Malaysian Consensus Guidelines on Antiretroviral Therapy 2017

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Acknowledgement

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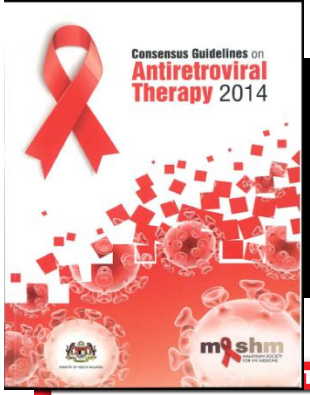

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Evolution of when to initiate therapy

- ART improves survival and delays disease progression with CD4 <200 cells/mm^3 and/or history of AIDS-defining conditions

(Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One. 2009;4(5):e5575.* Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS ClinicalTrials Group 320 Study Team. *N Engl J Med. Sep 11 1997;337(11):725-733.)*

- Randomized controlled trial in Haiti showed longer survival if started ART with CD4 between 200-350 cells/mm^3

(Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med. Jul 15 2010;363(3):257-265)*

Evolution of when to initiate therapy

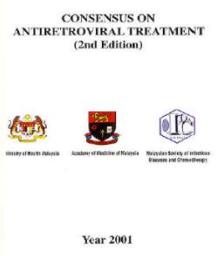
START and TEMPRANO trials

- Support the initiation of ART regardless of CD4 cell count
- about a 50% reduction in morbidity and mortality among those with CD4 >500 cells/mm3 randomized to receive ART immediately versus delaying initiation of ART

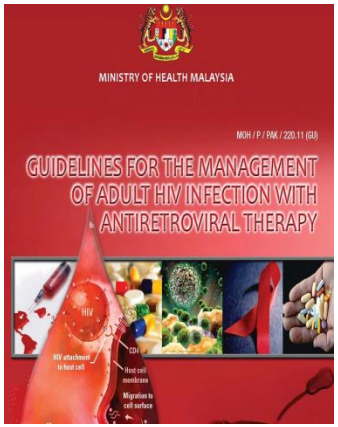
1. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med.* Jul 20 2015.

2.TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med. Aug 27 2015;373(9):808-822)*

Evolution of when to initiate therapy



Clinical Category	CD4 Count	Viral Load	Recommendation
Symptomatic - AIDS defining illness - Severe Symptoms *	Any value	Any value	Treat
Asymptomatic	< 200/mm³	Any value	Treat
Asymptomatic	> 200 but < 350/mm³	Any value	Treatment recommended
Asymptomatic	> 350/mm³	> 50,000** copies/ml	Treatment may be initiated #



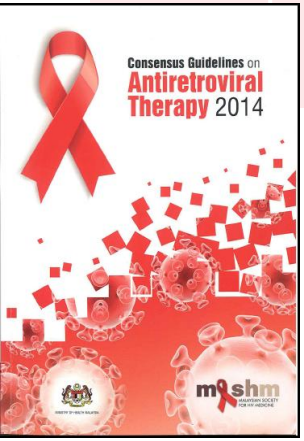
	CD4 Count	Recommendation
Symptomatic (AIDS defi ning illness according to WHO classifi cation)	Any value	To treat
Asymptomatic	<200 cells/mL	To treat
Asymptomatic	200-350 cells/mL	Treatment is recommended
Asymptomatic	>350 cells/mL	Not to treat *

** Consider ART in patients with CD4>350cells/uL but CD4 %< 14%.*

When to initiate ART

Population	Recommendation
Adults and dolescents (>10 years)	Initiate ART if CD4 cell count < 350 cells/mm^3
	For patients who have a CD4 count > 350 but < 500 cells/mm^3 ART may be considered for those who are 1. In a serodiscordant relationship [refer to Chapter 13] 2. Highly motivated to comply with treatment 3. Pregnant or breastfeeding [refer to Chapter 7] 4. Coinfected with Hep B [refer to Chapter 11] 5. MSM who cannot adhere to barrier methods 6. Active TB disease [refer to Chapter 10]

Target Population	Specific Recommendations
Adults (>18years)	All HIV-infected individuals, regardless of CD4 count As a priority, ART should be initiated in : • All adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) • Individuals with CD4 count ≤350 cells/mm^3 • HIV-associated nephropathy (HIVAN) • HIV/Hepatitis B virus co-infection • HIV/Hepatitis C virus co-infection • All pregnant ladies infected with HIV



Why change the target of treatment?

