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Update on HIV/AIDS Care

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05/06/2018

Outline

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- ART
  - When to start ART
  - What to start ART
  - Monitoring after ART
  - Drug interactions and adverse drug reactions
  - Common problems during ART
- HIV prevention
- OIs/Co-infections

HIV/AIDS in Thailand

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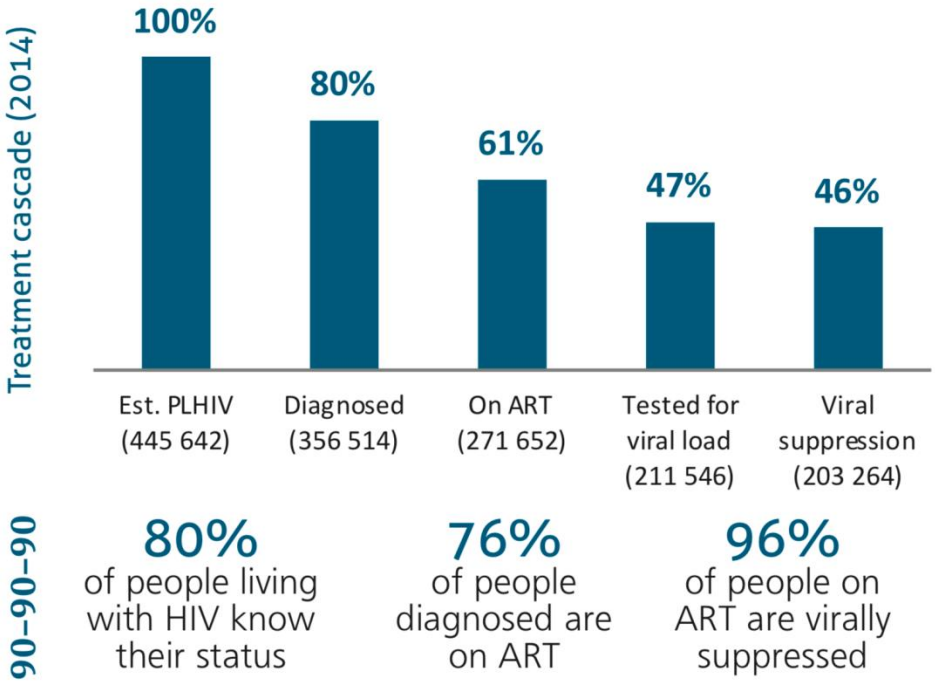
WHO report 2015

- **HIV prevalence**
  - 1.1% adult
  - 9.2% MSM
  - 19% PWID
  - 3.2% sex workers
- **HIV burden**
  - 450,000 PLHIV
  - 19,000 AIDS-related deaths
  - 7,900 new cases
  - 4,500 TB-related deaths



www.searo.who.int

HIV and ART: Life Expectancy

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The Netherlands

- From 25 y old (N = 4,620 cases) Median CD4 = 480
  - **Men =+52.7 y**
  - **Women =+57.8 y**

ART

Uganda

- From 30 y old (N = 22,315 cases)
  - **CD4 <50 =+14 y**
  - **CD4 >150=+40 y**

Thailand: overall **+25.4** y from age 20 years, but **+51.9** y if ART at CD4 >350 cell/mm^3

AIDS 2010;24:1527-35 Ann Intern Med 2011;155:209-16 Antivir Ther 2017;22(5):393-402

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Antiretroviral Treatment

Antiretroviral Treatment

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- **Goals**
  - ✓ Maximal and durable suppression of viral replication
  - ✓ Restoration and/or preservation of immune function
  - ✓ Reduced HIV-related morbidity and mortality
  - ✓ Improved quality of life
  - ✓ Reduced HIV transmission

Bureau of AIDS, TB, STIs and TAS. Asian Biomed 2010;4:515-28

Antiretroviral Treatment

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Factors for consideration

- **When to start?**
  - Asymptomatic HIV infection
    - All, regardless of CD4 count
  - Symptomatic/Opportunistic infections (OIs)
    - Type of active OIs: TB, cryptococcosis, etc.
- **What to start?**
  - Patient factors
  - Viral factors
  - Medication factors

DHHS Guideline Updated 2016

Question

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- A 30 YOF HIV with cryptococcal meningitis
- She received amphotericin B and fluconazole for 2 wks with clinical improvement and F/U CSF culture was negative
- Her CD4 50 cells/mm^3
- When will you initiate ART in this case?

  A. After 2 wks of antifungal agents

  B. After 5 wks of antifungal agents

  C. After 10 wks of antifungal agents

When to Start ART?

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Asymptomatic HIV infection

Guidelines	CD4	Note
IAS-USA 2016	All	✓ If patient ready to start ✓ Regardless of CD4 count *START study (n=4,685 cases): ○ Immediate ART (CD4>500) vs. Deferred ART (CD4 ≤350) ○ Reduced serious events & deaths (RRR 57%) esp. TB, Kaposi sarcoma, lymphoma
DHHS 2016	All	
EACS 2016	All	
WHO 2016	All	
BHIVA 2016	All	
Thai 2017	All	

IAS-USA (International Antiviral Society-USA) , DHHS (Department of Health and Human Services), European AIDS Clinical Society (EACS), WHO (World Health Organization), BHIVA (British HIV Association)

N Engl J Med 2015; 373:795-807

When to Start ART?

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Urgency to initiate ART

- Pregnancy
- AIDS-defining condition: dementia, malignancy
- Acute OIs
- CD4 <200 cells/mm3
- HIVAN
- Acute HIV infection
- HBV or HCV coinfection

DHHS Guideline Updated 2017

When to Start ART

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Active OIs	CD4 count (cells/mm³)		
	<50	≥50	
		Severe**	Non-severe
Tuberculosis*	≤2 wks (up to 4 wks)	≤2 wks (up to 4 wks)	2-8 wks
Cryptococcal meningitis***	4-6 wks		
PCP/MAC/Toxoplasmosis/others	2-4 wks		
CMV/PML/cryptoporidiosis	As soon as possible		

*CNS TB: Start ART after 2 wks of TB treatment (early ART: increased co-toxicity, severe IRIS, no survival benefit)

**Severe TB: disseminated TB, low BW, low albumin, anemia

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

DHHS Guideline Updated 2016 Thai guideline 2017

Question

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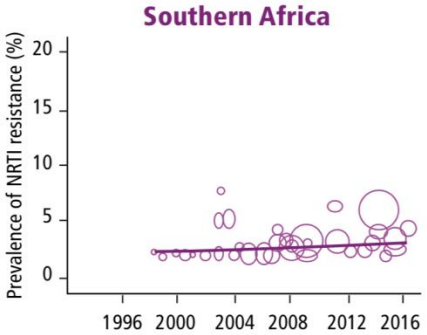
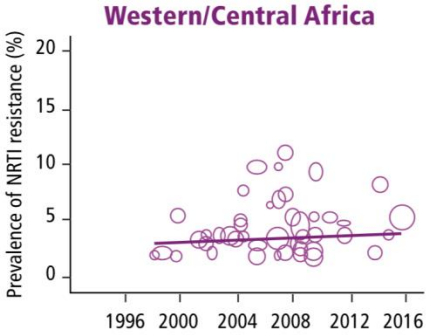
- Wound you send HIV-resistant testing before ART initiation in your routine practice?

A. Yes
B. No
C. Maybe

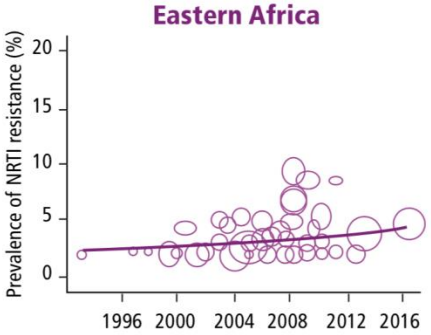
Pretreatment NNRTI Resistance



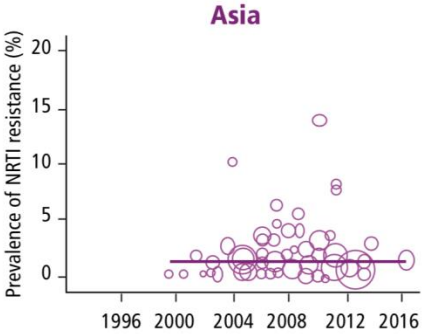
Studies: 61 Patients: 11 855
P-value for association: 0.0154



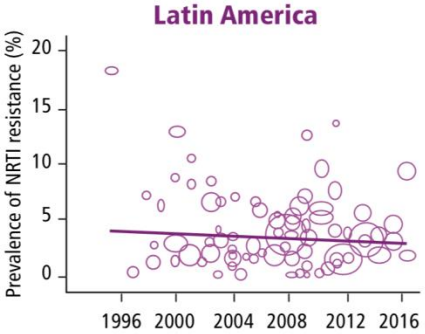
Studies: 52 Patients: 4 924
P-value for association: 0.3389



Studies: 50 Patients: 7 169
P-value for association: 0.0373



Studies: 90 Patients: 16 088
P-value for association: 0.8877



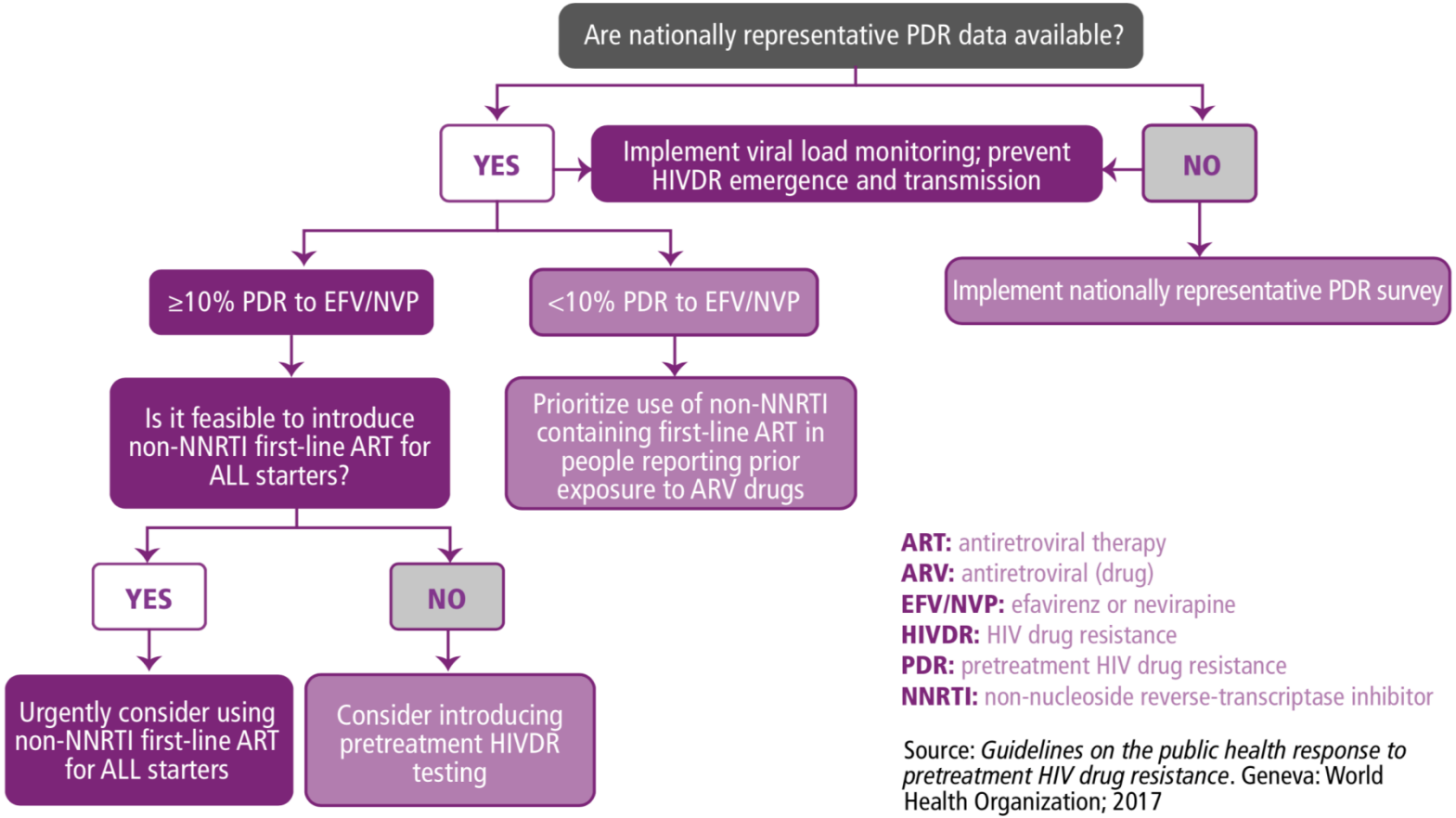
Studies: 83 Patients: 16 008
P-value for association: 0.4076

Thailand cohort during 2011-2014

- Primary HIVDR 7.9%
  - K103N 6%
  - M184V/I 4.5%

Fitted line

PLoS One 2016;11(2):e0147945 HIV Drug Resistance Report 2017



ART: antiretroviral therapy
ARV: antiretroviral (drug)
EFV/NVP: efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: pretreatment HIV drug resistance
NNRTI: non-nucleoside reverse-transcriptase inhibitor

Source: *Guidelines on the public health response to pretreatment HIV drug resistance*. Geneva: World Health Organization; 2017

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Question

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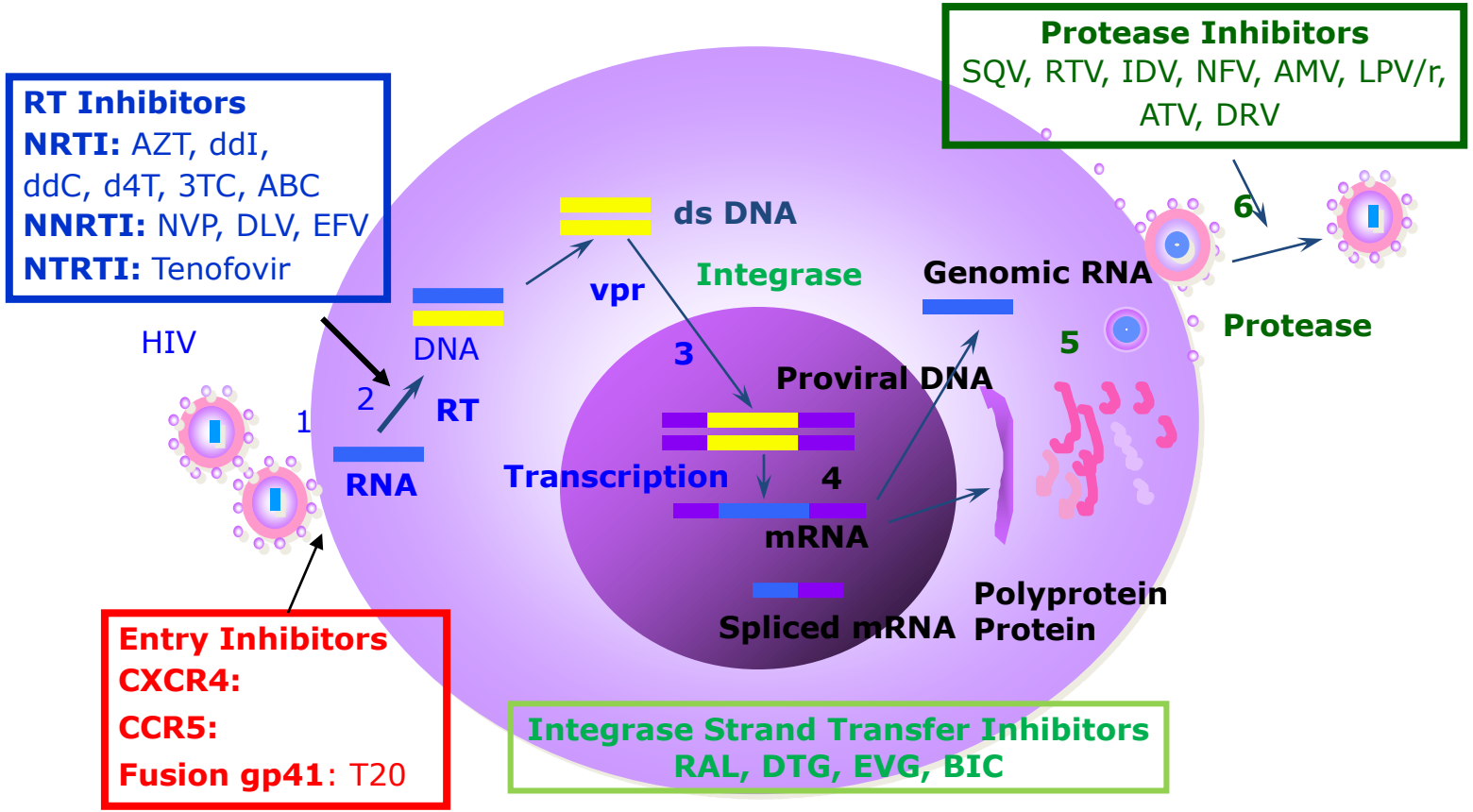
- A 40 YOF HIV with hyperlipidemia
- CD4 350 cells/mm^3
- HIV-RNA 60,000 copies/mL
- Current medication: Simvastatin 20 mg/d
- What is your ART choice?

