



First Encounter With The HIV-infected Patients: Tips and Tricks

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Disclosure

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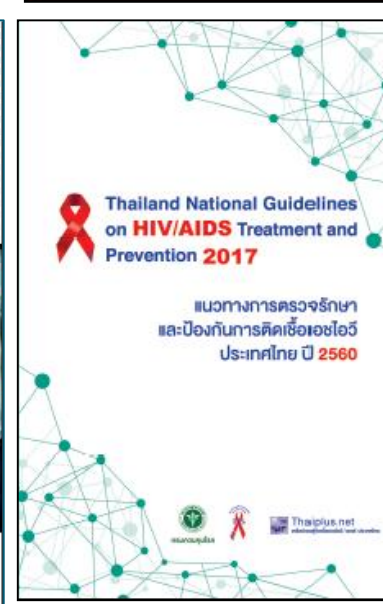
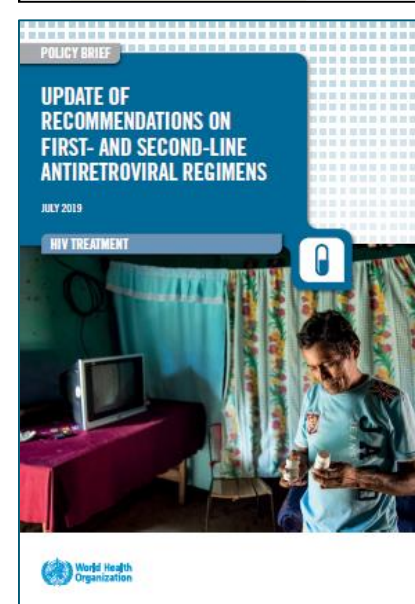
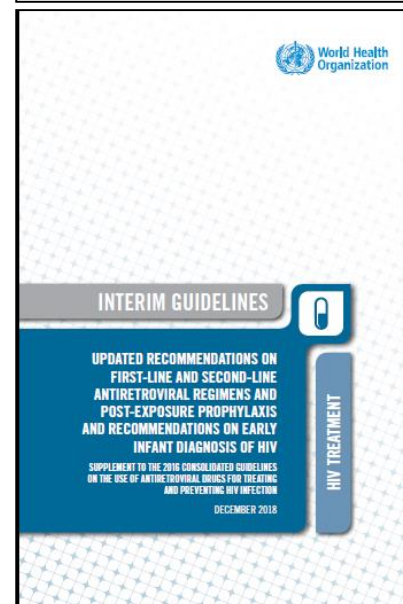
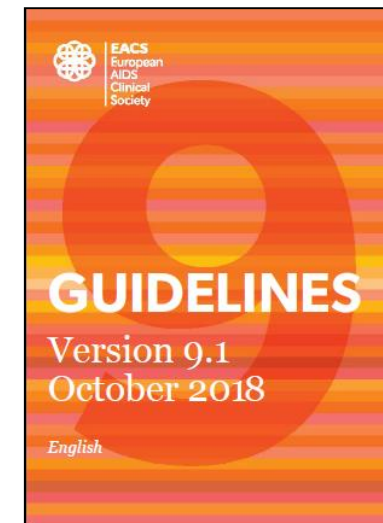
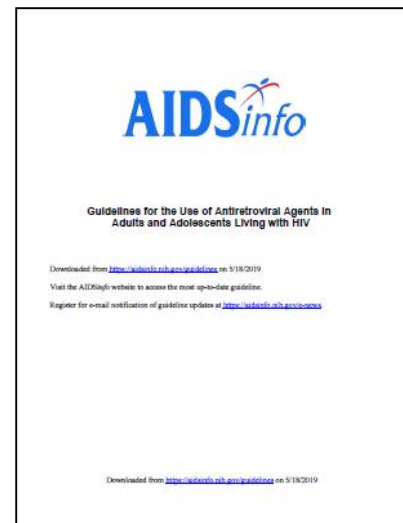
Disclosure

“I am an invited speaker receiving honorarium from various pharmaceutical companies, including MSD, Pfizer, Mylan, etc.”