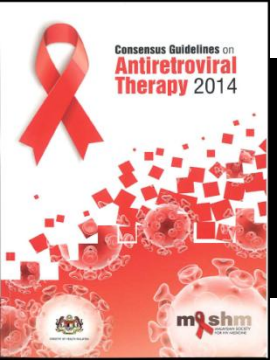
a. Effective ART can reduce viremia

b. Adequate viral suppression:

- improves immune function
- overall quality of life
- lowers the risk of both AIDS-defining and non-AIDS-defining complications
- prolongs life

c. Earlier ART initiation reduce HIV incidence at the population level (high uptake & sustained HIV testing, ART coverage and retention to care)

(Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. Jan 3 2009;373(9657):48-57)



New kids on the block

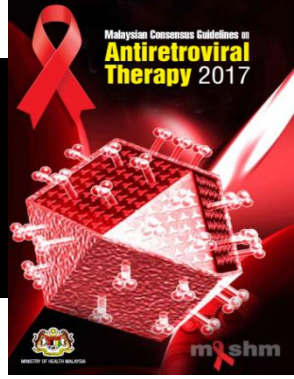


Table 1 • ARVs that are Registered in Malaysia

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI) / Nucleotide Reverse Transcriptase Inhibitors (ntRTI)

- Abacavir (ABC)
- ~~Didanosine buffered or enteric coated (DDI)~~
- Emtricitabine (FTC) (available as combination pill)
- Lamivudine (3TC)
- Stavudine (D4T)
- Tenofovir (TDF)
- Zidovudine (AZT)

2. Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

- Efavirenz (EFV)
- Etravirine (ETV)
- Nevirapine (NVP)

3. Protease Inhibitors (PI)

- Atazanavir (ATV)
- Darunavir (DRV)
- Lopinavir / ritonavir (LPV/r)
- Ritonavir (RTV)
- ~~Saquinavir (SQV)~~

4. Integrase Inhibitors

- Raltegravir

5. CCR5 Antagonist

- Maraviroc

6. Fusion Inhibitor

- Enfuvirtide

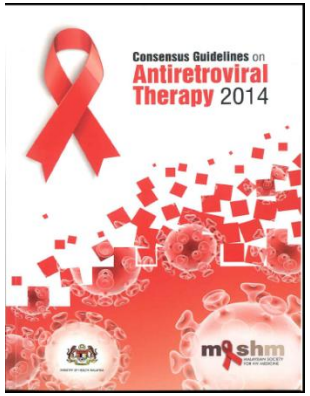
Table 1.0 • Antiretroviral Drugs in Malaysia

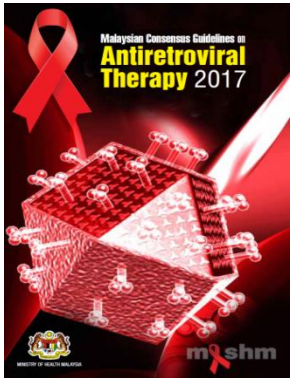
lass	Abbreviation
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTI)	
Abacavir	ABC
Emtricitabine	FTC
Lamivudine	3TC
Stavudine	3TC
Tenofovir disoproxil fumarate	TDF
Zidovudine	AZT or ZDV
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz	EFV
Etravirine	ETV
Nevirapine	NVP
Rilpivirin	RPV
Protease inhibitors (PI)	
Atazanavir	ATV
Darunavir	DRV
Lopinavir / ritonavir	LPV/r
Ritonavir	RTV
Integrase Inhibitors	
Raltegravir	RAL
Dolutegravir	DTG
CCR5 Antagonist	
Maraviroc	MVC
Fusion Inhibitor	
Enfuvirtide	T-20

