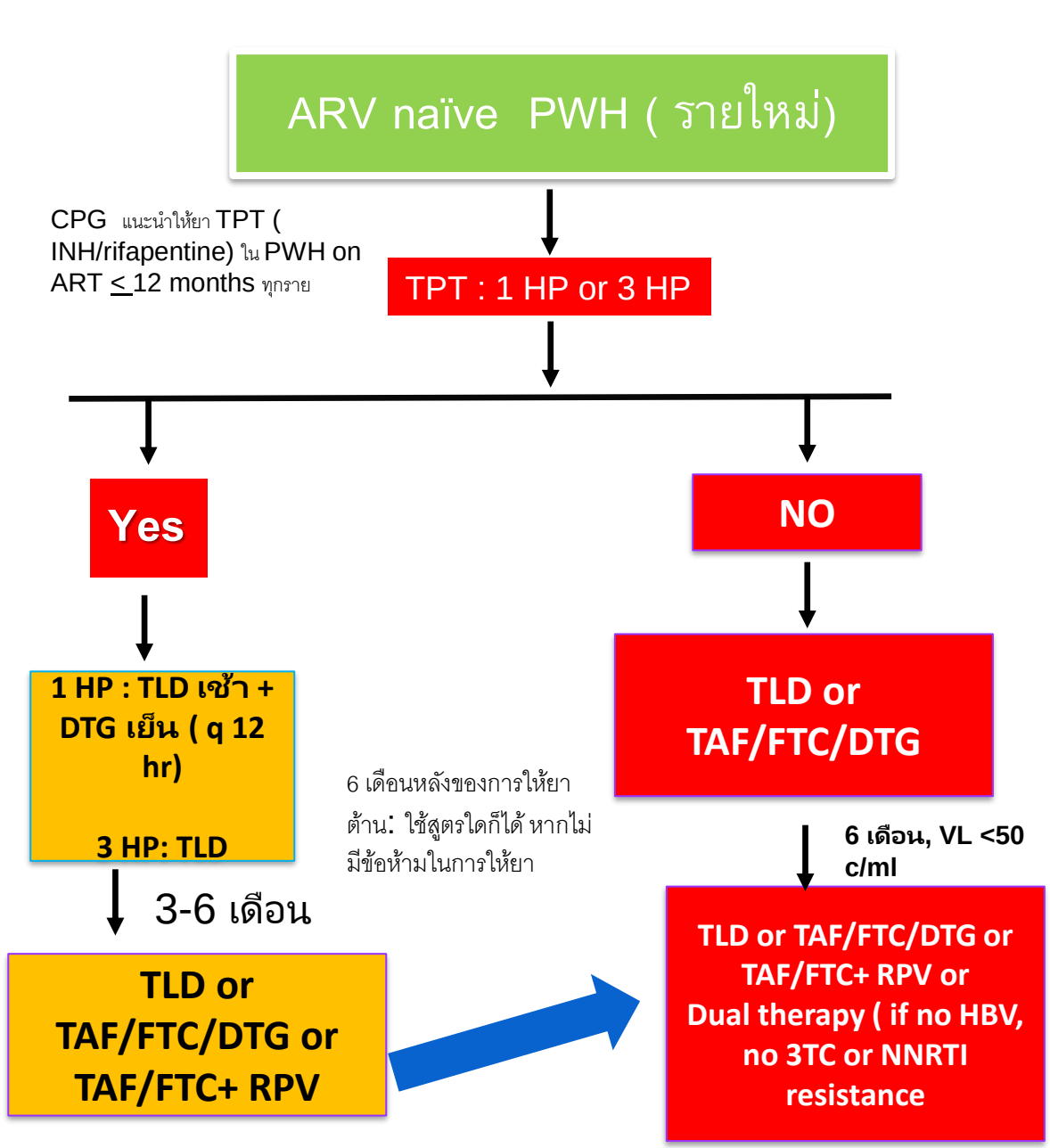
Treatment of NAFLD

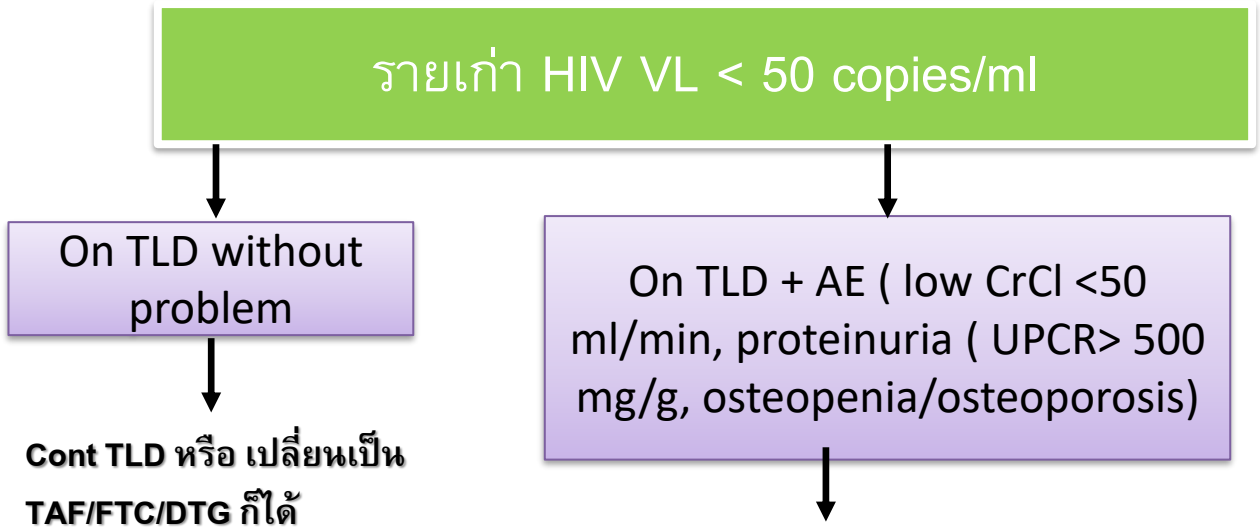
- Lifestyle modification and weight reduction is the cornerstone of treatment
- Dietary restriction **PLUS** progressive increase in aerobic exercise/resistance training: Caloric restriction (500-1,000 /day) targeting 7-10% weight loss in persons with central obesity and/or overweight; 150-200 min/ week of moderate intensity aerobic physical activities in 3-5 sessions
- A Mediterranean diet should be advised to improve steatosis and insulin sensitivity
- Pharmacotherapy should be reserved for individuals with NASH, particularly for those with significant fibrosis ≥ F2 and individuals with less severe disease, but at high risk of faster disease progression (i.e. with diabetes, metabolic syndrome, persistently increased ALT, high necroinflammation)
- Management of NASH should be discussed with hepatologists. Options with proven efficacy include pioglitazone, vitamin E and bariatric surgery. In the specific setting of HIV-associated NAFLD, tesamorelin and vitamin E have demonstrated efficacy, however larger studies are needed. Researchers advocate for inclusion of persons with HIV in ongoing global trials of new antifibrotic molecules for NASH
- Statins may be safely used but have demonstrated no impact on NAFLD thus far. The same is true for n-3 polyunsaturated fatty acids