Guidelines for Antiretroviral Therapy (ART)

- DHHS Guidelines 2018
- IAS-USA Guidelines 2018
- EACS Guidelines 2018
- WHO Guidelines 2018 & 2019
- Thai Guidelines 2017 & **2020**

(draft)



Case Presentation

- A 35-year-old male, BKK, Business man
- He was diagnosed with HIV infection since last week
- He asks you about ART initiation
- Lab:
 - CXR: no pulmonary infiltration
 - CBC: Hb 13 g/dL, WBC 7,500/mm³, platelets 350,000/mm³
 - BUN 20 mg/dL, Cr 0.5 mg/dL
 - HBs Ag: negative, anti HBs: 580 IU/L, anti-HCV: negative, VDRL: non-reactive
 - CD4: pending, HIV-RNA: pending

Case Presentation

- **When will you start ART in this patient?**
 - A. Today
 - B. Next 2 weeks
- **What is your recommended ART regimen for this patients?**
 - A. TDF/FTC/EFV
 - B. TDF/FTC + RPV
 - C. ABC/3TC/DTG
 - D. TAF/FTC/EVG/c
 - E. TDF/3TC/DTG
 - F. Others

Antiretroviral Therapy

When to Start?

Asymptomatic infection

- All, regardless of CD4 count

Active OIs

- Type of active OIs: TB, cryptococcosis, etc.

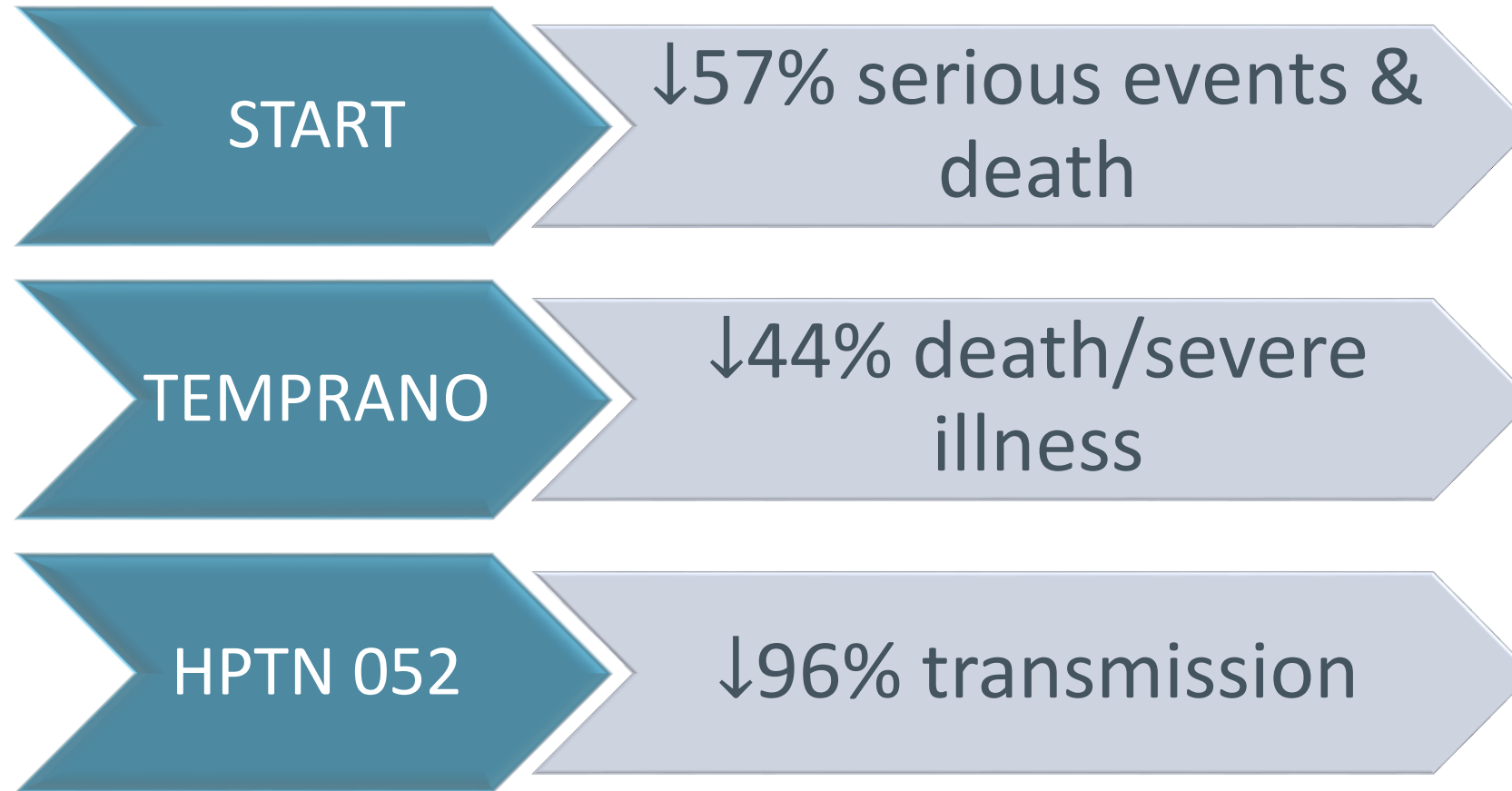
What to Start?