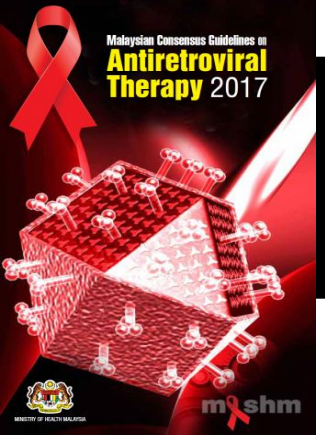
Recommended regime

Adult	Preferred First Line TDF + FTC + EFV	Alternative AZT+ 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
	• TDF/FTC + Raltegravir (if intolerant of nNRTI)	PI-Based Regimens: • ATV/r plus TDF/FTC • LPV/r plus TDF/FTCa
Pregnant	Refer PMTCT section	

Preferred first line ART	Alternative regimes
TDF + FTC + EFV	AZT + 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
TDF + FTC + Raltegravir TDF + FTC + Dolutegravir (if intolerant to NNRTI)	TDF + FTC + ATV/r TDF + FTC + LPV/r







New kid on the block: Dolutegravir

Preferred first line ART	Alternative regimes
TDF + FTC + EFV	AZT + 3TC + EFV (or NVP) ABC + 3TC + EFV (or NVP) TDF + FTC + NVP
TDF + FTC + Raltegravir TDF + FTC + Dolutegravir (if intolerant to NNRTI)	TDF + FTC + ATV/r TDF + FTC + LPV/r

