Opening Lecture: HIV Drug Resistance in Asia

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HIV Drug Resistance in Asia

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Disclosure

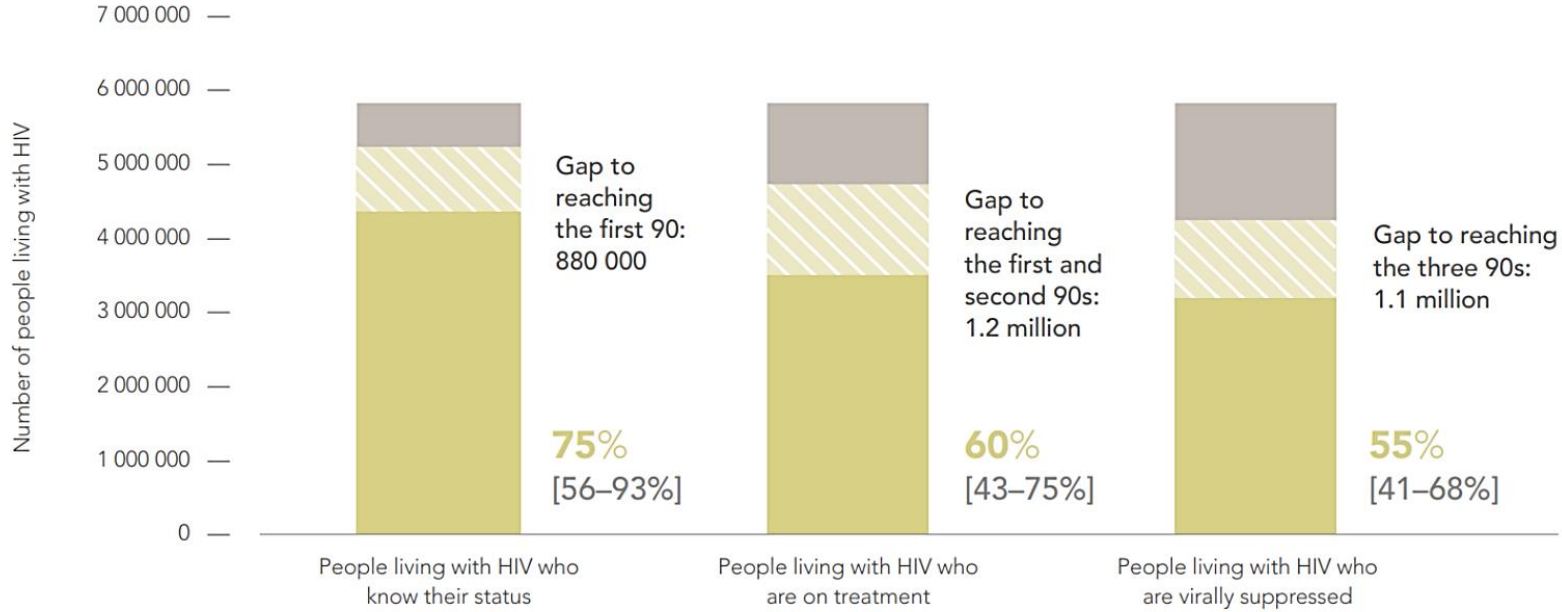
- Speakers Bureau
  - Pfizer, Astellas, MSD, Janssen, AztraZeneca, GSK, DKSH, BMS, AbbVie, Meiji, Siam, Daiichi, Takeda, Sanofi, Mylan, DCH Auriga, Biopharm, BLHua, Roche, Berlin, Zuellig Pharma, Medtronic
- Congress Travel
  - Astellas, Pfizer, MSD, Janssen, BMS, AbbVie, Siam, Daiichi, Takeda, DKSH
- Research Grant
  - Gilead, MSD, BMS, Daiichi, Biopharm, Medicago

Outlines: HIV Drug Resistance in Asia

- Definition of HIV drug resistance
- Guidance of HIV drug-resistance testing
- Transmitted and pretreatment HIV drug resistance
- HIV drug resistance after treatment failure