  A. Start TDF/FTC + LPV/r

  B. Start TDF/FTC/EFV

  C. Start TDF/FTC + NVP

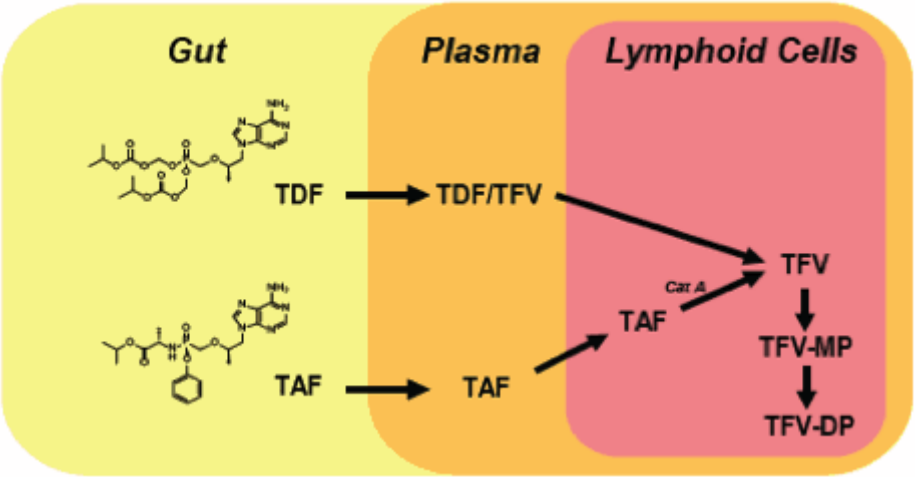
Targets of ART



Antiretroviral Agents

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
Abacavir (ABC)	Efavirenz (EFV)	Atazanavir (ATV)
Didanosine (ddI)	Etravirine (ETR)	Darunavir (DRV)
Emtricitabine (FTC)	Nevirapine (NVP)	Lopinavir (LPV)
Lamivudine (3TC)	Rilpivirine (RPV)	Ritonavir (RTV)
Stavudine (d4T)		Saquinavir (SQV)
Tenofovir (TFV)		Indinavir (IDV)
Zidovudine (AZT)		Tipranavir (TPV)
Integrase strand transfer inhibitors (INSTIs)	**Fusion inhibitors (FIs)**	**CCR5 antagonists**
Raltegravir (RAL)	Enfuvirtide (T20)	Maraviroc (MVC)
Elvitegravir(EVG)		
Dolutegravir (DTG)		
Bictegravir (BIC)		

TDF vs TAF



TAF: Fewer effect on kidney function and bone

TDF: Better lipid profiles

TDF = Tenofovir Disoproxil Fumarate

TAF = Tenofovir Alafenamide

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Single Tablet Regimens

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Components	Trade name	FDA approval
TDF/FTC/EFV	Atripla*	2006
TDF/FTC/RPV	Complera	2011
TDF/FTC/EVG/c	Stribild	2012
ABC/3TC/DTG	Triumeq	2014
TAF/FTC/EVG/c	Genvoya	2015
TAF/FTC/RPV	Odefsy	2016
TAF/FTC/BIC	Biktarvy	2018

Other FDCs: Combivir (AZT/3TC), Truvada (TDF/FTC), Descovy (TAF/FTC), Kivexa (ABC/3TC)

*Teevir (TDF/FTC/EFV)

DHHS Guideline Updated 2018

DHHS, IAS-USA Guidelines: Recommended First-line ART

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Class	DHHS 2018*	IAS-USA 2016**
INSTIs	▪ **ABC/3TC/DTG** ▪ (TAF or TDF)/FTC + DTG ▪ **(TAF or TDF)/FTC/EVG/c** ▪ (TAF or TDF)/FTC + RAL ▪ **TAF/FTC/BIC**	▪ **ABC/3TC/DTG** ▪ TAF/FTC + DTG ▪ **TAF/FTC/EVG/c** ▪ TAF/FTC + RAL

*Recommended regimens for most people with HIV
**IAS-USA guideline was not updated since the approval of TAF/FTC/BIC

- Recommendations may differ based on HIV-1 RNA, CD4+ cell count, CrCl, HLA-B*5701 status, HBV/HCV status, and co-morbidity status
- **With FDA approval of 1200-mg RAL, all options now available OD (except in pregnancy)**
- Cobiscistat (COBI; c): no activity against HIV, less drug interaction (COBI<RTV)

Günthard HF, et al. JAMA. 2016;316:191-210 DHHS Guideline updated 2018

DHHS Guideline 2018

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- "Recommended" initial regimens in **certain situations**

Class	Regimens
Boosted PIs	▪ (TAF or TDF)/FTC + (DRV/r or DRV/c) ▪ (TAF or TDF)/FTC + (ATV/r or ATV/c) ▪ ABC/3TC + (DRV/r or DRV/c) ▪ ABC/3TC + (ATV/r or ATV/c)
NNRTIs	▪ (TAF or TDF)/FTC + EFV ▪ (TAF or TDF)/FTC/RPV
INSTIs	▪ ABC/3TC + RAL

DHHS Guideline updated 2018

What to Start: Naïve patients?

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WHO guideline 2016

2 NRTIs + third agents

First line ART	Adults and adolescents
Preferred regimen	TDF + 3TC (or FTC) + EFV
Alternative regimen	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP TDF + 3TC (or FTC) + EFV (400) TDF + 3TC (or FTC) + DTG

WHO Guideline 2016

What to Start: Naïve patients?

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Thai Guideline 2017

2 NRTIs + third agents

NRTIs
TDF
ABC
AZT

Cytidine analog
FTC
3TC

Preferred FDCs

Third agents
EFV
RPV
NVP
LPV/r
ATV/r
INSTIs

RPV: CD4 count >350 cells/mm^3, VL <500,000 copies/mL

Thai Guideline 2017

What to Start: Naïve patients?

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EFV 400 mg OD

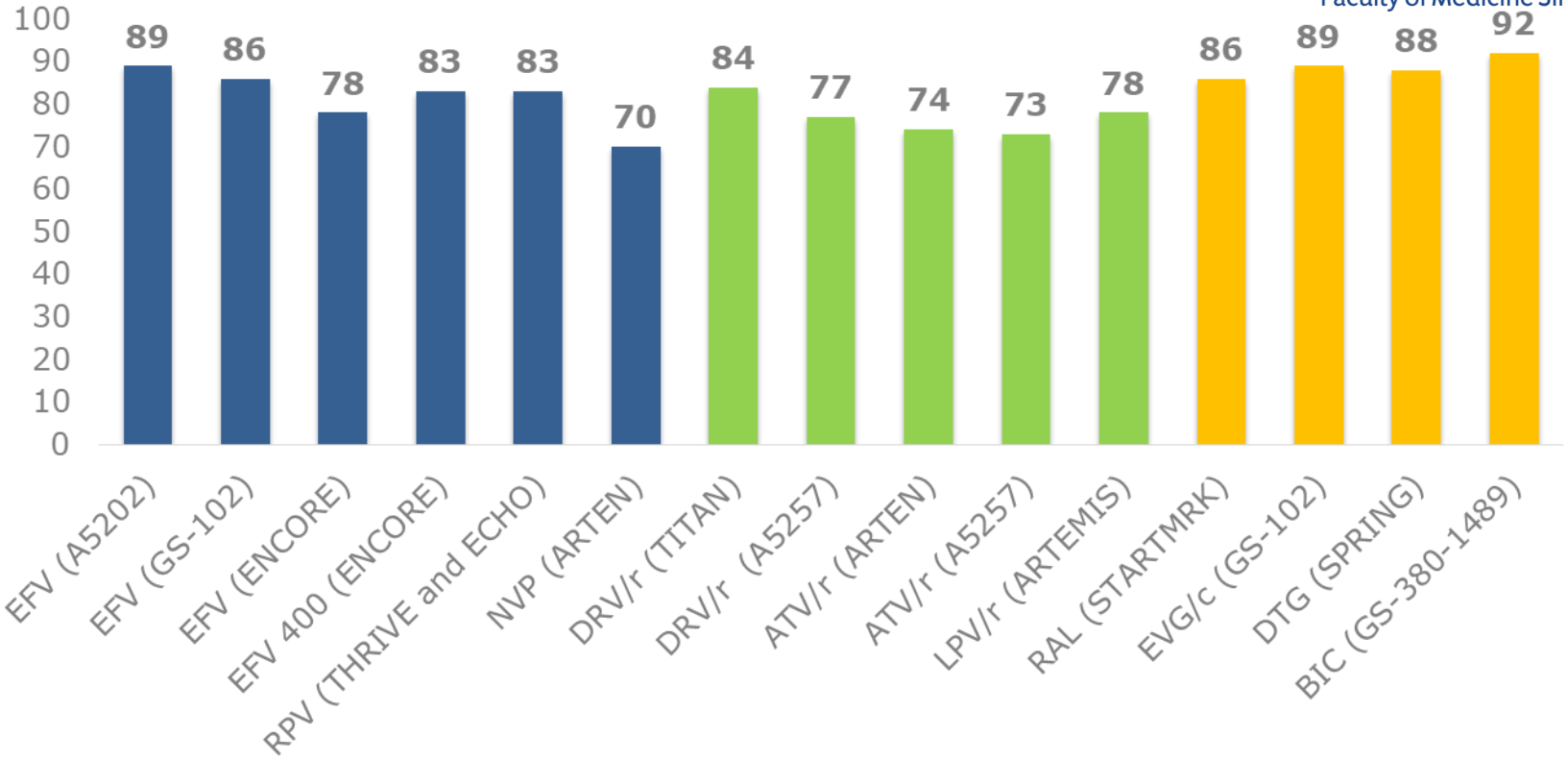
- Reduce side effects
- Do not use in
  - Pregnancy
  - Receiving rifampicin

LPV/r 800/200 mg OD

- Better compliance
- Higher rate of diarrhea
- Do not use in
  - Pregnancy
  - Receiving EFV, NVP
  - Receiving some AEDs (carbamazepine, phenytoin, phenobarbital)

Thai Guideline 2017

ART Efficacy at 48 Weeks



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What to Start: Special Considerations?

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Patient/Regimen characteristics	Clinical settings	Considerations
Pre-ART characteristics	CD4 <200 cells/mm^3	Do not use: - RPV - DRV/r + RAL
	CD4 >250 cells/mm^3 (female) >400 cells/mm^3 (male)	Do not use: - NVP
	VL >100,000 copies/mL	Do not use: - RPV - DRV/r + RAL - ABC/3TC + EFV or ATV/r (except ABC/3TC/DTG)
	HLA B*5701 +ve	Do not use: - ABC

DHHS Guideline Updated 2016 Thai Guideline 2017

What to Start: Special Considerations?

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Patient/ Regimen characteristics	Clinical settings	Considerations
Presence of other conditions	Psychiatric illness	Avoid EFV or RPV
	HAND	Avoid EFV
	Methadone use	Avoid EFV
	High cardiac risk	Avoid ABC, LPV/r
	Hyperlidemia	Associated with dyslipidemia: - PI/r (c), EFV, EVG/c - d4T>AZT>ABC Fewer lipid effect: - RAL, DTG, RPV, ETV, NVP, TDF
	Pregnancy	- Preferred: DRV/r, ATV/r, RAL, TDF, ABC, 3TC, FTC - Alternative: LPV/r, **EFV**, RPV, AZT

DHHS Guideline Updated 2016 Thai Guideline 2017

ART and Hyperlipidemia

www.clinicaloptions.com Best Pract Res Clin Endocrinol Metab 2011;25(3):429-42

Dolutegravir and Pregnancy

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Drug Safety Communications

FDA Drug Safety Communication

FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

Safety Announcement

[05-18-2018] The U.S. Food and Drug Administration (FDA) is alerting the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

ART in Pregnancy (Thailand)

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สูตรยาต้านเอชไอวีและระยะเวลาในการให้ยาต้านเอชไอวีสำหรับหญิงตั้งครรภ์ที่ไม่เคยได้รับยาต้านเอชไอวีก่อนเริ่มตั้งครรภ์

สูตรที่แนะนำ	การเริ่มยา (ไม่ต้องรอผล CD4 count)	การให้ยาต่อหลังคลอด
สูตรแรกที่แนะนำ*[$]: TDF/FTC + EFV หรือ TDF + 3TC + EFV **สูตรทางเลือก[#$]**: TDF/FTC + LPV/r หรือ TDF + 3TC + LPV/r หรือ AZT + 3TC + LPV/r	เริ่มยาทันทีโดยเร็วที่สุด	ให้ยาต่อเนื่องหลังคลอดในทุกราย โดยให้ส่งต่อเพื่อรักษาต่อเนื่องกับแผนกอายุรศาสตร์และเปลี่ยนสูตรยาตามแนวทางการดูแลรักษาผู้ใหญ่

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What to Start: Special Considerations?

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Patient/ Regimen characteristics	Clinical Settings	Considerations
Presence of other conditions	CKD (eGFR <50-60 mL/min)	Avoid TDF ART options: - ABC > AZT - TAF (if eGFR >30 mL/min) - LPV/r + 3TC* - DRV/r + RAL* (if CD4 >200, VL<100,000)
	Liver disease	Dose adjustment or avoid for some drugs - ABC, ddI, d4T, NVP, ATV/r, DRV
	Osteoporosis	Avoid TDF Use ABC or TAF

*Regimens with <2 NRTIs should only be used in patients who cannot receive ABC, TAF, TDF

EACS Guideline 2017 DHHS Guideline Updated 2018

CrCl Cutoffs for First-line ART

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First-line ART (US)	FDA Approved Without Dose Reduction for Patients With CrCl, mL/min
TDF/FTC/EVG/c	≥70
ABC/3TC/DTG	≥50
TDF/FTC + DTG	≥50
TDF/FTC + RAL	≥50
TAF/FTC/EVG/c	≥30
TAF/FTC + DTG	≥30
TAF/FTC + RAL	≥30
TAF/FTC/BIC	≥30

DHHS Guideline Updated 2016 www.clinicaloptions.com

ART and Kidney Disease

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Class	Dose adjustment
NRTIs	▪ Required dose adjustment for most NRTIs if CrCl <50 mL/min (for **d4T, ddI, FTC, 3TC, TDF**) ▪ **TAF**: not recommended if CrCl <30 mL/min ▪ **AZT**: required dose adjustment if CrCl <10 mL/min ▪ **ABC**: no dosage adjustment
NNRTIs	▪ No dosage adjustment
PIs	▪ No dosage adjustment
INSTIs	▪ **RAL, DTG**: no dosage adjustment ▪ **TDF/FTC/EVG/c**: not recommended if CrCl <70 mL/min ▪ **TAF/FTC/EVG/c, TAF/FTC/BIC**: not recommended if CrCl <30 mL/min

EACS Guideline 2017

ART and Liver Disease

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Class	Dose adjustment
NRTIs	▪ **ddI, d4T, ABC**: contraindicated (esp. CPS B or C) ▪ **AZT**: use 50% of dosage if CPS C ▪ **FTC, 3TC, TDF, TAF**: no dosage adjustment
NNRTIs	▪ **NVP**: contraindicated (esp. CPS B or C) ▪ **EFV**: no dosage adjustment, use with caution ▪ **ETV, RPV**: no dosage adjustment, no data in CPS C
PIs	▪ **ATV/r**: not recommended in CPS B or C ▪ **DRV, SQV, TPV**: not recommended in CPS C ▪ **LPV/r**: no dosage adjustment, use with caution
INSTIs	▪ **RAL**: no dosage adjustment ▪ **DTG, EVG, BIC**: no dosage adjustment, no data in CPS C

EACS Guideline 2017

Question

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- A 30 YOF HIV with disseminated TB and history of ART failure (AZT + 3TC + NVP)
- She received anti-TB (IRZE) for 2 wks
- Her CD4 17 cells/mm^3
- What is your ART choice?