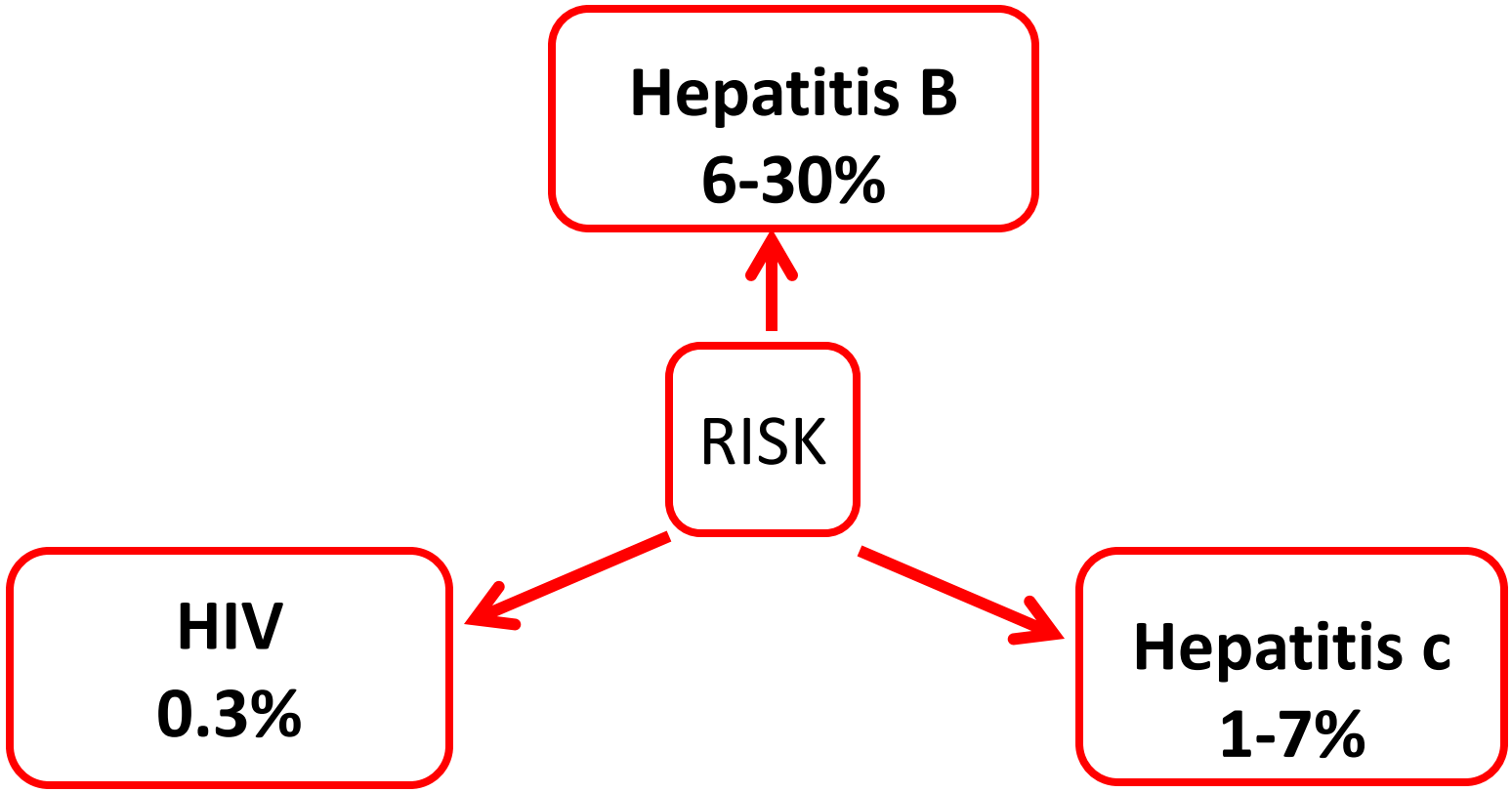
Table 15.1 • Choice of ARV in PEP

2 drug regime	Add for 3 drug regime
Preferred Tenofovir* 300mg od + Emtricitabine* 200mg od	**Preferred** Dolutegravir 50mg od/ Raltegravir 400mg bd
Alternative Zidovudine 300mg bd + Lamivudine* 150mg bd	**Alternative** Lopinavir/Ritonavir 2 tab BD

16.6 Recommended Regimes for HIV PEP Following Non-Occupational Exposure

Tenofovir 300 mg PO daily + Emtricitabine 200 mg PO daily
Plus Raltegravir 400 mg PO twice daily / Dolutegravir 50 mg od

AVERAGE RISK OF INFECTION POST NEEDLESTICK EXPOSURE FOR A HEALTH CARE WORKER (HCW)



PEP Recommendation When Exposed to HIV Positive Source Patient

Type of exposure with known HIV positive patient	PEP recommendation	
	Source already on HIV treatment and recent viral load is undetectable**	Source not on treatment or on HIV treatment but recent viral load is still detectable** or no recent viral load
* Needle stick injury or other sharps exposure	2 drugs	3 drugs
Mucous membrane or non-intact skin exposure	Consider 2 drugs	3 drugs

* penetrating injury to the skin with a sharp instrument containing fresh blood

** with our current HIV viral load assay, this will be < 20copies/ml

ART in PEP

Table 15.1 • Choice of ARV in PEP

2 drug regime	Add for 3 drug regime
Preferred Tenofovir* 300mg od + Emtricitabine* 200mg od **Alternative** Zidovudine 300mg bd + Lamivudine* 150mg bd	**Preferred** Dolutegravir 50mg od/ Raltegravir 400mg bd **Alternative** Lopinavir/Ritonavir 2 tab BD

* Requires dose adjustments if baseline creatinine clearance is <50mL/min

Tenofovir should be used with caution in those with renal insufficiency or taking other nephrotoxic drugs

In case of non-availability of the 3rd agent, a 2-drug ARV regimen (ie Tenofovir + Emtricitabine OR Zidovudine + Lamivudine) should be started as soon as possible.