The Way Forward

- **The goals of initial antiretroviral therapy**
  - Reduction of HIV-related morbidity and mortality
  - Restoration and preservation of immune function
- **Additional goals for HIV management:**
  - Quality of aging PWH
    - The number of older adults living with HIV is increasing steadily, giving rise to a new population of interest in HIV care
  - Non-communicable disease comorbidities in HIV patients: diabetes, hypertension and heart disease are prevalent. These comorbidities require intervention to improve QOL in PWH

หลักการเลือกใช้ TLD และ TAF/FTC/DTG ประเทศไทย 2024





พิจารณาปรับเป็น TAF/FTC/DTG หรือสูตรอื่นๆ เช่น TAF/FTC+ RPV (no prior NRTI/NNRTI resistance), หรือ dual therapy : DTG+3TC (HBV -, 3TC resistance -) or DTG + RPV (HBV-, NNRTI resistance-) โดยเฉพาะในผู้สูงอายุและมีปัญหาเรื่องไต, weight gain, dyslipidemia

➢ใช้ TAF/FTC/DTG และมีผลข้างเคียง (weight gain, dyslipidemia) : พิจารณาปรับเป็น TLD (ถ้าไตดี) หรือสูตรอื่นๆ เช่น TAF/FTC+ RPV หรือ dual therapy

➢ใช้ TDF/FTC or ABC/3TC or AZT/3TC+ LPV/r : พิจารณาปรับเป็น TAF/FTC/DTG (ถ้าไม่เคยมี Fanconi syndrome และ มี CrCl > 30 ml/min) หรือ เปลี่ยนเป็นdual therapy

➢ใช้ TDF/FTC/EFV :พิจารณาปรับเป็น TLD หรือTAF/FTC/DTG หรือ TAF/FTC+RPV

➢ใช้ ABC/3TC+ DTG หรือ AZT/3TC+ DTG : พิจารณาปรับเป็น TAF/FTC/DTG (ถ้าไม่เคยมี TDF associated Fanconi syndromeและมี CrCl > 30 ml/min) หรือ ปรับเป็น dual therapy