Patient factors

Viral factors

Medication factors

Early ART: Strong Evidences



Current guidelines: ART is recommended in all patients regardless of CD4

Same-Day ART: Evidences & Guidelines

- ✓ Improve in ART uptake, linkage to care, viral suppression
- ✓ Unknown in long-term safety, resistance, durability
- ✓ Different systems, resources & OIs may impact outcomes
- ✓ Resource-intensive, on-call HCPs

Guidelines

- **WHO 2017:** immediate ART initiation (within 7 d of HIV diagnosis)
- **DHHS 2018:** Same-day ART remains investigational
- **IAS-USA 2018:** Immediate ART (within 14 d of HIV diagnosis)
- **EACS 2018:** Immediate ART (same-day) should be considered (if patient is ready)
- **Thai 2020:** Rapid ART or same-day ART may be considered (if patient is ready)

Timing of Initiating ART in Active OIs

Active OIs	Time of Initiating ART (After Active OIs Treatment)	
	CD4 <50 cells/mm ³	CD4 ≥50 cells/mm ³
Tuberculosis	2-4 wks	2-8 wks
TB meningitis*	After TB treatment for 2 wks	
Cryptococcal meningitis**	4-6 wks	
PCP/MAC/others	2-4 wks	
CMV/PML/cryptosporidiosis	As soon as possible	

*TB meningitis: Early ART (increased co-toxicity, severe IRIS, no survival benefit)

**Cryptococcal meningitis: Early ART (<2 wks) vs. Late ART (5 wks); 6-mo mmortality rate 45% vs. 30% (p=0.03); (Delay ART if increased ICP or CSF WBC <5 cells/mm³)

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

'85-'89	1987 Zidovudine (NRTI)				
'90-'94	1991 Didanosine (NRTI)	1992 Zalcitabine (NRTI)	1994 Stavudine (NRTI)		
'95-'99	1995 Lamivudine (NRTI) Saquinavir (PI)	1996 Indinavir (PI) Nevirapine (NNRTI) Ritonavir (PI)	1997 Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	1998 Abacavir (NRTI) Efavirenz (NNRTI)	1999 Amprenavir (PI)
'00-'04	2000 Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC)	2001 Tenofovir DF (NRTI)	2003 Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	2004 Epzicom (FDC) Truvada (FDC)	
'05-'09	2005 Tipranavir (PI)	2006 Atripla (FDC) Darunavir (PI)	2007 Maraviroc (CA) Raltegravir (INSTI)	2008 Etravirine (NNRTI)	
'10-'14	2011 Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI)	2012 Stribild (FDC)	2013 Dolutegravir (INSTI)	2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)	
'15-'19	2015 Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC)	2016 Descovy (FDC) Odefsey (FDC)	2017 Juluca (FDC)	2018 Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab-uiyk (PAI) Symfi (FDC) Symfi Lo (FDC) Symtuza (FDC) Temixys (FDC)	2019 Dovato (FDC)

Drug Class Abbreviations:

CA: CCR5 Antagonist; FDC: Fixed-Dose Combination; FI: Fusion Inhibitor; INSTI: Integrase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PE: Pharmacokinetic Enhancer; PI: Protease Inhibitor; PAI: Post-Attachment Inhibitor

Note: Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.