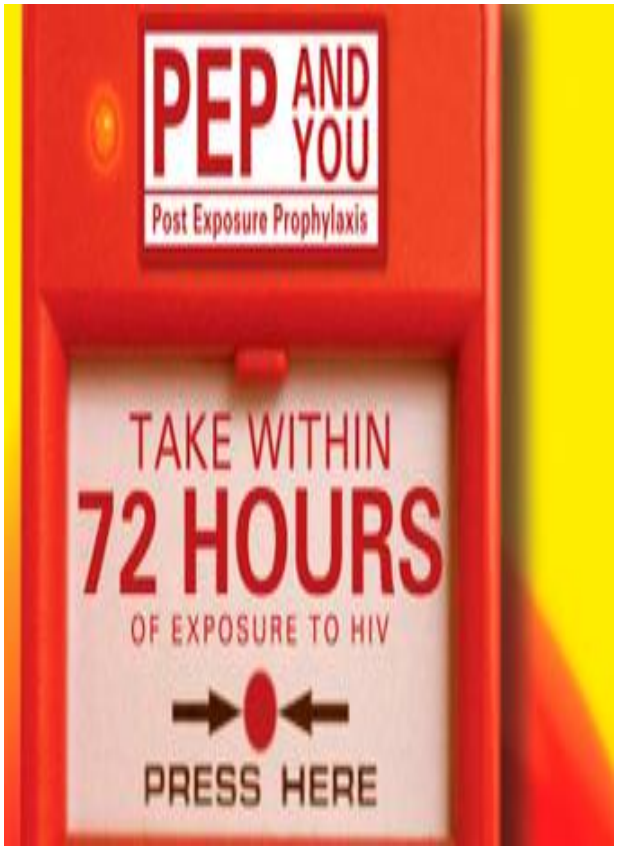
TIMING OF PEP TO PREVENT HIV INFECTION AFTER EXPOSURE

Percutaneous / mucosal exposure to HIV

Local replication of virus occurs in tissue macrophages or dendritic cells

HIV replicate in regional lymph nodes

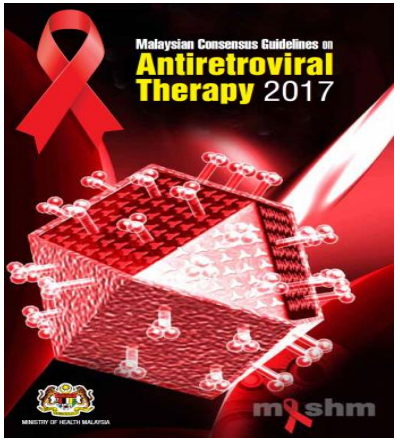
VIREMIA



Follow up for PEP

Table 15.2 • Monitoring after Initiation of PEP

	Baseline	1st week	2nd week	3rd week	4th week	12th week
Clinic visit	X	X or by telephone	X or by telephone	X or by telephone	X or by telephone	X or by telephone
Monitoring blood tests	FBC, RP LFT		FBC (if on zidovudine)		FBC (if on zidovudine), RP, LFT	
HIV test	X				X	X



Non Occupational Exposures

- Risk exposures following sexual or needle sharing activities, needle stick injuries outside occupational settings, and trauma including human bites

Estimated risk of HIV transmission per act

Table 1. Estimated per-act risk for acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act[a]

Exposure type	Rate for HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[b]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

Source: http://www.cdc.gov/hiv/policies/law/risk.html

[a] Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

[b] HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

0.0011 %

AIDS. 2014 Jun 19;28(10):1509-19.

Non Occupational HIV Post Exposure Prophylaxis (nPEP)

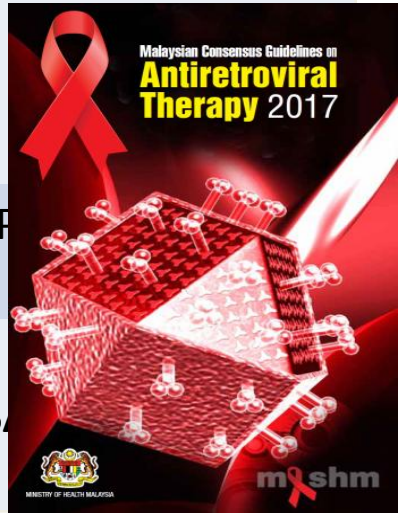
Key Recommendations

- nPEP should be offered to all persons who have sustained a mucosal exposure to HIV from a known infected source as soon as possible and, at most, within 72 hours after exposure