HIV Testing and Treatment Cascade

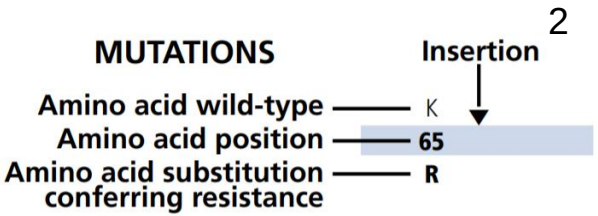
Asia and the Pacific, 2019



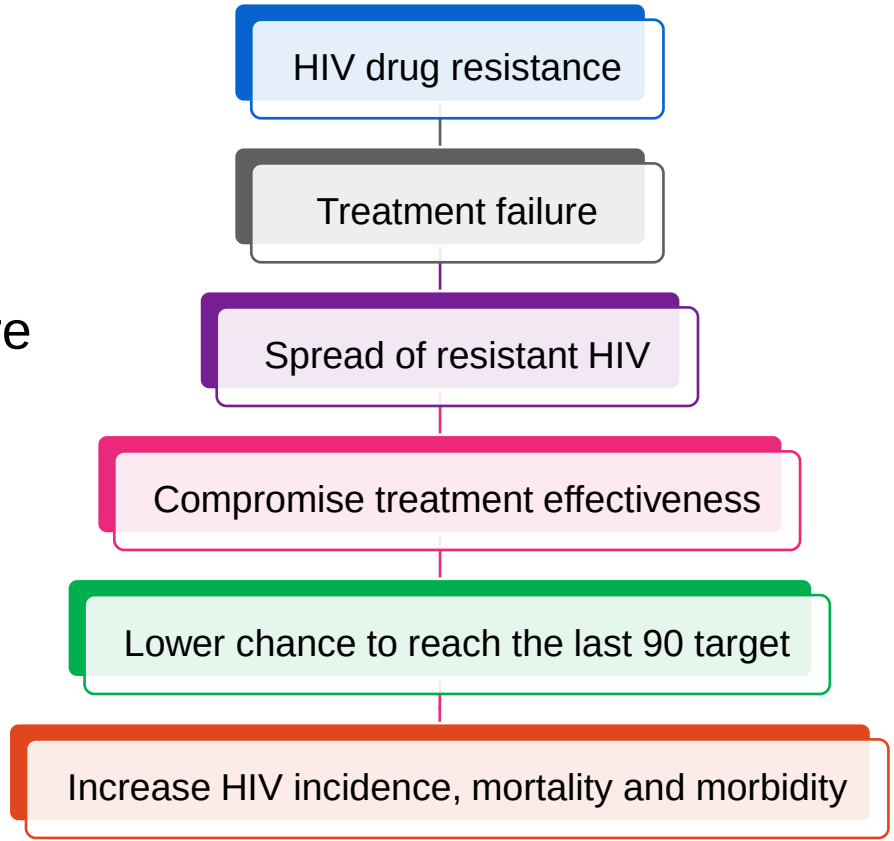
https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf

HIV Drug Resistance

- Ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs[1]
- Caused by ≥1 changes (mutation/s) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus[1]



[2]



1. WHO. https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/ (accessed 26 September 2020) 2. Wensing AM, et al. Top Antivir Med 2019;27:111-21.

HIV Drug Resistance: WHO Classification

Acquired HIV drug resistance (ADR)

- Develops because of viral replication in the presence of ARV drugs

Transmitted HIV drug resistance (TDR)

- Previously uninfected individuals are infected with virus that has drug resistance mutations

Pretreatment HIV drug resistance (PDR)

- Resistance among ARV drug–naïve people initiating ART or people with previous ARV drug exposure initiating or reinitiating first-line ART