Antiretroviral Agents

Single Tablet Regimen (STR)	Trade Name
TDF/FTC/EFV	Atripla
TDF/3TC/EFV	Symfi
TDF/3TC/EFV (400 mg)	Symfi Lo
TDF/FTC/RPV	Complera, Eviplera
TAF/FTC/RPV	Odefsy
TDF/FTC/EVG/c	Stribild
TAF/FTC/EVG/c	Genvoya
ABC/3TC/DTG	Triumeq
DTG/RPV	Juluca
TAF/FTC/BIC	Biktarvy
TAF/FTC/DRV/c	Symtuza
TDF/3TC/DOR	Delstrigo
DTG/3TC	Dovato

Other FDC: Combivir (AZT/3TC), Truvada (TDF/FTC), Cimduo or Temixys (TDF/3TC), Descovy (TAF/FTC), Kivexa or Epzicom (ABC/3TC), Trizivir (ABC/3TC/AZT), Kaletra (LPV/r), Evotaz (ATV/c), Prezcoibx (DRV/c)

*Green color = currently available in Thailand

Comparison of 3rd Agents for First-line ART

	INSTIs	PIs	NNRTIs
Tolerability	++++	+++	EFV ++ RPV, DOR +++++
Genetic resistance barrier	DTG, BIC: high RAL, EVG/c: low	High	Low
Drug-drug interaction	EVG/c: high DTG, RAL, BIC: low	High	Few
Metabolic effect*	EVG/c: high DTG, RAL, BIC: low	LPV/r > DRV/r > ATV/r	EFV: high RPV, DOR: low
Single tablet regimen	DTG, EVG/c, BIC: yes RAL: no	Yes (but not available in Thailand; TAF/FTC/DRV/c)	EFV: yes RPV, DOR: yes (but not available in Thailand)
Cost of treatment	DTG: high → low (Thailand) EVG/c, RAL, BIC: high	High	Low (DOR: high)

INSTIs: rapid viral suppression

DHHS & IAS-USA Guidelines 2018: First-line ART

Recommended ART	DHHS 2018	IAS-USA 2018
INSTIs	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ (TAF or TDF)/FTC + DTG ▪ (TAF or TDF)/FTC + RAL 	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ TAF/FTC + DTG

INSTIs

- **Recommended regimens may differ:** baseline HIV-1 RNA, CD4+ cell count, eGFR, HLA-B*5701, HBV/HCV, comorbidities & OIs, drug interaction, food effect and pregnancy status
- **RAL** can be given as 400 mg BID or 1200 mg (two 600-mg tablets) OD (BI-BII)
- **DTG** and **BIC** should not be used: 12-wk pregnancy, planning to become pregnancy, no effective contraception

DHHS & IAS-USA Guidelines 2018: First-line ART

Alternative ART	DHHS 2018	IAS-USA 2018
INSTIs	<ul style="list-style-type: none"> ▪ ABC/3TC + RAL ▪ (TAF or TDF)/FTC/EVG/c 	<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC/EVG/c ▪ (TAF or TDF)/FTC + RAL
NNRTIs	<ul style="list-style-type: none"> ▪ (TAF or TDF)/(FTC or 3TC)/DOR ▪ (TAF or TDF)/(FTC or 3TC)/EFV ▪ (TAF or TDF)/FTC/RPV 	<ul style="list-style-type: none"> ▪ TDF/3TC/DOR? ▪ TDF/FTC/EFV ▪ (TAF or TDF)/FTC/RPV
PIs	<ul style="list-style-type: none"> ▪ ABC/3TC + (DRV/r or DRV/c) ▪ (TAF or TDF)/FTC + (ATV/r or ATV/c) ▪ (TAF or TDF)/FTC + (DRV/r or DRV/c) 	<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC + (DRV/r or DRV/c)
Others (if ABC, TAF, TDF, cannot be used)	<ul style="list-style-type: none"> ▪ DTG + 3TC (DTG/3TC?) ▪ DRV/r or DRV/c + RAL 	<ul style="list-style-type: none"> ▪ DTG + 3TC? ▪ DRV/r + RAL ▪ DRV/c + 3TC

- DHHS: (TAF or TDF)/FTC/**EVG/c**: lower resistance barriers and more drug interactions
- IAS-USA: **EVG/c** & **RAL**-based ART : lower resistance barriers, more drug interactions and higher pill burden