  A. Start TDF/FTC + LPV/r

  B. Start TDF/FTC/EFV

  C. Start TDF/FTC + RAL

What to Start: Special Considerations?

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Patient/ Regimen characteristics	Clinical Settings	Considerations
Presence of other conditions	Malignancy	Avoid PIs, AZT, ddI, d4T
Presence of co-infections	HBV	TDF or TAF + FTC or 3TC
	HCV	Depend on HCV treatment (Preferred: DTG) Avoid AZT, ddI, d4T
	TB	If rifampicin is used: (↓ PIs level 80%) - EFV (600mg/d) - NVP (200 mg bid, no lead-in) - DTG (50 mg bid; no INSTI resistance) - RAL (800 mg bid; use RAL TDM) {TAF, RPV, EVG/c should not be used} If PI-based is selected: - Rifabutin or FQs

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ART and Rifampicin

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Drugs	Effect on AUC of ART
EFV	↓ 13-26%
NVP	↓ 37-58%
RVP	↓ 80%
LPV	↓ 75%
ATV	↓ 80%
RTV	↓ 35%
RAL	↓ 40%
DTG	↓ 54%

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Question

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- A 30 YOF HIV on TDF/FTC/EFV for 1 mo
- Her CD4 350 cells/mm^3 , HIV-RNA <50 copies/mL
- She had CNS symptoms and decided to change ART
- What is your ART choice?

  A. Start TDF/FTC + LPV/r

  B. Start TDF/FTC + RPV ★

  C. Start TDF/FTC + NVP

ART Switching

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- Maintain viral suppression without interfering future options
- Review full ART history (adherence, tolerance, toxicity, drug resistance)
- Intensive monitoring (adherence, tolerance, toxicity, viral suppression)
- Continue ART drugs active against HBV to prevent HBV reactivation in HBV/HIV coinfection

What to Start: Special Considerations?

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Patient/ Regimen characteristics	Clinical Settings	Considerations
ART- Specific characteristics	One pill OD regimens (FDC)	- ABC/3TC/DTG - TDF/FTC/EFV - TDF/FTC/EVG/c - TAF/FTC/EVG/c - TDF/FTC/RPV - TAF/FTC/RPV - TAF/FTC/BIC
	Food effects	With food: increase absorption - ATV/r (c), DRV/r (c), EVG/c, RPV Without food: decrease side effect - EFV No food effects: - RAL, DTG, LPV/r, NVP, etc.

DHHS Guideline Update 2018

Food Requirement and ART

	With or without food	With food	Empty stomach	Note*
NRTIs	**ABC, AZT, d4T, FTC, 3TC, TDF, TAF**		**ddI**	
NNRTIs	DLV, **NVP**	**ETR, RPV**	**EFV**	RPV: 533-928 kcal (≥400 kcal, 13 g fat)
PIs	FPV, TPV, IDV/r, **LPV/r**	**ATV/r, DRV/r** **RTV**, NFV, SQV/r		ATV: 350-721 kcal, 8.2-37.3 g fat DRV: 240-925 kcal, 12-56 g fat
INSTIs	**RAL, DTG, BIC**	**EVG**		EVG: 373-800 kcal, 20-50% fat
PK enhancer		**COBI**		
Entry inhibitors	T20, MVC			
FDC	**Combivir, Truvada,** Descovy, **Kivexa, Triumeq**, Biktarvy	**Stribild, Genvoya,** Complera, Odefsey	**Atripla**	

*Patient friendly advice: 400 kcal, 10 g fat (Mnemonics: **DAR$_2$E$_2$** you to eat that) (↑AUC 30-60%)

DHHS Guideline Update 2017 www.hiv-druginteractions.org

NRTIs: Tolerability

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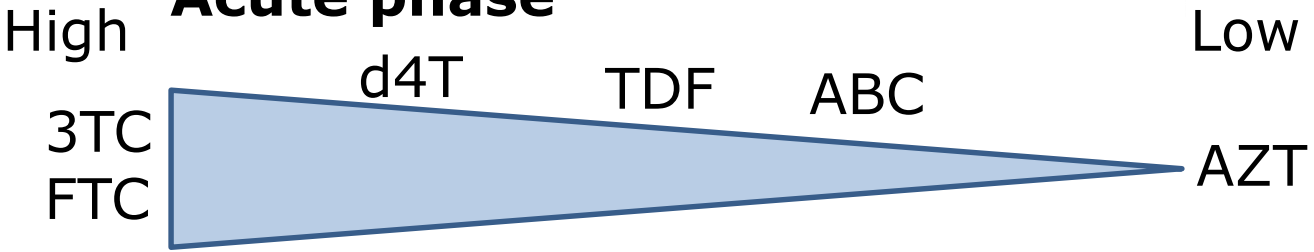
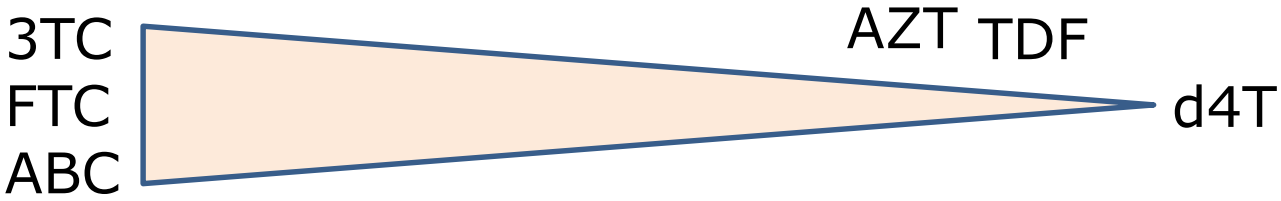
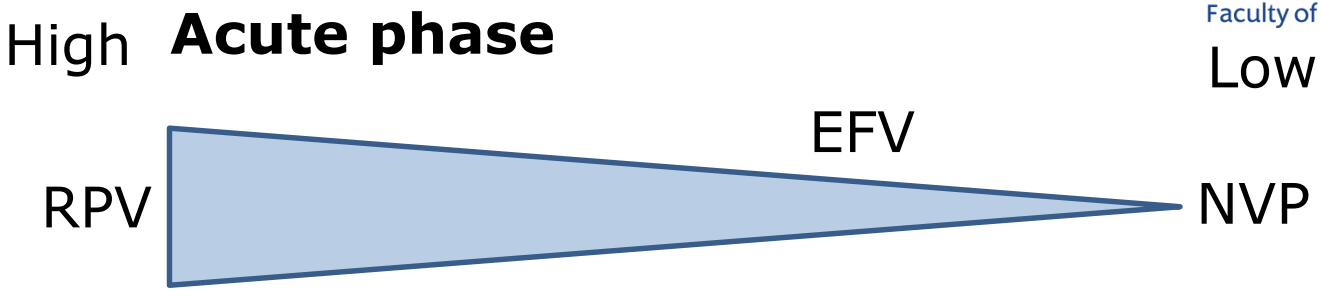
Acute phase

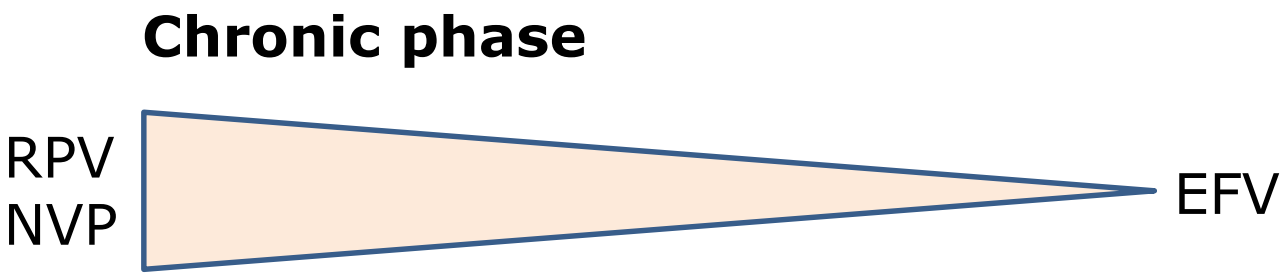


Chronic phase



NNRTIs: Tolerability





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ART Regimens: Not Recommended

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- Monotherapy with NRTI
- Dual NRTIs
- Triple NRTIs
- ddI + d4T
- ddI + TDF
- AZT + d4T
- ATV + IDV
- Unboosted PI

*d4T + 3TC: toxicity
*ddI + 3TC or FTC: inferior efficacy

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Question

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- A 30 YOM HIV with initial CD4 250 cells/mm^3
- He received TDF/FTC/EFV for 3 y with evidence of viral suppression for 2 times after ART
- This visit; CD4 500 cells/mm^3, HIV-RNA 100 copies/mL
- What is your management?

  A. Check ART adherence, recent illness/vaccination

  B. F/U HIV viral load at next 3 mo

  C. Perform HIV resistant test

  D. A + B

  E. A + B + C

Monitoring of Treatment

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- **Immunologic response** (CD4 count):
  - Increase 100-150 cells/mm^3 at first year (rapid in the first 3 mo)
  - Increase 20-50 cells/mm^3/y in next 3-5 y
  - Average 50-100 cells/mm3/y
- **Virologic response**:
  - Viral load <50 copies/mL after 6 mo
- **Virologic failure**:
  - Inability to achieve or maintain suppression of viral replication (persistent viral load ≥200 copies/mL)
  - Drug resistance testing: viral load >1,000 copies/mL and good ART adherence at least 2 wks

Bureau of AIDS, TB, STIs and TAS. Asian Biomed 2010;4:515-28 DHHS Guideline Updated 2013

Monitoring of Treatment

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Lab tests	Number of recommended tests/year by NAP
HIV-RNA (viral load)	✓ 2 times/y until undetectable then yearly ✓ Consider at 3-6 mo after ART for the 1st VL
CD4 count	✓ 2 times/y until ≥350 cells/mm^3 then yearly ✓ If CD4 ≥350 cells/mm^3 with VL <50 copies/mL for at least 2 y: ± F/U CD4 (unnecessary)
HIV resistant test	VL >1,000 copies/mL (with good ART adherence for 2-4 wks)
Cr and U/A	q 6-12 mo or if indicated
FBS and lipid profiles	q 12 mo or if indicated

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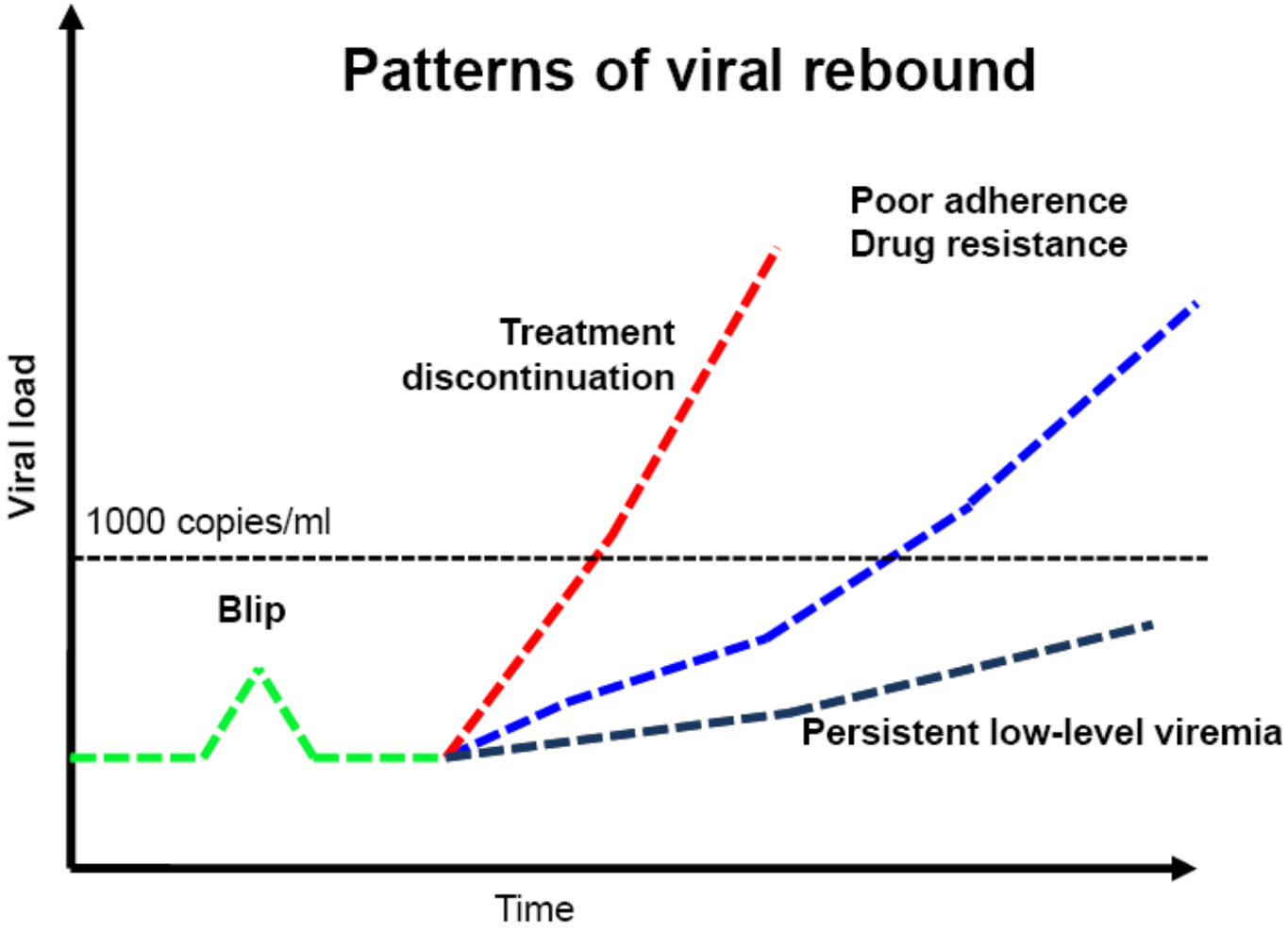
Patterns of viral rebound



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HIV-RNA <200 copies/mL

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- **Viral blip**: level of viral load returns to viral suppression

  Causes of viral blip
  - Assay variation
  - Activation of target cells with different drug sensitivity
  - Activation of latently infected cells
  - Non-adherence
  - Drug resistance
  - Virus release from reserviors
- **Low-level viremia (<200 copies/mL)**
- **Management**: Adherence + F/U viral load q 3 mo

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HIV-RNA ≥200-1,000 copies/mL

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- Increase risk for virologic failure
- **Management**
  - Assess adherence, tolerance, food/drug-drug effects
  - HIV resistant test (esp. HIV-RNA >500 copies/mL)
  - **Consider active ART for fully VL suppression**
  - F/U viral load

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HIV-RNA ≥1,000 copies/mL

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- **Management**
  - Assess adherence, tolerance, food/drug-drug effects
  - HIV resistant tests
  - **Consider active ART for fully VL suppression**
  - F/U viral load

Genotypic resistance

✓ No evidence of resistance

○ No mutation associated with that ART

○ Resistant strain <20% of all viruses

○ Do not take that ART

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ART for Drug-resistant HIV

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- At least 2-3 active ART drugs
- Do not add single ART to old failing regimen
- HBV/HIV: maintain HBV agents in modified regimen

	Mutation	Resistance	Prior ART	Expected R	New ART
NRTIs	M184V	3TC, FTC	TDF/FTC/EFV	R to NNRTIs ± M184V ± K65R	AZT+3TC+PIs
	K65R	TDF			
	TAMs	d4T, AZT			
NNRTIs	K103N	NVP, EFV	AZT/3TC/NVP d4T/3TC/NVP	R to NNRTIs ± M184V ± TAMs	TDF+3TC+PIs
	Y181C	NVP, EFV, ETR			
	E138K	RPV			