https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

Guidance on Drug-resistance Testing

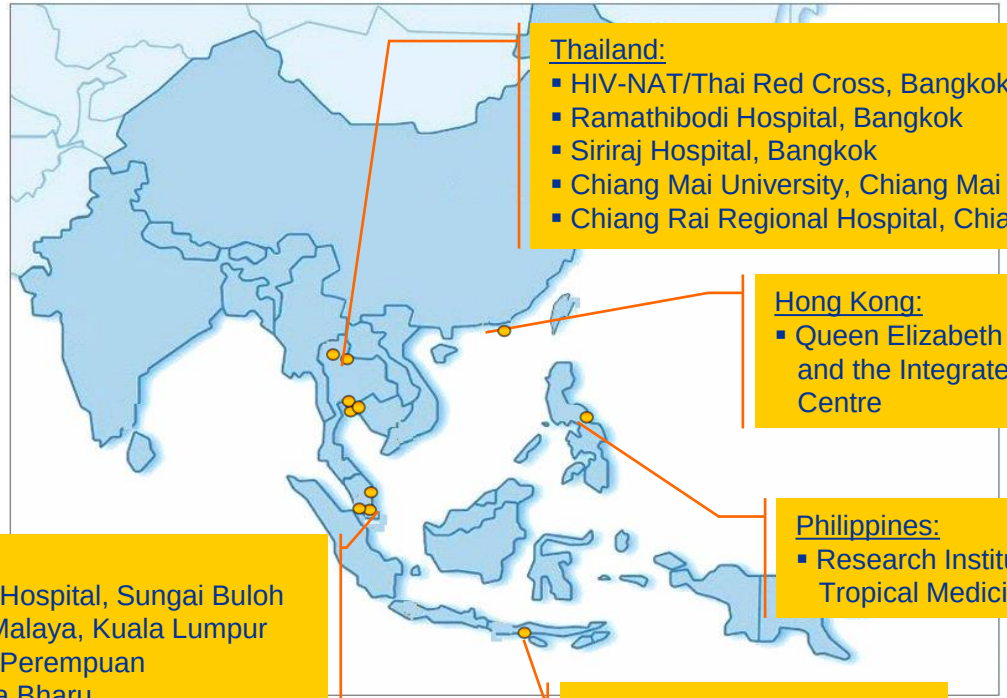
DHHS[1]	EACS[2]	Thai	WHO[3]
ART-naive persons ▪ Entry to care: recommended (AII) ▪ At time of ART initiation: should be considered (CIII) ***ART-experienced persons*** ▪ Should be performed to assist the selection of active drugs ▪ Virological failure with HIV RNA >1000 copies/mL (AI); 500-1000 copies/mL (BII)	***At HIV diagnosis*** ▪ Recommended (+) Prior to starting ART ▪ Considered (+/-) ***At virological failure*** ▪ Recommended (+)	***At HIV diagnosis, only if*** ▪ On PrEP or ▪ Having a partner suspected of drug resistance ***At virological failure*** ▪ Recommended, if HIV RNA >1000 copies/mL	Not recommended

1. DHHS ART Guidelines. (accessed 4 October 2020). 2. EACS Guidelines. October 2020.
3. WHO. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy July 2017.

TDR among TREAT Asia Network Sites

Therapeutics Research • Education • AIDS Training
TREATASIA

ART-naïve patients between 2007 and 2010
458 patients with recent and 1,340 patients with chronic HIV infection



Thailand:
- HIV-NAT/Thai Red Cross, Bangkok
- Ramathibodi Hospital, Bangkok
- Siriraj Hospital, Bangkok
- Chiang Mai University, Chiang Mai
- Chiang Rai Regional Hospital, Chiang Rai

Hong Kong:
- Queen Elizabeth Hospital and the Integrated Treatment Centre

Philippines:
- Research Institute for Tropical Medicine, Manila

Malaysia:
- Sungai Buloh Hospital, Sungai Buloh
- University of Malaya, Kuala Lumpur
- Hospital Raja Perempuan Zainab II, Kota Bharu

Indonesia:
- Udayana University, Bali

Kiertiburanakul S, et al. PLoS One 2013;8:e62057.

TDR among TREAT Asia Network Sites

Duration of HIV infection	No. of patients (n)	Prevalence of drug resistance (%)	NRTI RAMs	NNRTI RAMs	PI RAMs
Recent	458	6.11	5.2	2.8	3.9
Chronic	1,340	4.03	3.6	2.2	1.0
Total	1,798	4.56	4.1	2.3	1.8
p-value*		0.065	0.138	0.410	<0.001

- Patients with chronic HIV infection, heterosexual contact was less likely to be associated with TDR
  - OR 0.34, 95% CI 0.20-0.59, p <0.001

Kiertiburanakul S, et al. PLoS One 2013;8:e62057.