EACS Guidelines 2018: First-line ART

Class	Recommended Regimens	Alternative Regimens
INSTIs	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ (TAF or TDF)/FTC + DTG ▪ (TAF or TDF)/FTC + RAL 	<ul style="list-style-type: none"> ▪ ABC/3TC + RAL ▪ (TAF or TDF)/FTC/EVG/c <div>INSTIs</div>
NNRTIs	<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC/RPV 	<ul style="list-style-type: none"> ▪ ABC/3TC + EFV ▪ TDF/FTC/EFV <div>NNRTIs</div>
PIs	<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC + (DRV/r or DRV/c) 	<ul style="list-style-type: none"> ▪ ABC/3TC + (ATV/r or ATV/c) ▪ ABC/3TC + (DRV/r or DRV/c) ▪ (TAF or TDF)/FTC + (ATV/r or ATV/c) <div>PIs</div>
Others	-	<ul style="list-style-type: none"> ▪ DTG + 3TC (DTG/3TC?) ▪ DRV/r or DRV/c + RAL

RPV: CD4 count >200 cells/mm³, VL <100,000 copies/mL
 Boosted PI: preferred in high risk of DR or poor adherence
 ABC: only for HLA B*5701 negative
 Dual ART: if ABC, TAF, TDF cannot be used

WHO Guidelines 2018: First-line ART

First-line ART	Recommended Regimens
Preferred regimens	<div> <div>TDF + 3TC (or FTC) + DTG</div> <div>INSTIs</div> <div>TDF + 3TC (or FTC) + EFV</div> <div>NNRTIs</div> </div>
Alternative regimens	<div>TDF + 3TC (or FTC) + EFV (400mg)</div> <div>TDF + 3TC (or FTC) + ATV/r</div>
Special situations	<div>AZT + 3TC + EFV</div> <div>TDF + 3TC (or FTC) + PI/r</div>

- ✓ DTG: caution use during periconception period in women of childbearing potential (risk of neural tube defect)
- ✓ TDF + 3TC + DTG: available in STR form as **TLD**

WHO Guidelines 2019: First-line ART

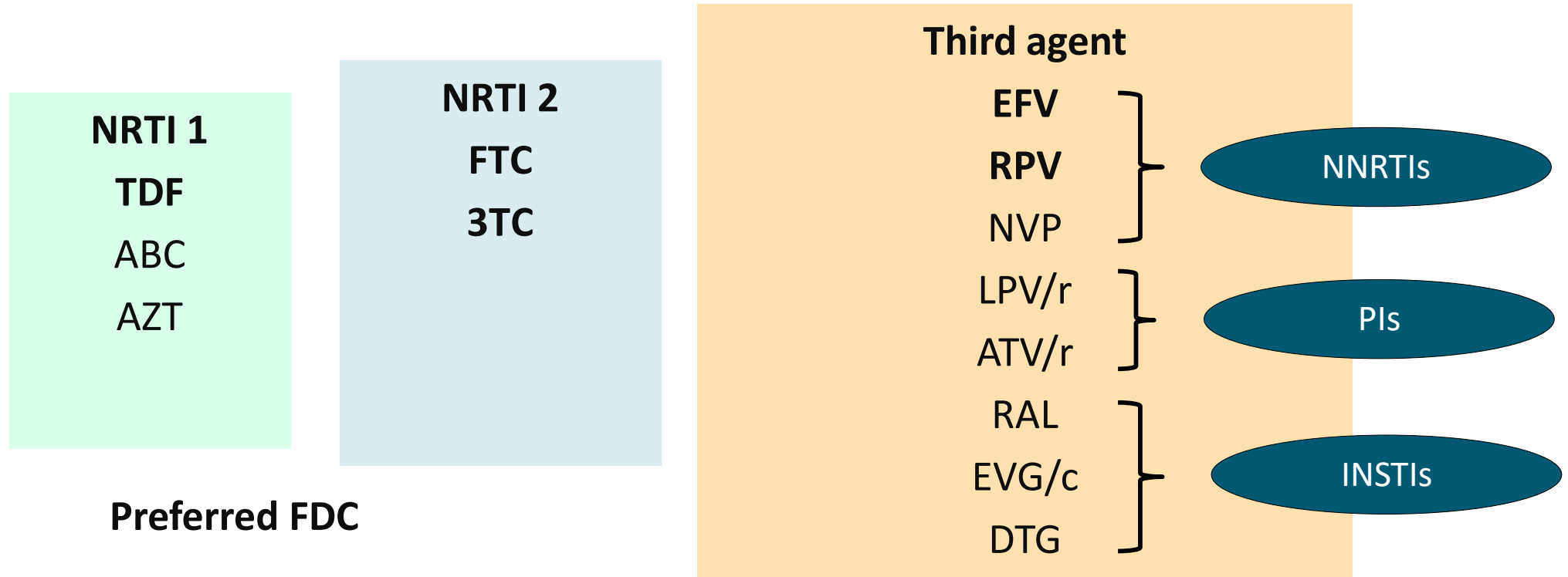
First-line ART	Recommended Regimens
Preferred regimen	TDF + 3TC (or FTC) + DTG
Alternative regimens	TDF + 3TC + EFV 400 mg
Special circumstances	TDF + 3TC (or FTC) + EFV 600 mg AZT + 3TC + EFV 600 mg TDF + 3TC (or FTC) + PI/r TDF + 3TC (or FTC) + RAL TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG