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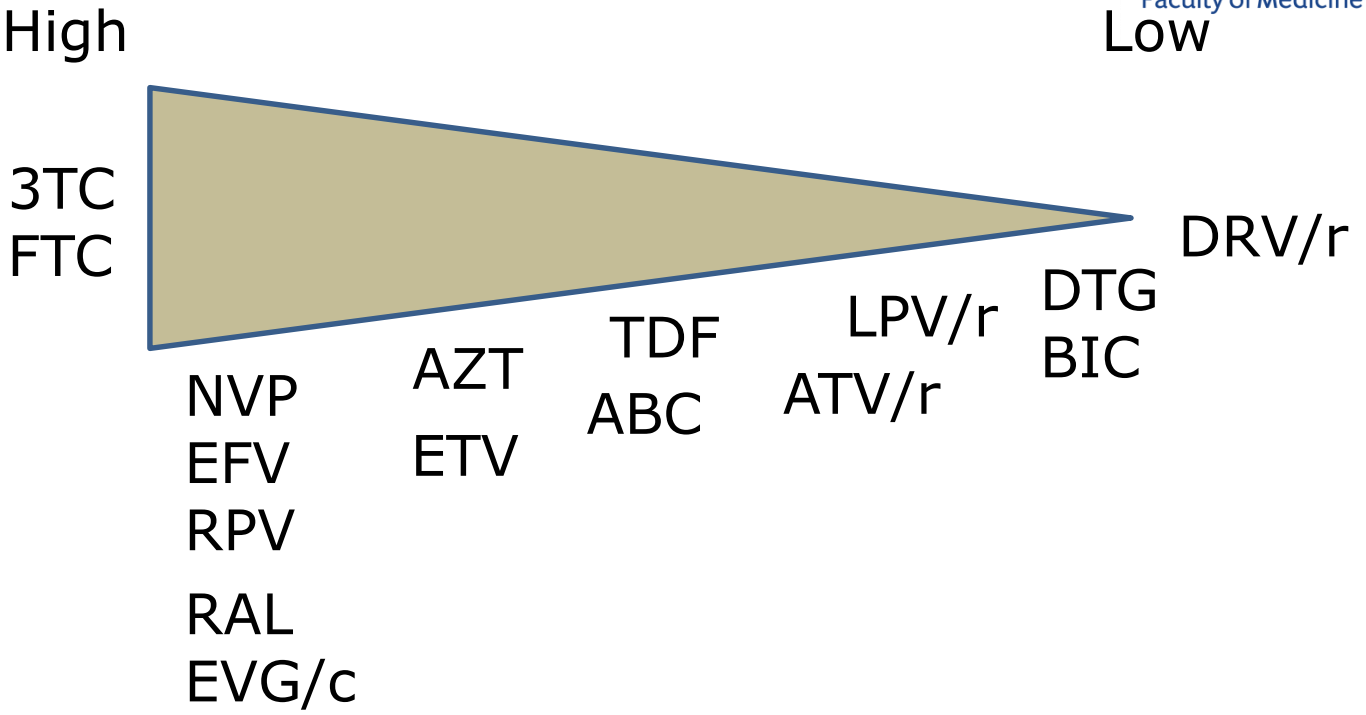
Risk of Drug Resistance



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Poor CD4 Recovery

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- 15-20% of very low initial CD4 may remain low CD4
- Persistent low CD4 & inflammation with viral suppression: increased non-AIDS M&M
- **Management for modifiable risk factors**
  - **Smoking, diet & exercise, HT, DLP**
- Treatment options (**not recommended**)
  - ART intensification
  - ART switching
  - Immune activation: IL-2, IL-7, GH

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Question

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- A 50 YOF HIV, admitted for pneumonia
- She received TDF/FTC + RPV for 5 y with evidence of viral suppression and CD4 500 cells/mm^3
- Medicine service orders:
  - Levofloxacin 750 mg OD
  - Pantoprazole 40 mg OD
  - Continue ART
- What is your management?

  A. Continue current treatment

  B. Off pantoprazole

  C. Change levofloxacin to azithromycin

Key Interactions: PIs and NNRTIs

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ART	Drug–drug interactions
LPV/r **ATV/r** **DRV/r**	▪ Avoid **lovastatin, simvastatin**, some **HCV agents** (eg, **simeprevir, elbasvir/grazoprevir**), some specific drugs (eg, **ergots, pimozide, midazolam, triazolam, cisapride, salmeterol, rifampicin)** ▪ Use caution with/avoid specific **antiarrhythmics** (eg, **amiodarone**) ▪ Avoid **PPIs** with ATV ▪ Use caution with/avoid **specific glucocorticoids** (eg, **budesonide, fluticasone, betamethasone**) (Note: **beclomethasone** can be used safely) ▪ Use caution with **hormonal contraceptives**
EFV	▪ Avoid **voriconazole** at standard dose (↓ azole level exp. fluconazole), some **HCV agents** (eg, **simeprevir, elbasvir/grazoprevir, sofosbuvir/velpatasvir**) ▪ Avoid **pimozide, midazolam, triazolam** (↑ drug levels) ▪ Use caution with **hormonal contraceptives**
RPV	▪ Avoid **PPIs, dexamethasone, rifampicin** (↓ RPV level)

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Key Interactions: INSTIs

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Regimen	Drug–Drug interactions
All INSTIs	▪ Use caution with/avoid polyvalent cation-containing **antacids**
DTG	▪ Avoid **dofetilide** (antiarrhythmic) ▪ Dose adjust **metformin** (↑ metformin level)
EVG/c	▪ Avoid **lovastatin, simvastatin,** some **AEDs,** some **cardiac drugs** (eg, **eplerenone, ranolazine**), some specific drugs (eg, **ergots, pimozide, midazolam, triazolam, cisapride, salmeterol, rifampicin)** ▪ Use caution with/avoid **specific glucocorticoids** (eg, **budesonide, fluticasone, betamethasone**) (Note: **beclomethasone** can be used safely) ▪ Use caution with **hormonal contraceptives**
BIC	▪ Avoid **dofetilide, rifampicin** ▪ Dose adjust **metformin**
RAL	▪ No notable co-medications to avoid for RAL aside from Al/Mg **antacids**

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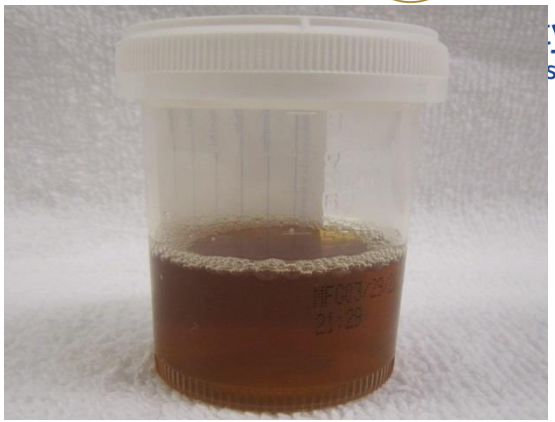

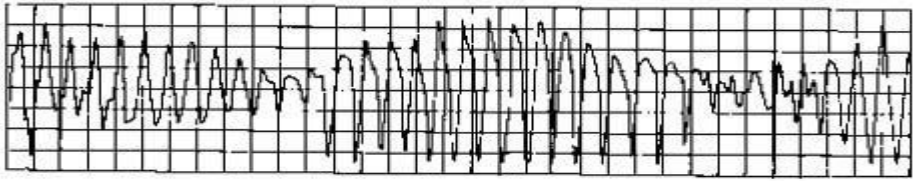

Torsade de pointes ventricular tachycardia

versity
riraj Hospital

Cases From the Field

Ergotism in Thailand Caused by Increased Access to Antiretroviral Drugs: A Global Warning

Anchalee Avihingsanon, MD, PhD; Reshmie A. Ramautarsing, MD, PhD; Gompol Suwanpimolkul, MD; Ploenchan Chetchotisakd, MD; Chureeratana Bowonwatanuwong, MD; Supunnee Jirajariyavej, MD; Patcharee Kantipong, MD; Hutsaya Tantipong, MD; June Pirapon Ohata, BSc; Chusana Suankratay, MD, PhD; Kiat Ruxrungtham, MD, PhD; and David M. Burger, PharmD, PhD

Keywords: *HIV, ergotamine, ergotism, drug-drug interaction, migraine, toxicity, cytochrome P450 3A4 inhibitor, CYP3A4, protease inhibitor, cobicistat, efavirenz*

Ergotism is a toxic condition resulting from overexposure to the ergot compounds produced by various fungi of the genus *Claviceps*. Traditionally, such exposure was due to ingestion of infected grains, but long-term or excessive use of medications containing ergot derivatives or drug-drug interactions between these medications can result in ergotism. Ergotamine, typically used to treat migraine, has less than 5% bioavailability due to extensive first-pass metabolism by cytochrome

HIV-infected patients. The first submitted case and a summary of 22 additional cases are presented below.

Case Presentations

A 47-year-old HIV-infected woman was on an antiretroviral regimen consisting of lamivudine (300 mg once daily), tenofovir (300 mg once daily), and ritonavir-boosted (/r) saquinavir (1500 mg/100 mg once daily). She presented with necrosis of the left foot and gen-

ART and Drug Interactions

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ART and stomach acid

Boosted ATV/r or ATV/c

- Antacids: ATV 2 h before or 1-2 h after
- H2RAs: ATV at least 10 h after
  - Famotidine <20 mg BID
- PPIs: PPI at least 12 h before
  - Omeprazole ≤20 mg (ATV AUC↓42%) (if use 40 mg, ATV AUC↓ 75%)

RPV

- Antacids: Give 2 h before or 4 h after RPV
- H2RAs: Give 12 h before or 4 h after RPV
- PPIs: Contraindicated

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Drug Interactions between ART and Statin

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ART	Contraindication	Titrate dose	No dose adjustment
EFV, NVP, ETR		Atorvastatin Simvastatin Pravastatin	Pitavastatin Rosuvastatin
RPV			Atorvastatin Pitavastatin
LPV/r, ATV/r, DRV/r	**Lovastatin** **Simvastatin**	Atorvastatin Pravastatin Rosuvastatin	Pitavastatin
EVG/c	**Lovastatin** **Simvastatin**	Atorvastatin Rosuvastatin	
DTG or RAL			All

*Fibrates, ezetimibe: can use safely with any ART

www.clinicaloptions.com DHHS Guideline Updated 2017

Statin Dosing in ART Setting

NNRTI-, RAL-, or DTG-Containing Regimens		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Pravastatin 10-20 mg
Rosuvastatin 20 mg	Rosuvastatin 10 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	Lovastatin 20 mg
	Lovastatin 40 mg	Simvastatin 10 mg
	Simvastatin 20-40 mg	

PI- or COBI-Containing Regimens		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 20 mg	Atorvastatin 10 mg	Pravastatin 10-20 mg
Rosuvastatin 10-20 mg	Rosuvastatin 5 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg*	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	

Simvastatin and lovastatin are contraindicated for patients receiving a PI or COBI

*With darunavir, reduce pravastatin to 20-40 mg

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ART and Drug Interactions

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ART and anticoagulants

ART	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Boosted PI	Not recommended ↓ apixaban 50%	Not recommended	Not recommended	PI/r: ↓ warfarin Monitor INR
COBI	Not recommended ↓ apixaban 50%	Not recommended	Not recommended	↑ or ↓ warfarin Monitor INR
NNRTIs	EFV, ETR, NVP: Consider alternative Rx	EFV, NVP, RPV: No dose adjustment ETR: Consider alternative Rx	EFV, ETR, NVP: Consider alternative Rx	↑ or ↓ warfarin Monitor INR

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ART and Drug Interactions

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ART and AEDs

AEDs	ART	Note
Carbamazepine	PIs, RPV, EVG/c	Contraindicated
	EFV, NVP	Monitor drug levels, or consider alternative Rx
	ETR, RAL	Avoid
	DTG	Increase DTG to 50 mg BID
Phenytoin Phemobarbital	PIs, RPV, EVG/c	Contraindicated
	EFV, NVP	Monitor drug levels, or consider alternative Rx
	ETR, RAL, DTG	Avoid
Lamotrigine Valproic acid	PIs	Monitor drug levels, use with caution
	NNRTIs	Monitor drug levels, use with caution
Levetiracetam safe to use with all ART		

www.hiv-

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Reference Website

Mahidol University
Faculty of Medicine Siriraj Hospital

Mahidol University

DESIGN I

DESIGN II

FRONT

GPO องค์การเภสัชกรรม

"เรียนผู้เกี่ยวข้อง
ข้าพเจ้าไม่สามารถใช้ยาต่อไปนี้ได้"

กลุ่มยา	ชื่อยา
ยาโรคหัวใจ	Amiodarone, Flecainide, Propafenone, Quinidine
ยาลดไขมัน	Simvastatin, Lovastatin
ยาระบบทางเดินอาหาร	Cisapride
ยานอนหลับ	Midazolam, Triazolam
ยารักษาโรคปวดศีรษะและไมเกรน	Ergotamine (Cafergot), Dihydroergotamine (Dihydergot)

พลิก

GPO องค์การเภสัชกรรม

"เรียนผู้เกี่ยวข้อง
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ยาระบบทางเดินอาหาร	Cisapride
ยานอนหลับ	Midazolam, Triazolam
ยารักษาโรคปวดศีรษะและไมเกรน	Ergotamine (Cefergot), Dihydroergotamine (Dihydergot)
ยารักษาโรคจิตเวช	Pimozide

BACK

GPO องค์การเภสัชกรรม

"เรียนผู้เกี่ยวข้อง
ข้าพเจ้าไม่สามารถใช้ยาต่อไปนี้ได้"

กลุ่มยา	ชื่อยา
ยารักษาโรคจิตเวช	Pimozide
ยารักษาต่อมลูกหมากโต	Alfuzocin (Xatral)
ยาขยายหลอดเลือด	Sildenafil (Viagra)
ยาพ่นขยายหลอดลม	Salmeterol Fluticasone
ยารักษาวัณโรค	Rifampicin

พลิก

บริษัท สวัสดี มีเดีย คอนซัลแทนท์ จำกัด

SAWA SDEE
MEDIA CONSULTANT CO.,LTD.

PROJECT : HEALTHY CARD (PREVIEW)

CLIENT : GPO

PROJECT MANAGER :

SITE ORIENTATION :

Graphic Designer :

DATE :

NOTE :

Do not scale drawings all measurements must be checked on site.

ART and Common ADRs

ADR	NRTIs	NNRTIs	PIs
Lipodystrophy	**d4T, AZT** - Lipoatrophy	**EFV** - Lipohypertrophy - Gynaecomastia	**All** - Lipohypertrophy
Nephrotoxicity	**TDF** - Fanconi's syndrome - Cr rising		**IDV, ATV** - Stone, azotemia
Peripheral neuropathy	**d4T, ddI** - GBS like		
BM suppression	**AZT**		
Myopathy	**AZT**		
Bleeding			**All** - Spontaneous bleeding
Dyslipidemia	**d4T**	**EFV**	**All RTV boosted**

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ART and Common ADRs

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ART	ADRs
TDF	Osteopenia
AZT	Nail pigmentation
ddI	Optic neuritis, retinitis; non-cirrhotic portal hypertension
ABC	Hypersensitivity reaction (6-8%, HLAB*5701, esp. first 6 wks)
EFV	Neuropsychiatric symptoms, False +ve cannabinoids/BDZ assays
NVP	SJS, TEN, severe hepatitis (risk 3-10x with high CD4)
ATV	Indirect hyperbilirubinemia, 1st degree AV block
LPV/r	Diarrhea, GI disturbance
RAL	Rhabdomyolysis

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Summary of New ART in NAP

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Drugs	Characteristics
RPV	Take with meal, avoid use with PPIs, antacids, H2RAs Use in naïve case if VL <100,000 and CD4>200 Low risk of rash and metabolic events (but avoid in depression disorder) Good efficacy for switching ART (SPIRIT study) Cheap price only 200 Baht/mo
ABC	Take with or without meal Advantages for renal problems, osteopenia, TDF-induced weight loss Disadvantage in hypersensitivity, CAD events?, liver disease
DRV	Should take with meal Must use with ritonavir or cobicistat, potential drug interactions Low risk of resistance with virologic failure
RAL	Take with or without meal Fewest drug interactions, longest safety record

Common Problems During ART

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Missed dose

- Take right away
- Almost time for next dose: do not take missed dose
- Do not take 2 doses at one time

Changing of dosing schedule

- Too late → change to earlier time; OK
- Too early → change to late time;
  may induced drug resistance

Common Problems During ART

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Fasting in Ramadan

- OD regimen: start new schedule at night
- BID regimen: change to OD regimen

ART	Management
TDF	Same dose (hs)
3TC	300 mg OD (hs)
AZT or d4T	Change to TDF (if undetectable VL)
EFV	Same dose (hs)
NVP	400 mg OD (hs)
LPV/r	Change to ATV/r or 800/200 mg OD

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Common Problems During ART

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Treatment interruption

- Severe drug toxicity
- Severe underlying illnesses
- Surgery (planned or unplanned)