Geographic and Temporal Trends of TDR

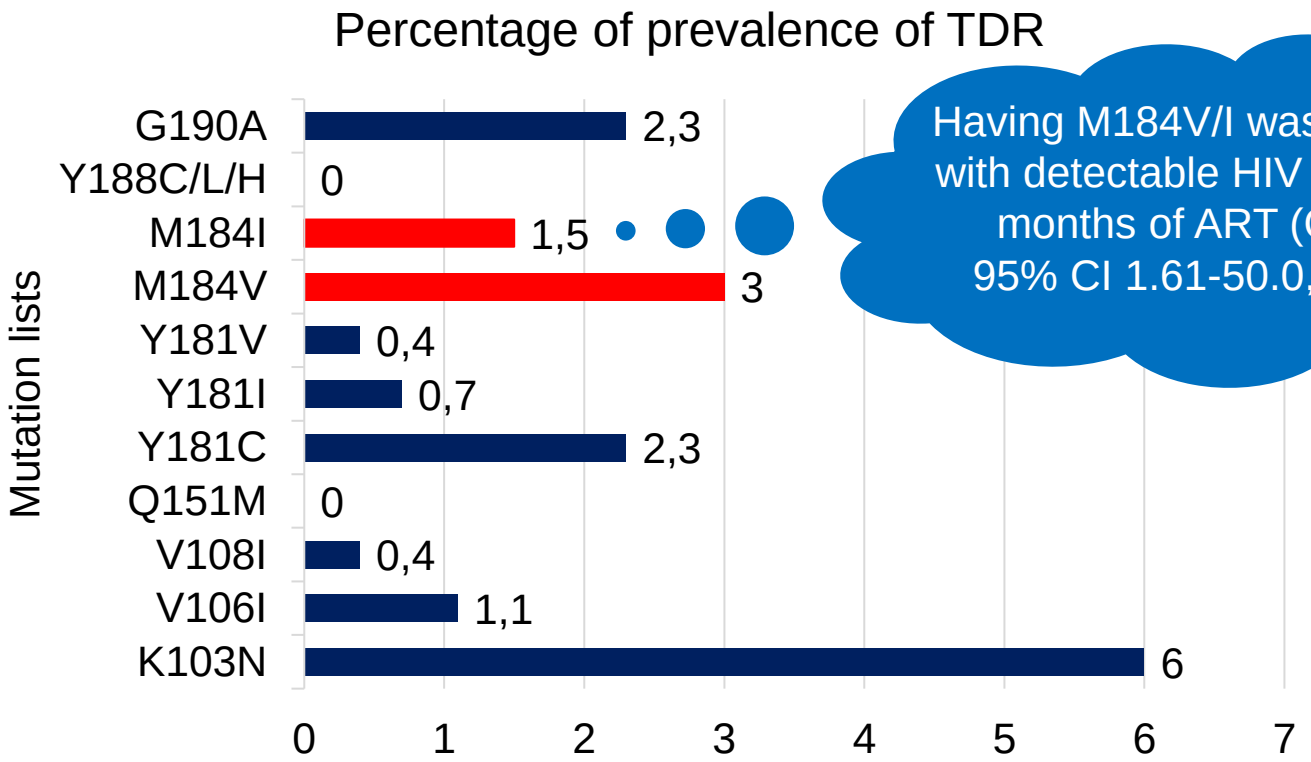
- Review GenBank submissions of HIV-1 RT sequences with or without PR
  - Published between 2000 and 2013
- Odds of NNRTI-associated TDR increased yearly in upper-income Asian countries (OR 1.33; 95% CI 1.12-1.55)

Characteristic	South/Southeast Asia	Upper Income Asia
Number of studies (number of individuals)	56 (6,522)	12 (4,950)
Number of countries; most common countries (number of studies)	7; CN (22), VN (12), IN (11)	5; KR (5), JP (4), TW (2)
Overall TDR	2.9% (1.8%-5.3%)	5.6% (3.5%-9.0%)
NRTI-associated TDR	1% (0%-2.4%)	3.5% (1.5%-5.0%)
NNRTI-associated TDR	0.8% (0%-2.1%)	1.1% (0.2%-1.6%)
PI-associated TDR	0.5% (0%-1.9%)	1.6% (0.6%–3.0%)

Rhee SY, Kiertiburanakul S, et al. PLoS Med 2015;12:e1001810.

Prevalence of TDR in Thailand

Overall prevalence of PDR: 7.9% (n=265, 2011-2014)