16.6 Recommended Regimes for HIV PEP Following Non-Occupational Exposure

Tenofovir 300 mg PO daily + Emtricitabine 200 mg PO daily Plus Raltegravir 400 mg PO twice daily / Dolutegravir 50 mg od

- Duration of nPEP is 28 days
- Follow up HIV testing using a 4th generation assay (HIV Ag/Ab test) is recommended at
  - 4, 12 weeks and
- If HIV test is positive after nPEP has already been initiated, nP continued
- nPEP is no longer recommended if the source is on ART with **sustained** (>6 months) undetectable plasma HIV viral load **(BA**



Differences

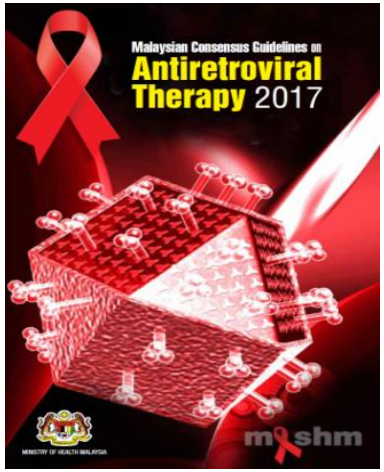
	Occupational PEP	Non occupational PEP
Source status	Easy to ascertain	Difficult to ascertain
Time to PEP	+	+++
$$$	FOC	Borne by pt
Risk of pregnancy	-	+
Risk of STIs	-	+

Pre-Exposure Prophylaxis (PrEP):

- when a HIV-negative person at substantial risk of HIV infection takes **TDF** and (**FTC or 3TC**) to prevent him/herself from contracting the virus.
- a temporary method for reducing the chances of contracting HIV during phases of high-risk behaviour.

Eligibility criteria for PrEP

- HIV seronegative, and no suspicion of acute HIV infection (that is, RNA or antigen present before seroconversion)
- Substantial risk for HIV infection (by history in the last 6 months)
  - Sexual partner with HIV who has not been on effective therapy for entire 6 months, OR Sexually active in a high HIV prevalence population (define high prevalence population) AND any of the following:
    - Vaginal or anal intercourse without condoms with more than one partner, OR
    - A sex partner with one or more HIV risk factors, OR
    - A history of an STI by lab testing or self-report or syndromic STI treatment, OR
    - Use of stimulant drugs
    - Commercial sex work
    - Any sharing of injection materials with other people, OR
    - Any use of non-occupational post-exposure prophylaxis (nPEP).



- No contraindications to Tenofovir or Emtricitabine
- Willingness to use PrEP as prescribed

Evidence of the Safety and Efficacy of Antiretroviral Prophylaxis

Study	Outcome Analyses— HIV incidence (mITT)		Effect — HR [Efficacy Estimate] (95% CI)		
	Agent	Control			
iPrEx (MSM)	36 infections among 1224 persons	64 infections among 1217 persons	0.56 [44%] (0.37–0.85)		
US MSM Safety Trial	3 infections among 201 persons (all 3 in delayed arm, not on TDF)	4 infections among 199 persons (1 acute infection at enrollment)	Not Reported		
Partners PrEP (heterosexual men and women)	TDF 17 infections among 1572 persons TDF/FTC 13 infections among 1568 persons	52 infections among 1568 persons		TDF	TDF/FTC
			All	0. 33 [67%] (0.19–0.56)	0.25 [75%] (0.13–0.45)
			Women	0.29 [71%] (0.13–0.63)	0.34 [66%] (0.16–0.72)
			Men	0.37 [63%] (0.17–0.80)	0.16 [84%] (0.06–0.46)
TDF2 (heterosexual men and women)	9 infections among 601 persons 1.2 infections/100 person-years	24 infections among 599 persons 3.1 infections per 100 person-years	0.38 [62%] (0.17–0.79)		
FEM-PrEP (heterosexual women)	33 infections among 1024 persons 4.7 infections per 100 person-years	35 infections among 1032 persons 5.0 infections per 100 person-years	0.94 [6%][a] (0.59–1.52)		
West African Trial (heterosexual women)	2 infections among 427 persons 0.86 infections per 100 person-years	6 infections among 432 persons 2.48 infections per 100 person-years	0.35 [65%][a] (0.03–1.93)		
VOICE (heterosexual women)	TDF 52 infections among 993 persons 6.3 infections per 100 person-years TDF/FTC 61 infections among 985 persons 4.7 infections per 100 person-years	35 infections among 999 persons 4.2 infections per 100 person-years	TDF	TDF/FTC	
			1.49 [-50 %][a] (0.97–2.3)	1.04 [-4%][a] (0.73, 1.5)	
BTS (injection drug users)	17 infections among 1204 persons 0.35 infections per 100 person-years	33 infections among 1207 persons 0.68 infections per 100 person-years	0.51 [49%] (9.6, 72.2)		