Stop ART with different T1/2

- Monotherapy of longer T1/2 ART → ↑ drug resistance

ART	Serum T1/2 (h)
d4T	1
AZT	1.1
ABC	1.5
3TC	5-7
FTC	10
TDF	17
NVP	25-30
EFV	40-55
RPV	50
LPV/r	5-6
ATV	7
DRV/r	15
RAL	9

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Common Problems During ART

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Unplanned interruption

- All ART should be discontinued simultaneously

Planned interruption

- If similar T1/2: Discontinued simultaneously
- If different T1/2: Prior to interruption (i.e. surgery)
  - Change longer T1/2 ART to shorter T1/2 ART (for 4 wks)
    - Change NNRTIs to PIs for 4 wks PTA
  - Stop longer T1/2 ART, then stop shorter T1/2 ART (2-4 wks later)
    - Stop NNRTIs then stop 2 NRTIs at 2 wks later

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HIV Prevention

HIV Prevention

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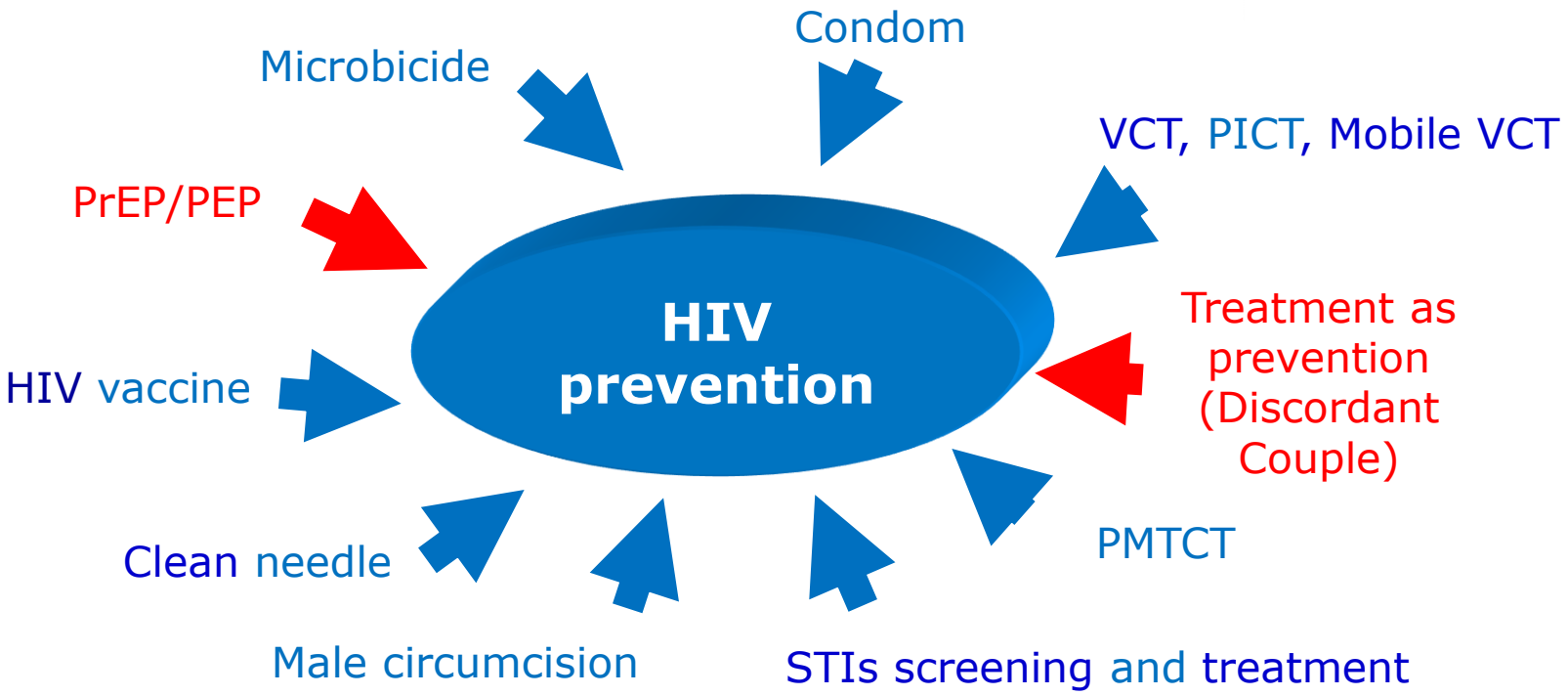

Treatment As Prevention

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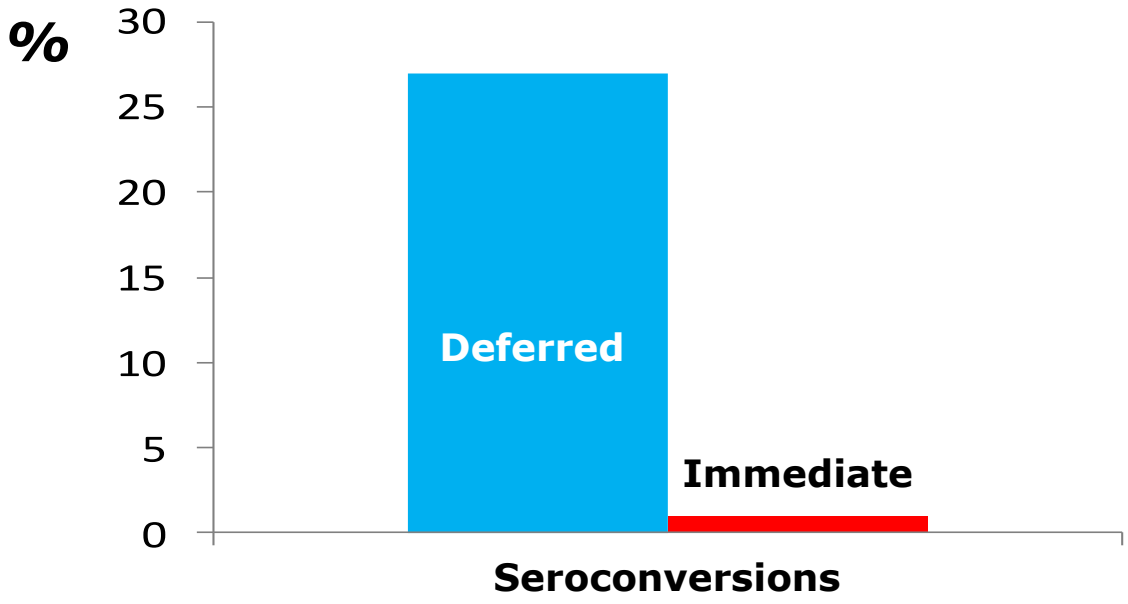
HPTN 052: Immediate vs. Delayed ART in serodiscordant couples



96.3% reduction in transmission

No linked HIV transmissions where index partner suppressed on ART

Curr Opin HIV AIDS. 2012 Mar;7(2):99-105

Treatment As Prevention

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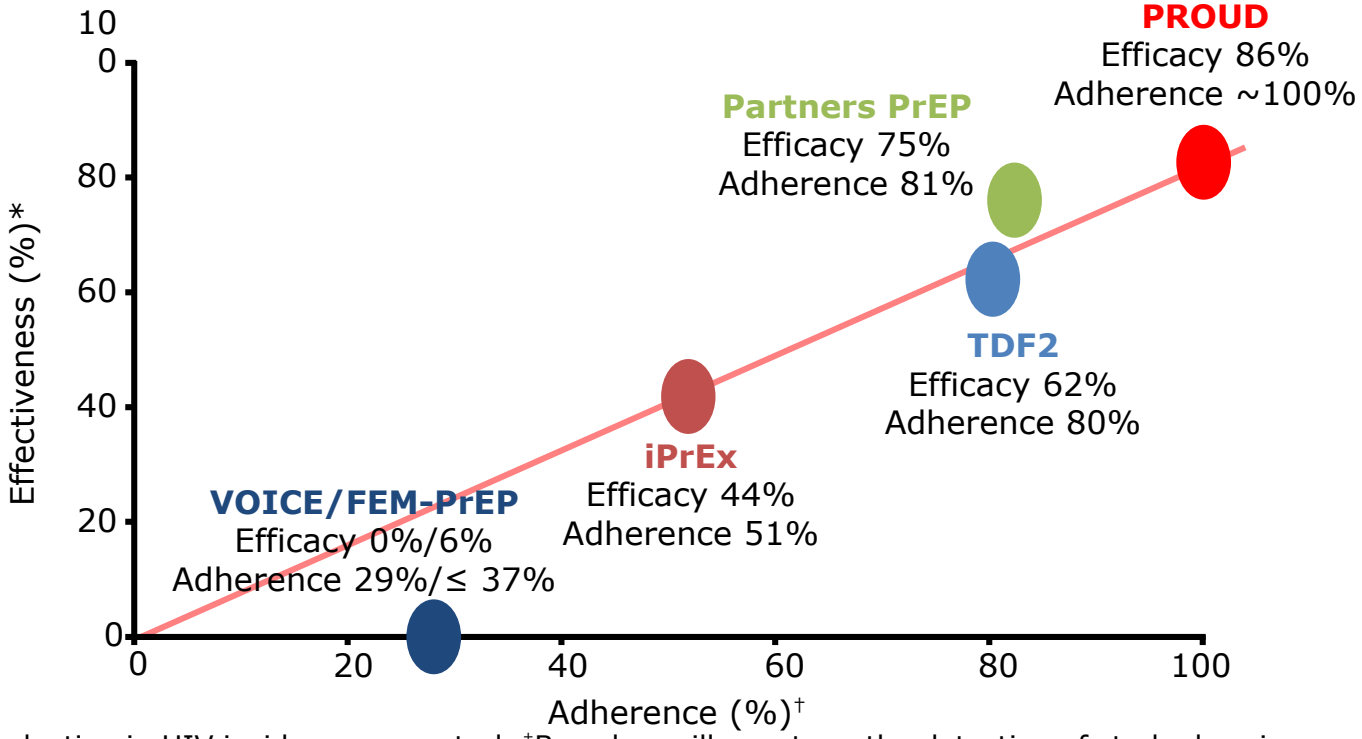
Zero linked transmission

A person living with HIV is considered 'undetectable' (virally suppressed) when HIV treatment brings levels of HIV in the body to such low levels that tests cannot detect it.

As long as treatment is adhered to and viral load remains undetectable (and monitored), they cannot transmit HIV to others and their health is not affected by HIV.

Avert

Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence

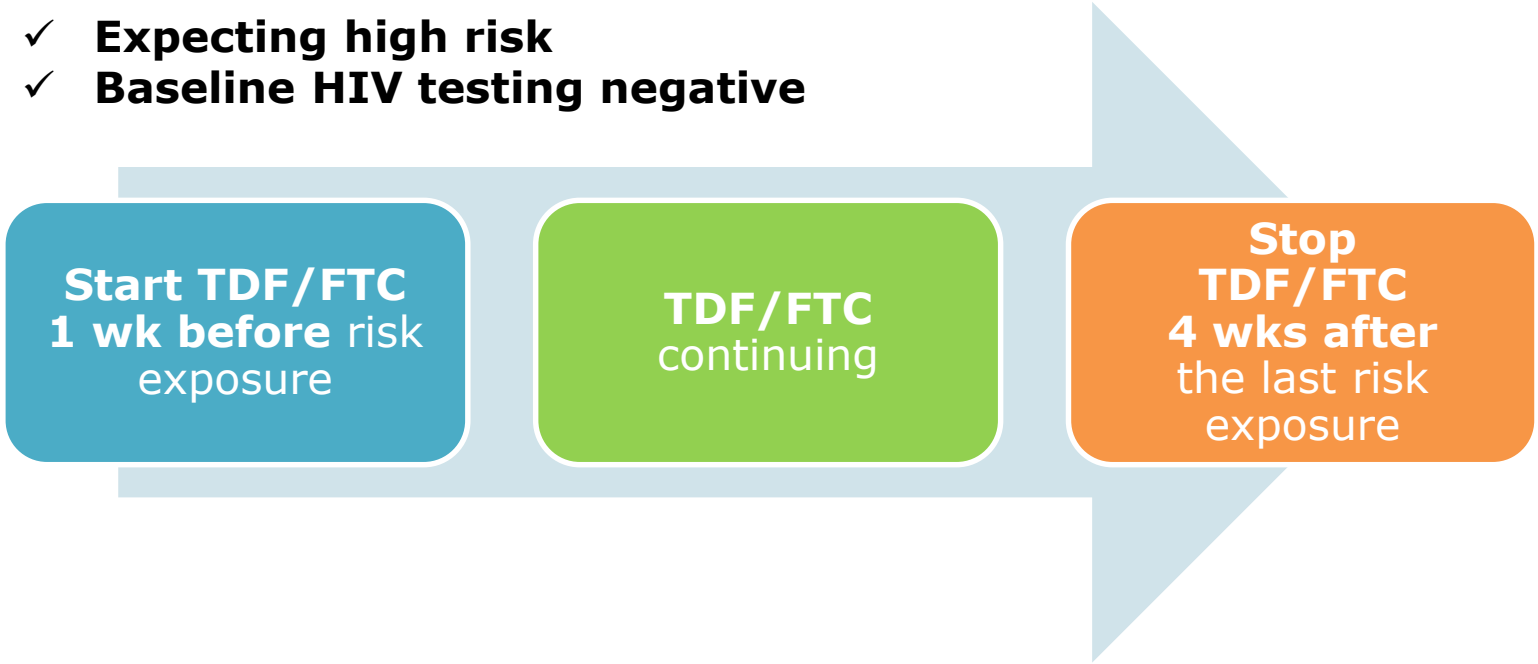


*Reduction in HIV incidence vs control. †Based on pill counts or the detection of study drug in plasma

PrEP

- **Stop** –when further risk behavior
- **Repeat HIV testing** anytime stopping TDF/FTC

✓ **Expecting high risk**
✓ **Baseline HIV testing negative**



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Opportunistic Infections

Management of HIV-OIs

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- **Screening**
  - OIs
  - Co-infections: HBV, HCV and syphilis
- **Prophylaxis**
- **Diagnosis**
- **Treatment**
- Antiretroviral regimen
- Monitoring

Question

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True or False?

- Routine use of serum cryptococcal Ag screening and antifungal primary prophylaxis are recommended in the ART-naïve patients with CD4<100 cells/mm^3

A. True

B. False

Serum Cryptococcal Ag

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- Serum cryptococcal Ag screening
  - High risk case (CD4 < 100 cells/mm^3) AND
  - High prevalent area i.e. South Africa and Asia
    - >3% of prevalence of cryptococcal antigenemia
    - Cost-effective method
- Antifungal primary prophylaxis
  - Lack of survival benefit
  - No routine recommendation

CDC:Preventing Deaths from Cryptococcal Meningitis WHO Guideline 2011 DHHS Guideline 2016

OIs Screening and Prophylaxis

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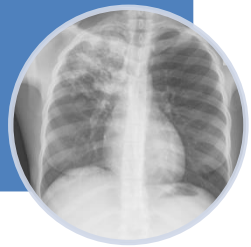
- CXR (all cases)
- If CD4 <100 cells/mm^3:
  - Serum cryptococcal Ag
  - Indirect ophthalmoscope for CMV

Screening



- Co-trimoxazole
  - CD4 <200 cells/mm^3
  - CD4 <14%
  - Oral candidiasis
  - AIDS defining illness
- Start After ART 2-4 wks
- Other OIs primary prophylaxis: optional

Primary prophylaxis

Thai Guideline 2017

Question

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- A 30 YOM with the first diagnosed of HIV
  - Asymptomatic, His CD4 80 cells/mm3
  - CXR –ve, cryptococcal Ag +ve
  - HBs Ag –ve, anti-HCV Ab –ve and VDRL –ve
- Will you perform a lumbar puncture for this case?