INSTIs

- **DTG:**
 - Risk of DTG-associated NTD is low but remains higher than other ART (waiting for ongoing studies) (current data: 0.3% vs. 0.1%)
 - Effective contraception should be offered in women of childbearing age (esp. at conception & until end of 1st trimester)
 - **Can be used in any women if fully informed the potential risk of NTD** (woman-centred approach)
 - If pregnancy identified after 1st trimester, DTG should be initiated or continued
- **EFV 400 mg:** (better tolerated than EFV 600 mg)
 - Should not be used if **pretreatment resistance to EFV $\geq 10\%$**
 - Clinical data on efficacy in **pregnancy & rifampicin** using is lacking (only PK/PD available)

Thai Guidelines 2017: First-line ART

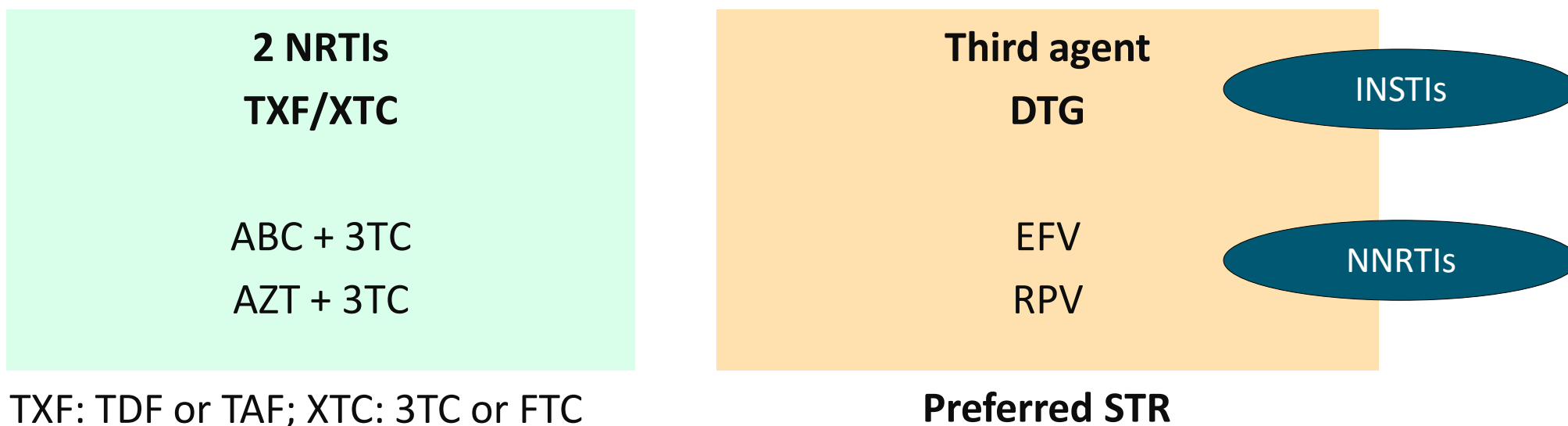
2 NRTIs + third agent



- RPV: CD4 count >350 cells/mm³, HIV-VL <500,000 copies/mL
- EFV: 400 mg can be used except **pregnancy, rifampicin**