Scenario 1

- John is a flight attendant, MSM
- Usually asks his partners about their HIV status
- Last sexual contact ~10 d ago
- sex without a condom with a man of unknown HIV status
- Heard and keen for PrEP

scenario 2:

- 31-year-old lady
- Anxious, she thinks she needs an HIV test
- Boyfriend of 1 month told her he is HIV positive (on regular abacavir and efavirenz with well suppressed viral load)

PrEP is effective and can be used before conception, and during and after pregnancy

- PrEP during periconception and pregnancy by the uninfected partner offer additional tool to reduce the risk of sexual HIV acquisition.

  -FDA approved, pregnancy category B

  - DHHS recommend PrEP used during pregnancy when the risk of HIV acquisition is substantial

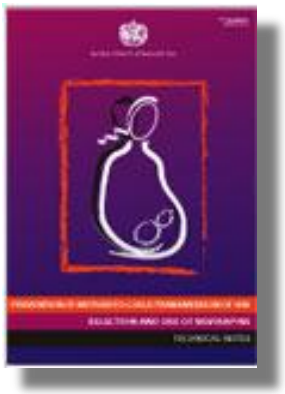
Hiv and pregnancy

MTCT risk: Preventive Strategy

Strategy	Range of probability of transmission (%)
Without AZT	18.9 – 24.9[1]
With AZT	7.3 - 15.7[2]
With C-section alone	10.4 [3]
With C-section and AZT	2 – 8.2[3]
HAART	<1% (2006)

1. WITS 1993
2. ACTG 076 1994
3. International Perinatal HIV Group NEJM 1999:340-977

Evolution of WHO PMTCT ARV Recommendations



2001

2004

2006

2010

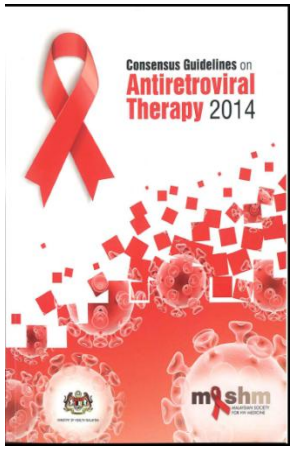
Launch July 2013

PMTCT	4 weeks AZT; AZT+ 3TC, or SD NVP	AZT from 28 wks + SD NVP	AZT from 28wks + sdNVP +AZT/3TC 7days	**Option A** (AZT +infant NVP) **Option B** (triple ARVs)	**Option B or B+** Moving to ART for all PW/BF
ART	No recommendation	CD4 <200	CD4 <200	CD4 ≤350	CD4 ≤500

Move towards: more effective ARV drugs, extending coverage throughout MTCT risk period, and ART for the mother's health

Evolution of MOH PMTCT ARV Recommendations

CD4	CD4 >250	CD4<250	CD4 >350	CD4 ≤350
PMTCT	LPr/r/AZT/ 3TC after 1st trimester; IP AZT during delivery for mother	AZT/3TC/NVP after 1st trimester; IP AZT during delivery for mother	Triple ARVs by 14th week POA	Triple ARVs ASAP, even in the 1st trimester
ART	optional	continue post delivery 2014	stop in option B, continue in option B+	continue post delivery 2017