  A. Yes

  B. No

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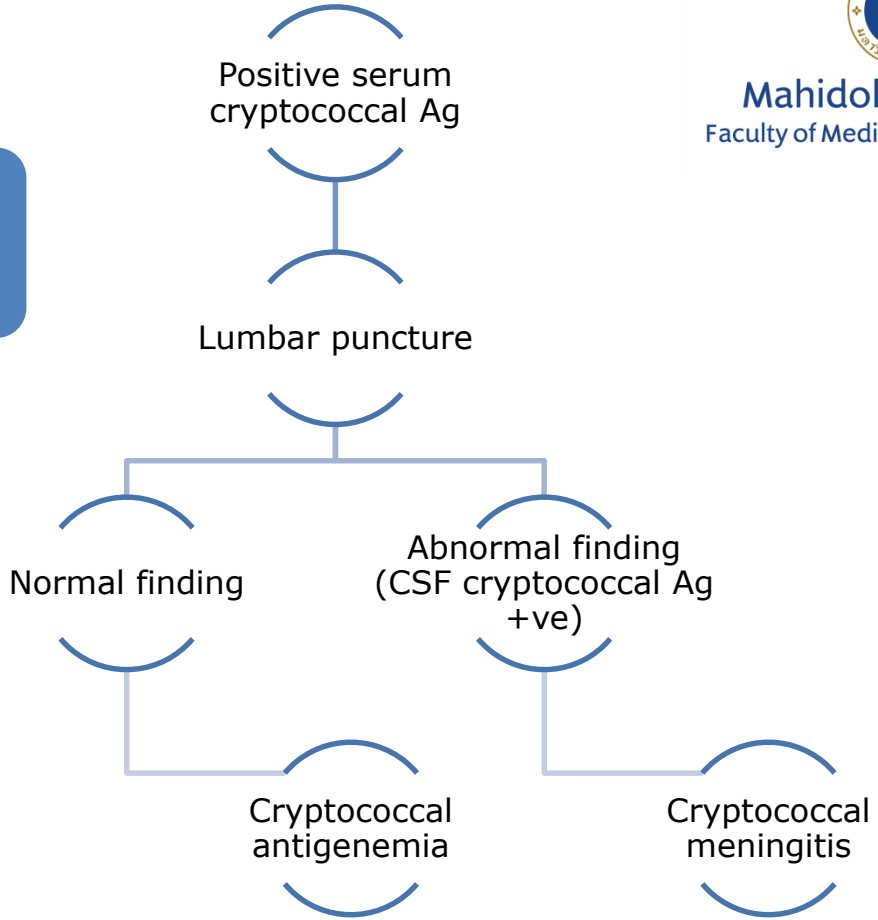
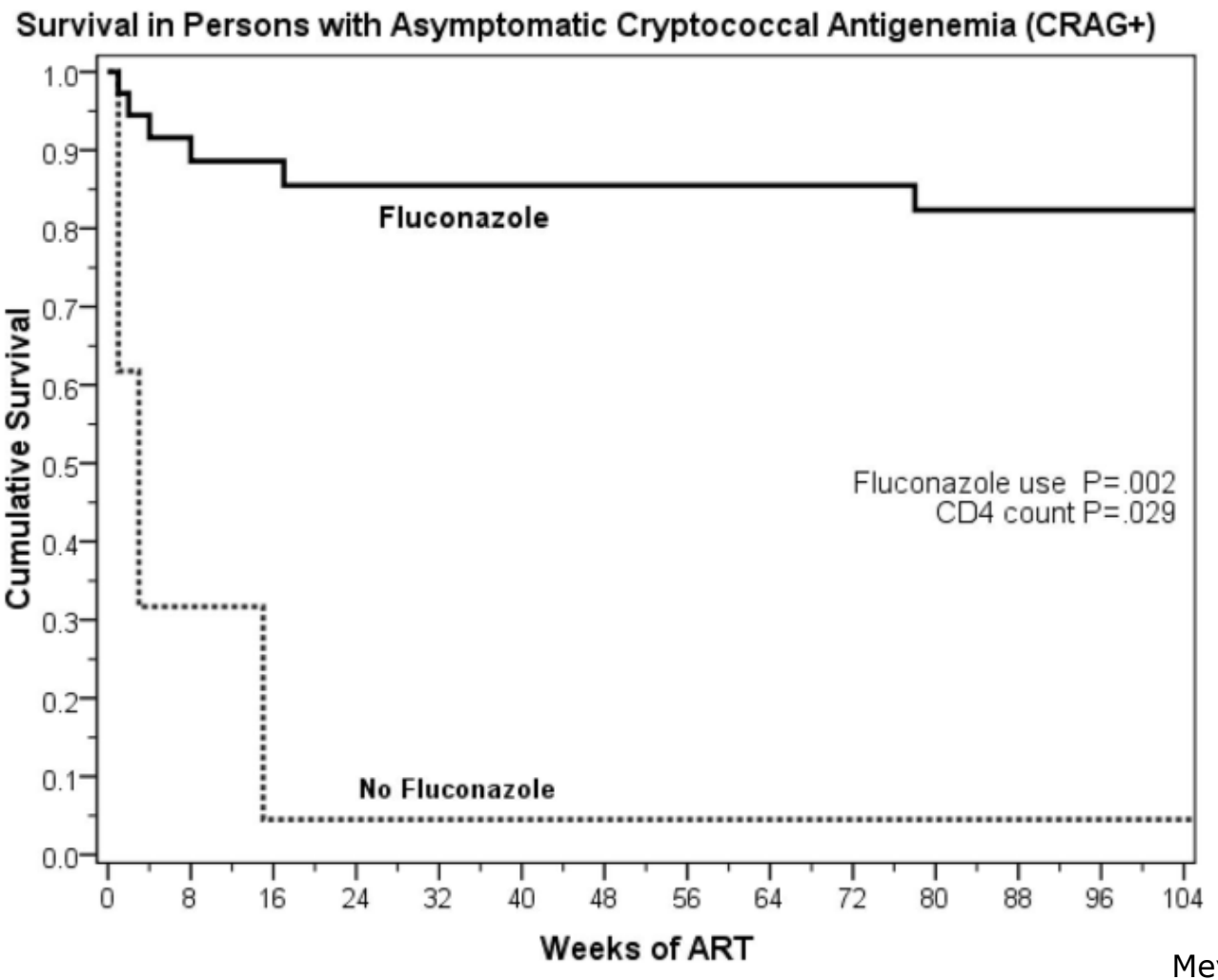
Highly predictive disease
Serum CrAg detection before symptomatic meninigitis develop median 22 d (5-234 d)
Prevent to disease progression



French et al, AIDS 2002

Thai guideline 2017



Meya et al, CID 2010

Cryptococcal Antigenemia

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Treatment

Fluconazole 800 mg/d for 2 wks then 400 mg/d for 8 wks (total 10 wks)

ART after 2 wks of antifungal treatment

After 10 wks of treatment; fluconazole 200-400 mg/d until complete 1 y of therapy and CD4 > 100 cells/mm^3 for 3 mo

Thai guideline 2017

Question

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- A 30 YOF HIV with initial CD4 17 cells/mm3
- He never has any episodes of OIs
- She receives ART(TDF/FTC/EFV) for 2 years with PCP primary prophylaxis
- Her current CD4 150 cells/mm^3
- What is your next management?

A. Continue PCP primary prophylaxis

B. Stop PCP primary prophylaxis

Stop OIs prophylaxis

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- Asymptomatic
- Sustained CD4 response
- On ART with sustained viral suppression
- Completed course of treatment (if + previous infection)

PCP Prophylaxis: Current Evidences

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Discontinuation of PCP prophylaxis if CD4 < 200 cells/mm^3

- Discontinuation of primary PCP prophylaxis
  - CD4 count >100 cells/mm^3
  - On ART with suppressed HIV viral load
- Discontinuation of secondary PCP prophylaxis
  - No consensus recommendation from the current evidences

Thai guideline 2017

- Discontinuation of primary PCP prophylaxis
  - CD4 100-200 cells/mm^3 and sustained viral suppression > 1 y

COHERE. CID 2010;51:611-9 Ann Pharmacother 2015; 49:1343-8 Thai Guideline 2017

OIs prophylaxis

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OIs	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
PCP	CD4 < 200	CD4 > 200 for 3 mo	CD4 < 200	Prior PCP	CD4 > 200 for 3 mo	CD4 < 200
Toxoplasmosis	CD4 < 100	CD4 > 200 for 3 mo	CD4 < 100–200	Prior TE	CD4 > 200 for 6 mo and completed therapy and asymptomatic	CD4 < 200
MAC	CD4 < 50	CD4 > 100 for 3 mo	CD < 50–100	Documented disseminated disease	CD4 > 100 for 6 mo and completed 12 mo of MAC treatment and asymptomatic	CD4 < 100
Cryptococcosis	CD4 < 100	CD4 > 100 for 3 mo	CD4 < 100	Documented disease	CD4 > 100 for 3 mo and completed 12 mo of therapy and asymptomatic	CD4 < 100-200
CMV	None	N/A	N/A	Documented end-organ disease	CD4 > 100 for 3-6 mo and completed therapy and no evidence of active disease	CD4 < 100

DHHS Guideline 2016 Thai Guideline 2017

Tuberculosis Screening

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การคัดกรองวัณโรคในผู้ติดเชื้อเอชไอวีผู้ใหญ่
1) ไอผิดปกติ ที่อธิบายสาเหตุไม่ได้*
2) ไข้ภายใน 1 เดือนที่ผ่านมา
3) น้ำหนักตัวลดลงอย่างน้อย5%ของน้ำหนักเดิม ใน 1 เดือน
4) มีเหงื่อออกผิดปกติกลางคืนติดต่อกัน 3 สัปดาห์ใน 1 เดือน
*หากพบ ไอเป็นเลือด หรือไอนานกว่า 2 สัปดาห์เพียงข้อเดียว ให้พิจารณาตรวจเพิ่มเติมเพื่อหาวัณโรค

Isoniazid Preventive Treatment (IPT)

3. การอ่านผล TST

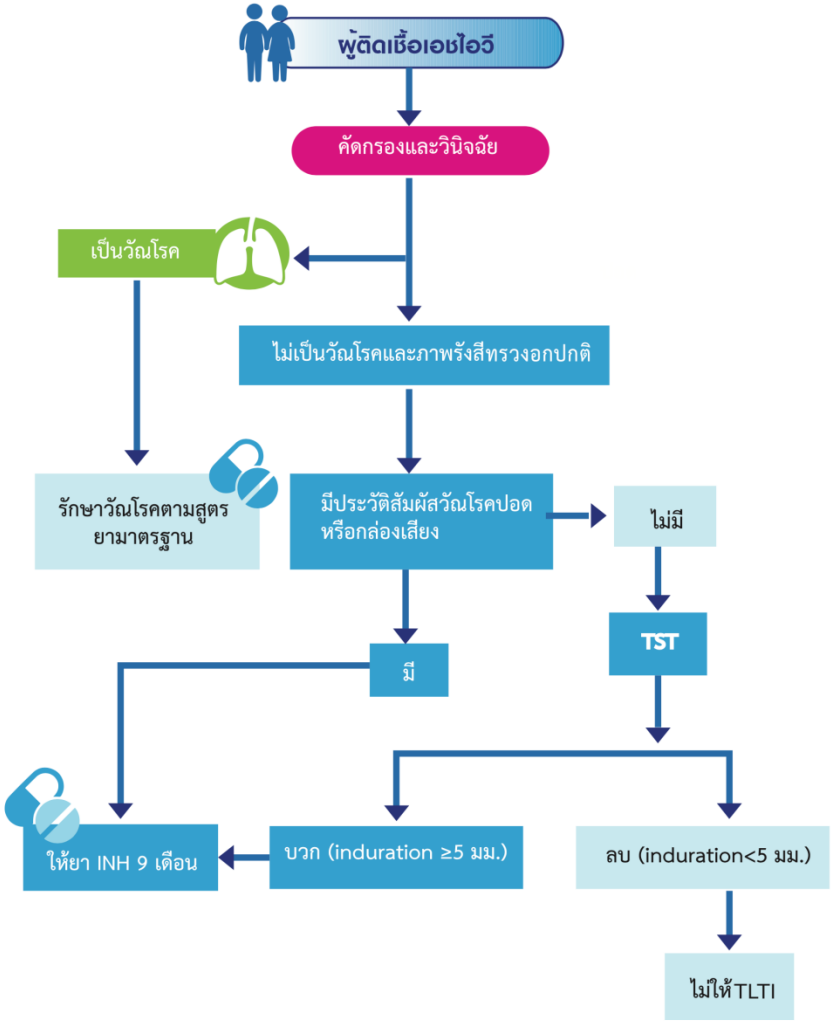
ก. กรณี TST บวก ≥ 5 มม. และ
ข. มีผลเอกซเรย์ทรวงอกปกติภายใน 3 เดือน
ค. มีผลการตรวจร่างกายไม่พบต่อมน้ำเหลืองโต
พิจารณาให้ IPT (ให้ INH 9 เดือน)
ง. กรณีผล TST ลบ < 5 มม. ไม่ให้ IPT พิจารณาให้ TST ทุก 1 ปี

4. การติดตามหลังให้ IPT

ก. 1 เดือน ติดตามผลข้างเคียงของการรักษา
ข. หากมีอาการของตับอักเสบให้ตรวจ AST , ALT
ค. พิจารณาหยุดยา INH หากมีผลข้างเคียง
ง. กรณีผล TST เป็นลบพิจารณาทำซ้ำทุกปี
จ. กรณีผู้ต้องขังในเรือนจำ ให้ทำ TST ร่วมกับการคัดกรอง

ข้อห้ามให้ TLTI

- ตับอักเสบ (hepatitis)
- มีอาการปลายประสาทอักเสบ (symptoms of peripheral neuropathy)
- แพ้ยา isoniazid



TB/HIV แนวทางการปฏิบัติผสมผสานวัณโรคและเอดส์ ปี 2560

Question

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- Which of the following is **NOT** diagnostic method of active tuberculosis?

  A. AFB

  B. Interferon Gamma Releasing Assay

  C. GeneXpert MTB/RIF

  D. Lipoarabinomannan (LAM)

Diagnosis of TB in HIV

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Tests	Sensitivity	Specificity	Remarks
Active TB			
AFB	low	low	
CXR	✓	low	
Culture	✓	✓	✓DST
GeneXpert	✓	✓	✓DST, RIF
LAM	low	✓	CD4<100, urine
Latent TB			
TST	medium	✓	
IGRA	medium	✓	

Treatment Action Group 2017

Question

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- Which of the following is the most likely diagnosis of CMV disease?

  A. CMV viremia ~ 50,000 copies/mL

  B. Positive serum CMV Ab

  C. Positive CMV culture in BAL

  D. Positive CMV PCR in CSF

Diagnosis of CMV in HIV

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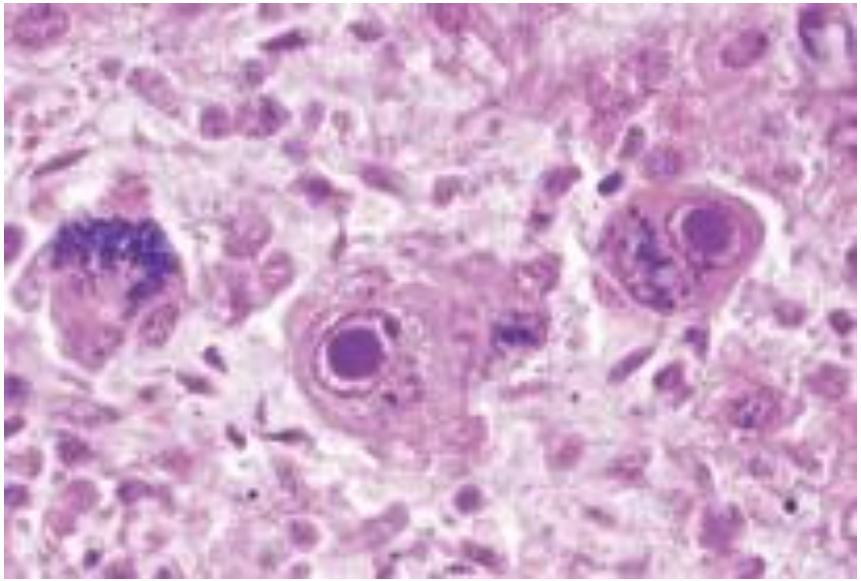
Samples	Tests	Remarks
Blood	CMV Ag, PCR, and culture CMV Ab	No recommendation for diagnosis of CMV end-organ disease
CSF	PCR	Highly suggestive CMV disease
Aqueous or vitreous fluid	PCR	Highly suggestive CMV disease (CMV retinitis is clinical diagnosis)
Respiratory sample	Cytology Histopathology	Presence of characteristic intranuclear and intracytoplasmic inclusions
GI sample	Histopathology	Presence of characteristic intranuclear and intracytoplasmic inclusions
Positive CMV culture is insufficient to establish the diagnosis of CMV disease*		

DHHS Guideline 2016



Owl’s eye

Diagnosis of Other OIs

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OIs	Remarks
PCP	Induced sputum: sens. 55-78% spec. 100% BAL: sens. 90-98% spec. 100% 1,3 BDG: sens. 93% spec. 75% PCR: increased sensitivity
Cryptococcosis	Cryptococcal Ag (LFA): sens. 99% (CSF) > 95% (blood) > 70% (urine) Culture- gold standard
Toxoplasmosis	Toxoplasma IgG +ve > 90% PCR: sens. 50-80% spec. 100% Histopathology- gold standard

Eur Respir J. 2012;39(3):730-45

Question

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Faculty of Medicine Siriraj Hospital

- A 30 YOF HIV with suspected severe PCP has no response to a combination of co-trimoxazole and corticosteroid for 3 days
- What should you do next?