Thai Guidelines 2020: First-line ART

2 NRTIs + third agent



- **TXF/XTC/DTG: Preferred first-line ART regimen**
- ABC + 3TC: HIV-VL <100,000 copies/mL (except use with DTG)
- DTG: Effective contraception should be used in woman of childbearing age
- EFV: 400 mg can be used, except in **pregnancy**
- RPV: CD4 count >350 cells/mm³, HIV-VL <500,000 copies/mL

Summary of Recommended First-line ART

ART	DHHS 2018	IAS-USA 2018	EACS 2018	WHO 2019	Thai 2020
INSTIs	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ (TAF or TDF)/FTC + DTG ▪ (TAF or TDF)/FTC + RAL 	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ TAF/FTC + DTG 	<ul style="list-style-type: none"> ▪ ABC/3TC/DTG ▪ TAF/FTC/BIC ▪ (TAF or TDF)/FTC + DTG ▪ (TAF or TDF)/FTC + RAL 	<ul style="list-style-type: none"> ▪ TDF + 3TC (or FTC) + DTG 	<ul style="list-style-type: none"> ▪ TXF/XTC/DTG
NNRTIs			<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC/RPV 		
PIs			<ul style="list-style-type: none"> ▪ (TAF or TDF)/FTC + (DRV/r or DRV/c) 		

Note: DHHS (Department of Health and Human Services), IAS-USA (International Antiviral Society-USA), European AIDS Clinical Society (EACS), WHO (World Health Organization)

Factors for Consideration of First-line ART

Clinical Settings	Considerations
CD4 <200 cells/mm ³	Do not use: RPV, DRV/r + RAL
HIV-RNA >100,000 copies/mL	Do not use: RPV, DRV/r + RAL, ABC/3TC + EFV or ATV/r
HLA B*5701 positive	Do not use: ABC
Food effect	With food: increase absorption: ATV/r (c), DRV/r (c), EVG/c, RPV, ETR Without food: decrease side effect: EFV No food effects: RAL, DTG, BIC, LPV/r, DOR, NVP, NRTIs
CKD (CrCl <60 mL/min)	Avoid TDF (ATV/r or ATV/c?) ART options: ABC, TAF (if CrCl >30 mL/min) DTG + 3TC, DRV/r + RAL (if CD4 >200, VL<100,000) or DRV/r + 3TC
Liver disease	Avoid ABC, d4T, ddI, NVP, ATV/r
Dyslipidemia	Associated with dyslipidemia: PI/r, PI/c, EFV, EVG/c Fewer lipid effect: RAL, DTG, BIC, RPV, DOR Note: TDF <ABC or TAF
High cardiac risk	Avoid ABC, LPV/r
Active TB	Rifampicin treatment: EFV or DTG
Pregnancy	Avoid DTG during contraception and early pregnancy

First-line Dual-Therapy ART

Study	N	Regimen	Results
PI-Based Dual Therapy			
NEAT001	805	DRV/r + RAL	Similar efficacy as DRV/r + TDF/FTC; poor efficacy in pts with high HIV-1 RNA ($>10^5$), low CD4+ cell counts (<200)
GARDEL	426	LPV/r + 3TC	Similar efficacy as LPV/r + 2 NRTIs
ANDES	145	DRV/r + 3TC	Similar efficacy as DRV/r + TDF/FTC Efficacy maintained when BL HIV-1 RNA $> 100,000$ copies/mL
SPARTAN	94	ATV + RAL	Similar virologic suppression, higher VF and hyperbilirubinemia rates vs ATV/r + FTC/TDF
DTG-Based Dual Therapy			
PADDLE	20	DTG + 3TC	18/20 pts achieved virologic suppression
ACTG A5353	120	DTG + 3TC	90% success (HIV VL <50 at 24 wk)
GEMINI1&2	1433	DTG + 3TC	Similar efficacy as DTG + TDF/FTC

Summary of First-line ART

- When to start
 - **Early ART (within 1-2 wks) at any CD4 level**
 - Appropriate time in active OIs
- What to start
 - Triple ART (2 NRTIs + 3rd agent)
 - Preferred 3rd agent: INSTIs > NNRTIs, PIs
 - Dual therapy: more data
 - **Thai Guidelines 2020 → DTG-based ART**



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