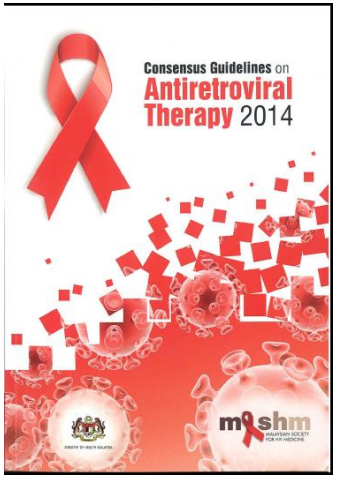


Notes

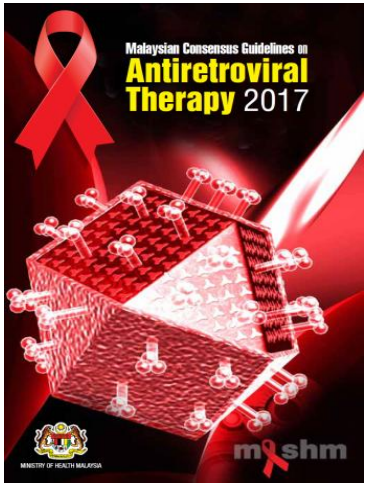
Option B + Lifelong cART for all pregnant women (regardless of CD4)	Start cART and maintain post-delivery
Option B cART only during pregnancy for women with CD4 > 350	Start cART and stop post-delivery

Intrapartum IV zidovudine infusion

- Recommended routinely irregardless of viral load

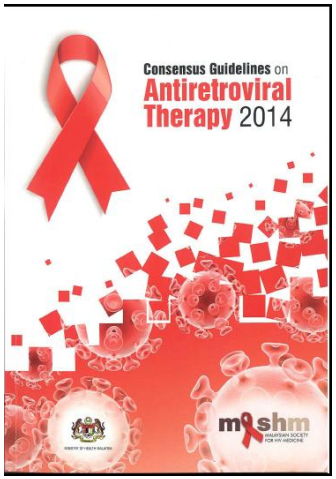


- Recommended for viral load >1000 copies/ml
- No benefit if viral load <1000 copies/ml

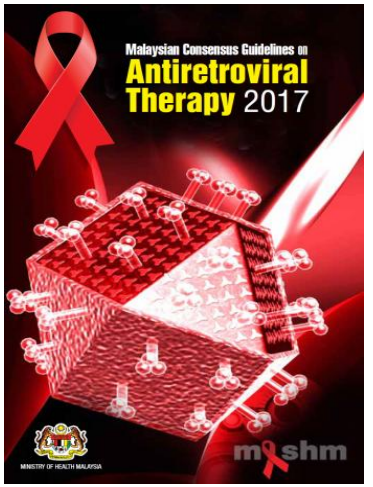


Women (HIV) presented in labor without prior ART

- Intravenous zidovudine
- Intrapartem nevirapine not necessary



- Intravenous zidovudine
- Zidovuidine+lamivudine+ Raltegravir(preferred as rapidly cross placenta)
- If no raltegravir, may use efavirenz / nevirapine
- Post delivery, switch ART to reommended 1st line therapy



Why consider *Raltegravir* in late-presenting women?

- Preventing MTCT in late-presenting (after 28 weeks) HIV-infected pregnant women remains a clinical challenge, and ensuring a rapid decrease of maternal VL is an important preventive strategy.

- Advantages of starting Raltegravir during 3rd trimester:
  - ✓ higher first and second phase viral decay rate
  - ✓ high placental transfer
  - ✓ potential preloading effect for neonate
  - ✓ effective accumulation in cervicovaginal secretions.

summary

- Initiate ART regardless of CD4 level
- 2017 guideline available on MASHM website
- New chapters on nPEP and PrEP to help further prevent HIV transmission

Thank you