  A. Bronchoscopy with BAL

  B. Switching to another regimen

  C. Continue the previous regimen

PCP Treatment

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- Response of PCP: >4-8 days after treatment
  - Patients often worsen within the first 3-5 days
- Treatment failure: Clinical RS & ABG
  - Concomitant infections
    - Bronchoscopy with BAL
  - Drug toxicity
    - Switching to another regimen
  - Lack of drug efficacy (10%)
    - No correlation with DHPS mutation

DHHS Guideline 2016

Salvage Treatment of PCP

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Salvage treatment of PCP

- No consensus guideline for co-trimoxazole non-responsive PCP

Meta-analyses

- Clindamycin and primaquine: First choice (superior efficacy)
- Pentamidine: comparable efficacy and more frequent toxicity

Case reports

- Caspofungin plus other agents i.e. co-trimoxazole (data from non-HIV cases)

ECIL Guideline 2016 DHHS Guideline 2016

Question

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- A 30 YOF HIV with CMV retinitis and colitis
- She receives IV ganciclovir for 3 wks and ART(TDF/FTC/EFV) for 2 wks with clinical response
- Her initial CD4 17 cells/mm^3
- What is your next management?

A. Stop anti-CMV treatment, continue ART

B. Continue anti-CMV treatment and ART

Treatment of CMV in HIV

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Diseases*		Induction phase	Maintenance phase	Stop anti-CMV treatment
CMV retinitis	Central (impending sight loss)	Intravitreal ganciclovir **PLUS** systemic agents (oral or IV) for 14-21 d	Continue anti-CMV treatment at least 3-6 mo	- Complete duration of treatment **AND** - Inactive lesions **AND** - CD4>100 cells/mm^3 for 3-6 mo in response to ART - If CD4<100 cells/mm^3 reinstitute maintenance therapy
	Peripheral	Oral valganciclovir or IV ganciclovir for 14-21 d		
CMV diseases	GI, RS, CNS	IV ganciclovir for 21-42 d	None	Resolved signs and symptoms

* CMV replication is controlled within 1-2 wks after anti-CMV treatment; early ART (< 2wks) is recommended

DHHS Guideline 2016

Question

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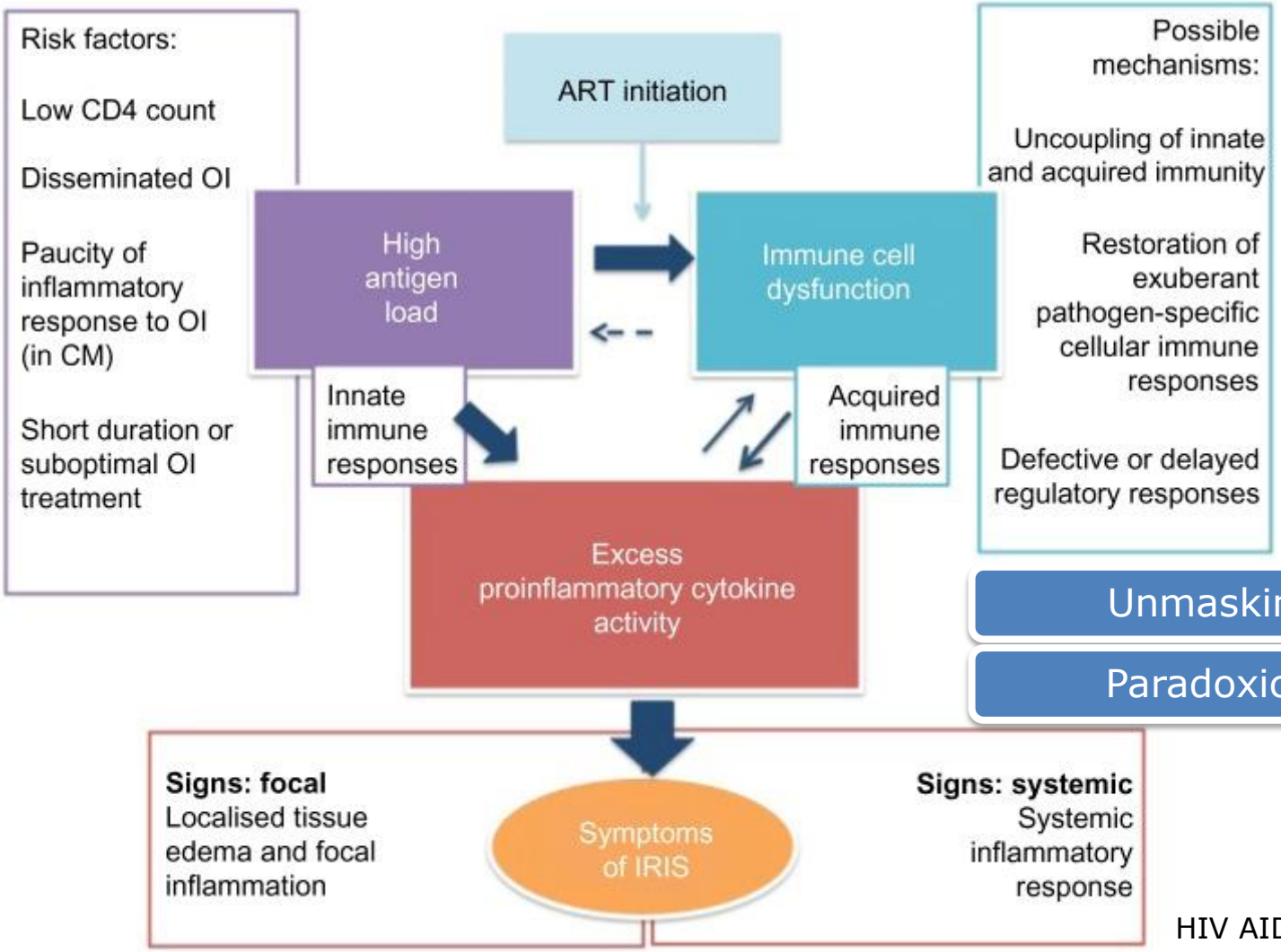
- A 30 YOF HIV CD4 33 cells/mm^3 with pulmonary TB is treated with IRZE, At first there is a good response
- 2 wks after starting treatment he's getting fever, cervical lymphadenopathy and dyspnea
- What is your differential diagnosis?

  A. Poor compliance
  B. Resistant organisms
  C. IRIS
  D. Other OIs
  E. All of above



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Unmasking IRIS

Paradoxical IRIS

HIV AIDS (Auckl) 2015;7:49-64

Common IRIS

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ospital

	TB-IRIS	Cryptococcal-IRIS
Incidence	2-54%	13-45%
Key risk factors	Shorter interval between anti-TB and ART Disseminated TB Low CD4 count prior to ART	High fungal burden (fungemia, high CrAg titer) Lack of CNS inflammation prior to ART
Onset	<3 mo (median 14 days)	<12 mo (median 4-9 wks)
DDx	Drug-resistant TB Drug toxicity Another OI Poor adherence to therapy	Relapse cryptococcal meningitis Fluconazole resistance Another OI Poor adherence to therapy
Investigations	Culture and DST Molecular tests for DR	Culture and DST CrAg titers are not helpful
Treatment	Moderate-severe cases: Prednisolone 1.5 mg/kg for 14 d then 0.75 mg/kg for 14 d (RCT data)	Optimize antifungal treatment Management of increased ICP Steroid of severe or refractory (no support evidence)

HIV AIDS (Auckl) 2015;7:49-64

Co-infections

Thai HIV Guideline 2017

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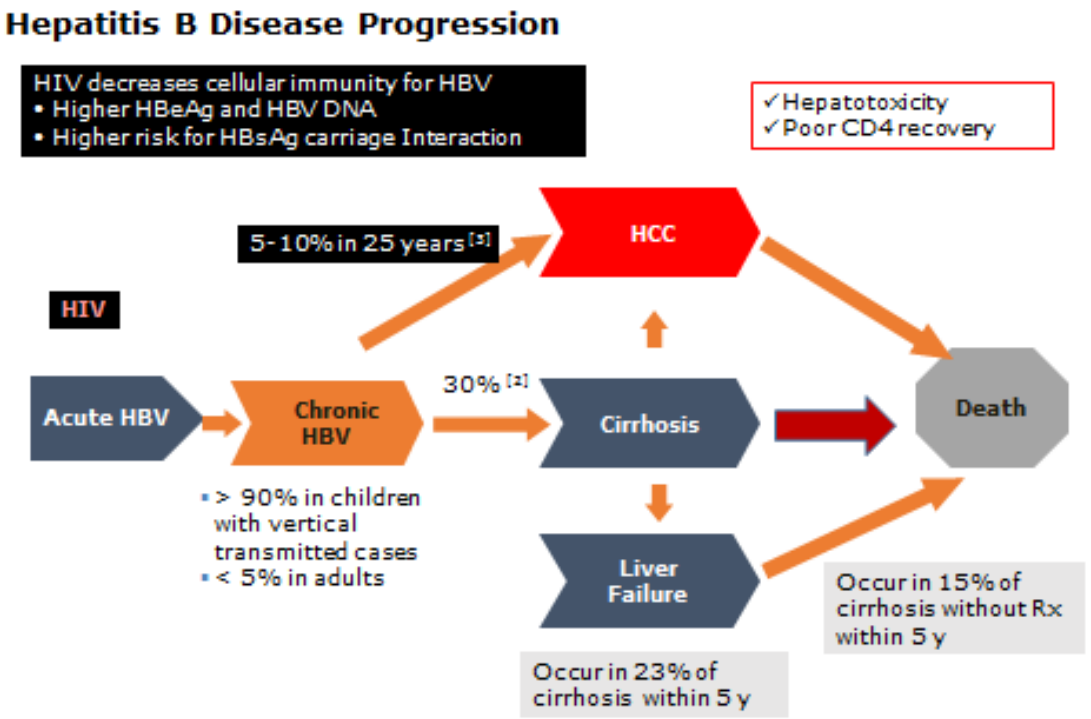
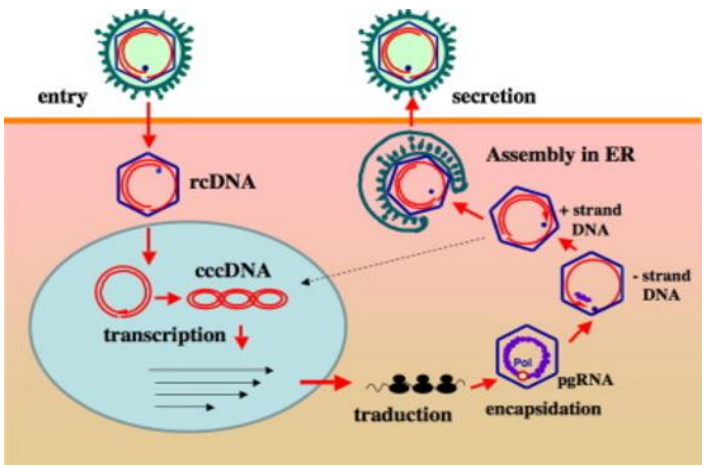
โรคหรืออาการ	วิธีการตรวจคัดกรองและความถี่
ไวรัสตับอักเสบบี (hepatitis B)	• ตรวจเลือดหา anti-HBc, anti-HBs และ HBsAg ครั้งแรกหลังจากพบว่าติดเชื้อเอชไอวี • ถ้าตรวจ HBsAg ได้ผลลบ ควรให้ HBV Vaccine
ไวรัสตับอักเสบซี (hepatitis C)	• ตรวจเลือดหา anti HCV ในผู้ป่วยติดเชื้อเอชไอวีทุกรายที่มี CD4 > 200 cells/mm^3 (ถ้า CD4 ต่ำอาจจะพบผลลบลวง) • ในคนที่ตรวจแล้วผลเป็นลบ แต่ยังมีปัจจัยเสี่ยงที่จะติดเชื้อไวรัสตับอักเสบซีเช่นผู้ที่ใช้ยาเสพติดด้วยวิธีฉีด ประวัติเป็นผู้ต้องขัง หรือกลุ่มชายที่มีเพศสัมพันธ์กับชายที่มีคู่นอนหลายคน ใช้ยาไอซ์ หรือมีอาการของซิฟิลิส

HBV





Ccc DNA=covalently Closed Circular DNA

- Difficult to eradicate HBV
  - With oral antiviral agents (52 y for HBV cure)

HIV/HBV Co-infection

Mahidol University

Management	Note
Assessment	▪ LFT, liver U/S, HBe Ag, HBV DNA (if applicable) ▪ Anti-HCV Ab, Anti-HAV Ab
Advice	▪ Avoid alcohol, hepatotoxicity, transmission (blood, SI) ▪ Vaccination (HAV vaccine if non-immune)
ART	▪ ART for all HIV/HBV cases (TDF or TAF + 3TC or FTC)

- **"FTC, 3TC", "TDF, TAF", "entecavir"**
  - Activity against HIV and HBV
  - Selected HIV mutations can occur if not use fully suppressive HIV-ART regimens
    - M184V: **FTC, 3TC, entecavir**
    - K65R: **TDF, TAF**
  - Entecavir: use in addition to fully suppressive HIV-ART, not be considered as a part of HIV-ART

Thai HIV Guideline 2017 DHHS Guideline Updated 2018

HIV/HBV Co-infection

ART management	Note
Standard ART	▪ TDF + 3TC or FTC ▪ No 3TC/FTC monotherapy for HBV (↑resistant)
Discontinue TDF, 3TC, FTC	▪ Beware "hepatic flare" ▪ Use entecavir for preventing hepatic flare
HIV resistant to TDF, 3TC, FTC	▪ Continue TDF + 3TC or FTC ▪ Appropriate HIV-ART regimen
Change AZT, d4T to TDF	▪ Check viral suppression before ART switching
Renal impairment	▪ Adjust dose of TDF, 3TC, FTC If discontinue TDF;(check HBsAg, HBV DNA before) ▪ Change TDF to entecavir **PLUS** ▪ Add new NNRTI i.e. ABC **OR** ▪ Use LPV/r or ATV/r + 3TC (if HIV VL suppressed)
HCC screening	▪ Male >40 y, female >50 y ▪ HCC in family ▪ Cirrhosis

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HIV/HCV Co-infection

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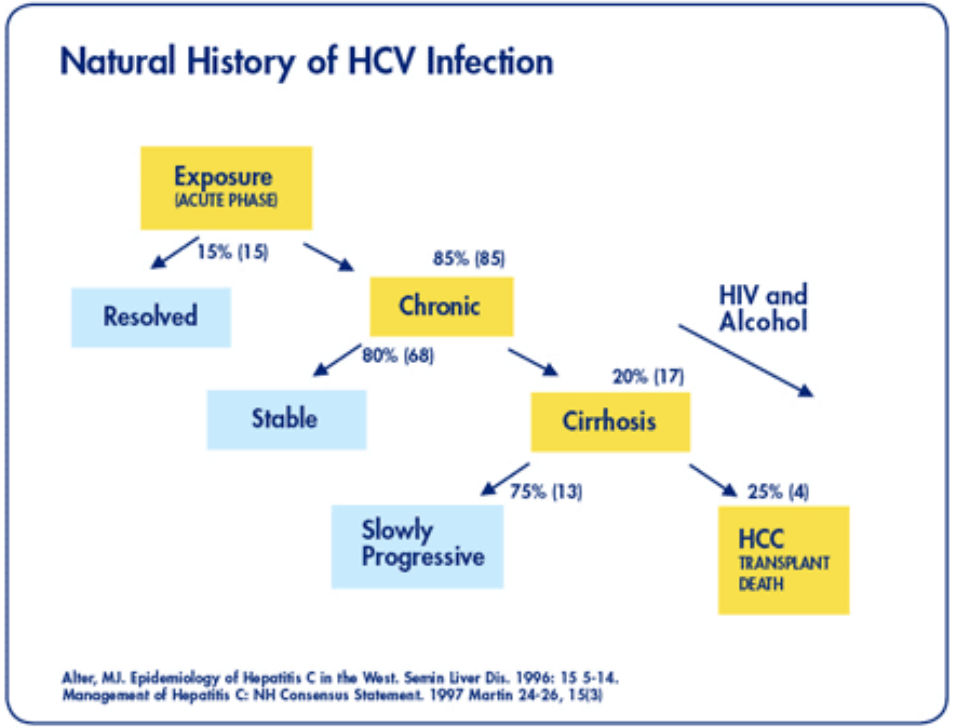

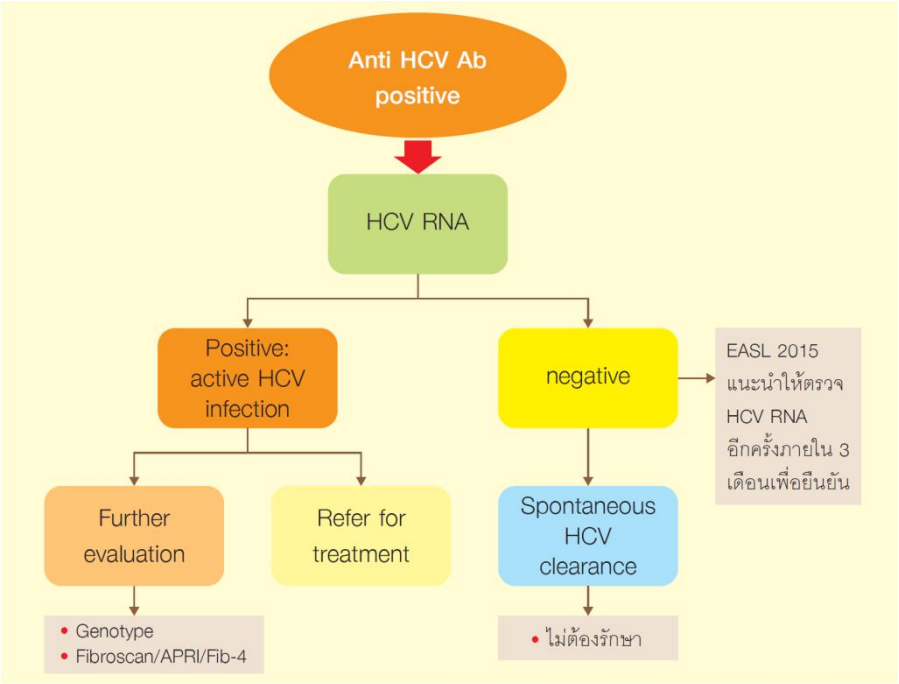

EASL: European Association for the Study of the Liver
APRI: AST to Platelet Ratio Index
Fib: Fibroscan

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HIV/HCV Co-infection

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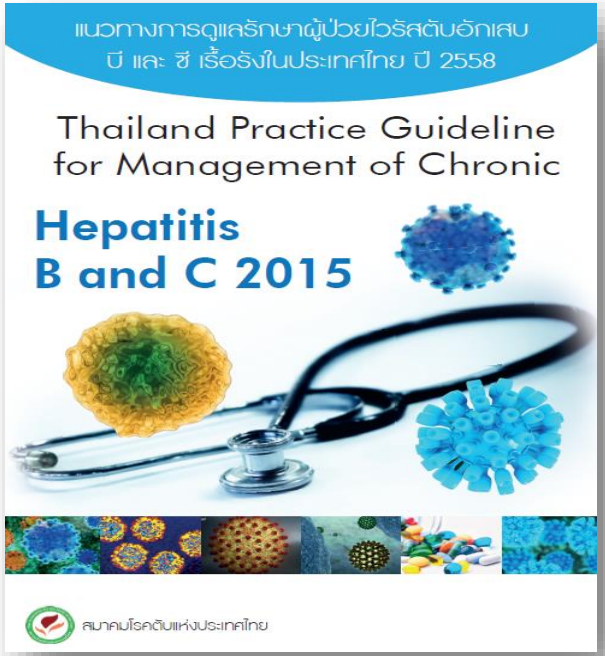

- Who should be treated?
  - With HAART
  - VL<50
  - CD4 >350
- Treatment : PegIFN + RBV 48 wks
- If Sofosbuvir available : Sofosbuvir (400 mg) + Peg/RBV (800-1,000 mg) 24 wks

Avoid using ddI, AZT, d4T during Peg/RBV

ข้อพิจารณาและข้อห้ามในการรักษาไวรัสตับอักเสบซีด้วย pegylated interferon

ผู้ควรได้รับการรักษา	ข้อห้ามการรักษาโรคตับอักเสบเรื้อรังจากไวรัสซี ด้วย pegylated interferon
- อายุ18 ปีขึ้นไป - หยุดดื่มเหล้ามา > 6 เดือน - ตรวจพบ HCV RNA ในเลือด ≥ 5,000 IU/mL - ได้รับยาต้านไวรัสเอชไอวีมา อย่างน้อย 3 เดือน และมี HIV RNA < 50 copies/mL - ไม่มีข้อห้ามของการรักษา	- ผู้ป่วยตับแข็งที่เป็นมากแล้ว (decompensated cirrhosis) ยกเว้นระหว่างรอการผ่าตัดเปลี่ยนตับ - มีประวัติแพ้ยา interferon และ ribavirin - ภาวะซึมเศร้ารุนแรงที่ยังควบคุมไม่ได้ - ตั้งครรภ์หรือไม่เต็มใจที่จะยินยอมในการคุมกำเนิด - มีโรคประจำตัวที่ยังควบคุมรักษาได้ไม่ดีเช่นความดันโลหิตสูง เบาหวานโรคหัวใจและหลอดเลือดถุงลมโป่งพองและโรคไทรอยด์ เป็นต้น

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HCV Direct-acting Antivirals (DAAs)

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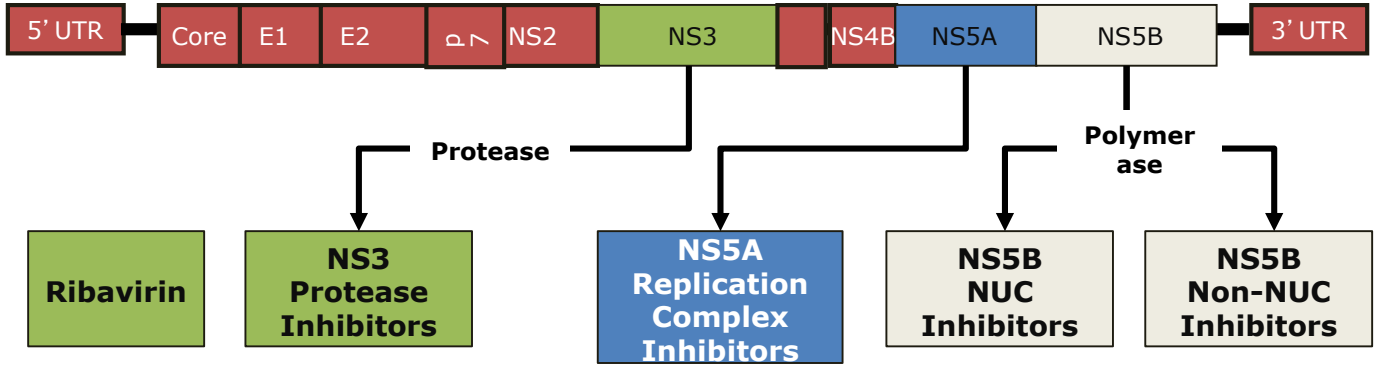


Telaprevir
Boceprevir
Simeprevir
Paritaprevir
Asunaprevir
Grazoprevir
Glecaprevir

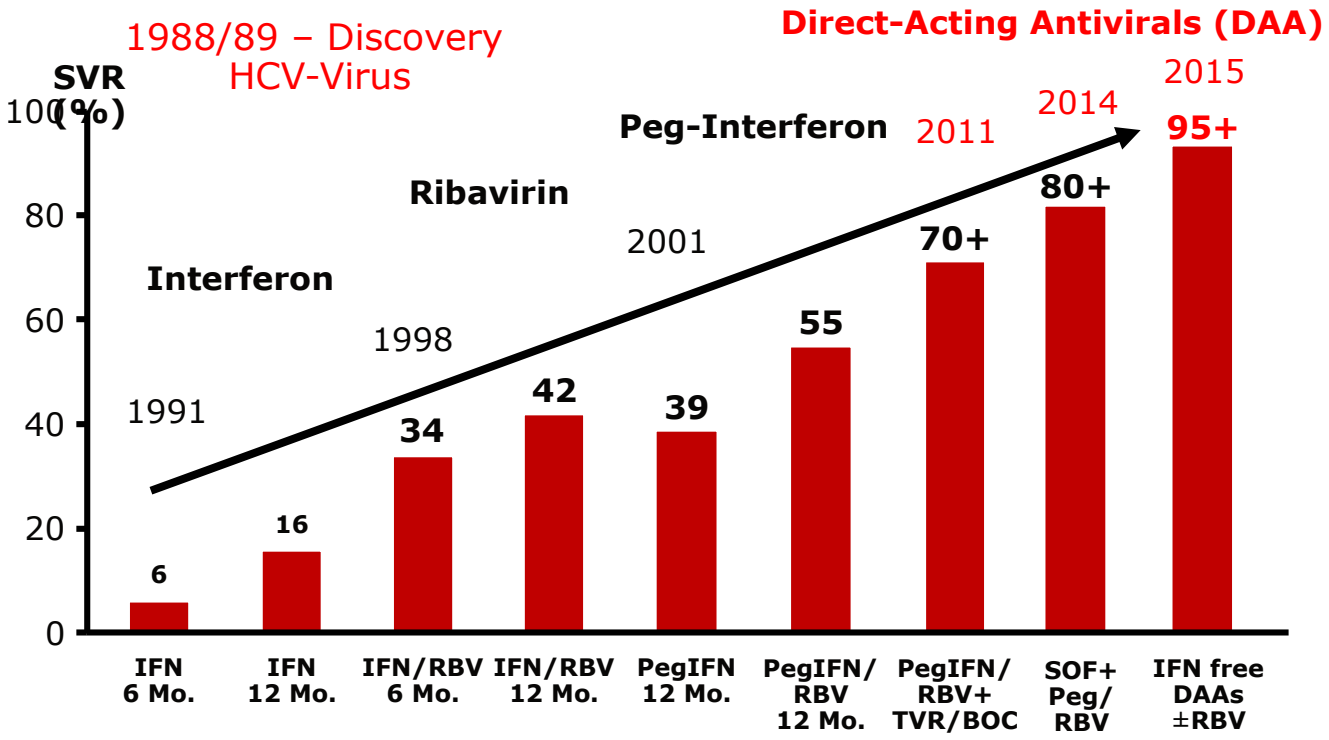
Daclatasvir
Ledipasvir
Ombitasvir
Velpatasvir
Elbasvir
Pibrentasvir
GS-5816

Sofosbuvir
VX-135
IDX21437
ACH-3422

Dasabuvir
Beclabuvir

-previr **-asvir** **-buvir**

HCV: Curable Disease



Kronenberger B et al. Dtsch. Med. Wochenschr 2013; 138:1796-800.

Question

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Faculty of Medicine Siriraj Hospital

- A 30 YOM with the first diagnosed of HIV
  - Asymptomatic, His CD4 350 cells/mm^3
  - CXR –ve
  - HBs Ag –ve and anti-HCV Ab –ve
  - VDRL 1:16 and TPHA +ve
- Will you perform a lumbar puncture for this case?

A. Yes

B. No

Syphilis

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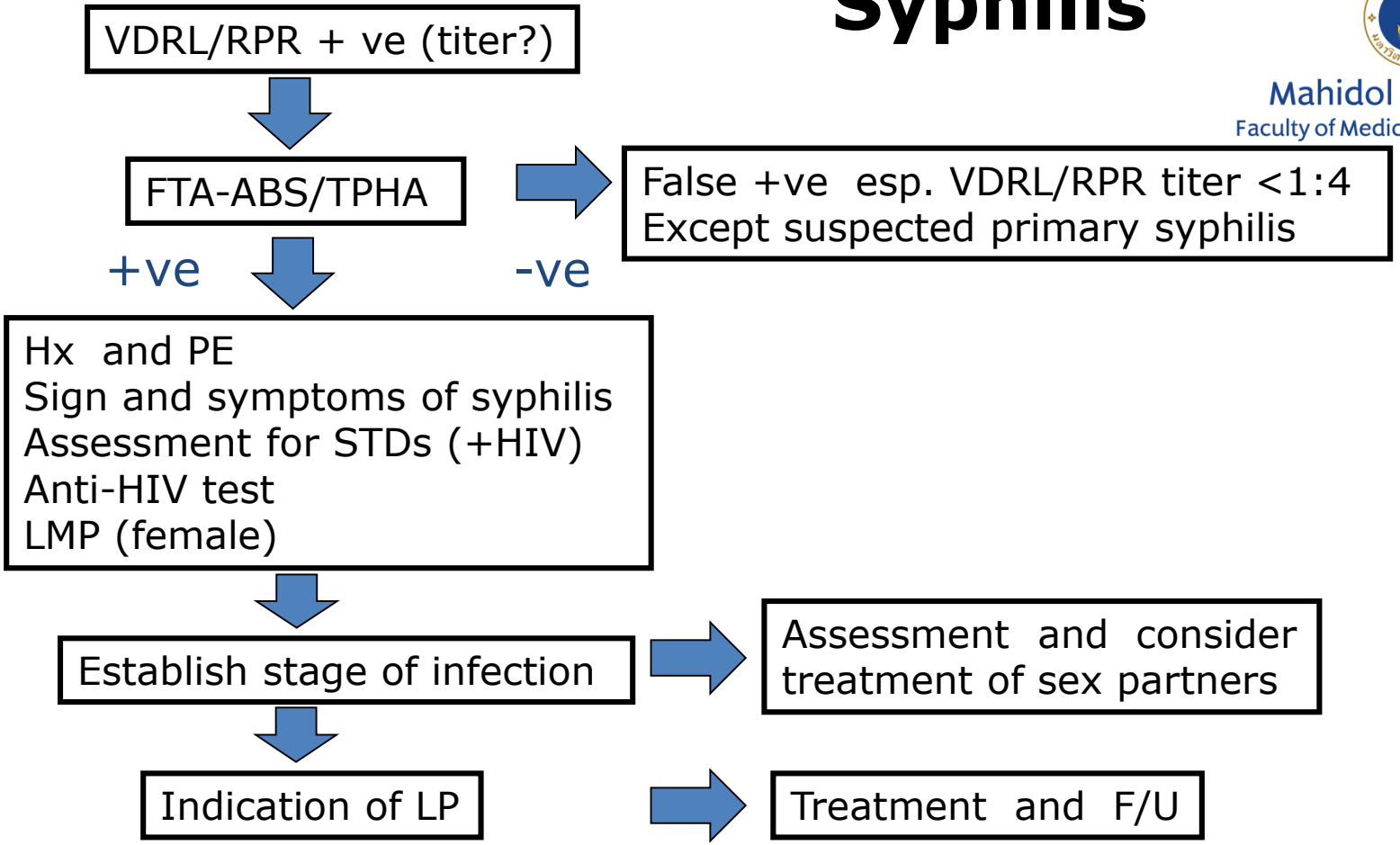

STD Guideline 2015

Syphilis: Lumbar Puncture

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- Neurologic, ophthalmic, or otic signs and symptoms
- Active tertiary syphilis
- Treatment failure
  - Sustained ≥4-fold increase of titer (>2 wks)
  - High titer (≥1:32) fails to decline ≥4-fold within 12–24 mo of therapy
  - Signs or symptoms develop

STD Guideline 2015

Syphilis in HIV

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- Atypical presentation
  - Severe or neurological involvement
- Modified serologic response
  - False negative and false positive test
- Treatment failure
  - More frequent F/U (q 3 mo during the first year after treatment)
- LP is not routinely indicated in all HIV cases

STD Guideline 2015

Causes of Death in HIV/AIDS

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Causes of death for all enrolled patients who died (N = 142), Thailand, 2005–2007*

Cause of death	No. (%) patients
TB	38 (27)
Disseminated TB (3 with MDR TB)	20 (53)
Central nervous system TB (1 with MDR TB)	7 (18)
Pulmonary TB (2 with MDR TB)	10 (26)
Peritoneal TB	1 (3)
HIV-associated condition	50 (35)
Bacterial infection	6 (12)
Cerebral toxoplasmosis	4 (8)
Disseminated CMV	1 (2)
Fungal infection (other than PCP)	8 (16)
Liver disease	1 (2)
Nontuberculous mycobacteria	10 (20)
PCP	7 (14)
Other infectious cause	5 (10)
Other noninfectious cause	1 (2)

Dead case review

- Overall prevalence
- Major causes and contributing factors
  - Identify problems
  - Physical, psychological, social factors
- How to improve?
  - Quality improvement
  - Priority setting
  - Network

Emerg Infect Dis 2009; 15(2): 258-64

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Update on HIV/AIDS Care

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05/06/2018