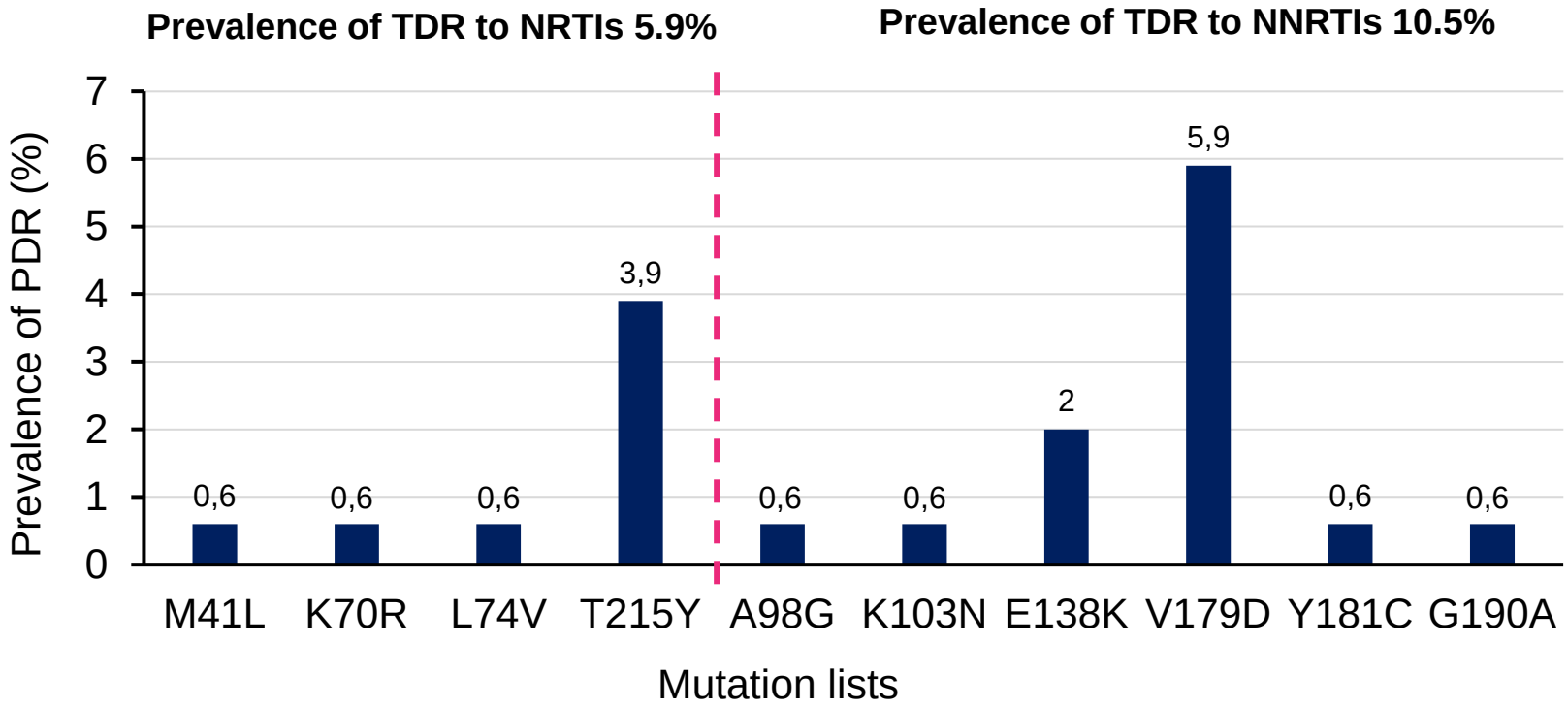


Having M184V/I was associated with detectable HIV RNA after 6 months of ART (OR 9.09; 95% CI 1.61-50.0, p=0.013)

Kiertiburanakul S, et al. PLoS One 2016;11:e0147945.

Prevalence of TDR in Thailand

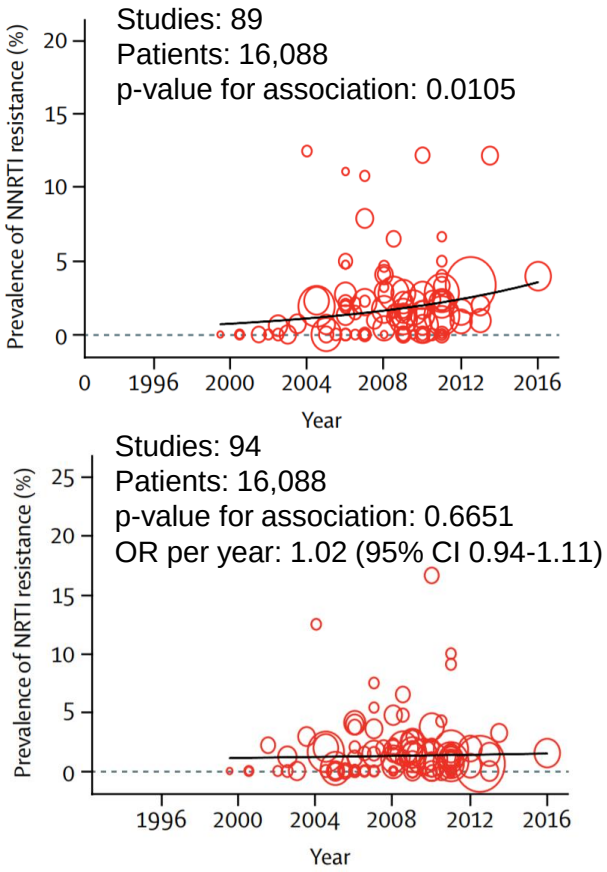
Overall prevalence of TDR 13.7% (n=153, 2016-2017)



Pinsai S, Kiertiburanakul S, et al. IDWeek 2018. Abstract 72663.

PDR in Asia: A Systematic Review and Meta-regression Analysis

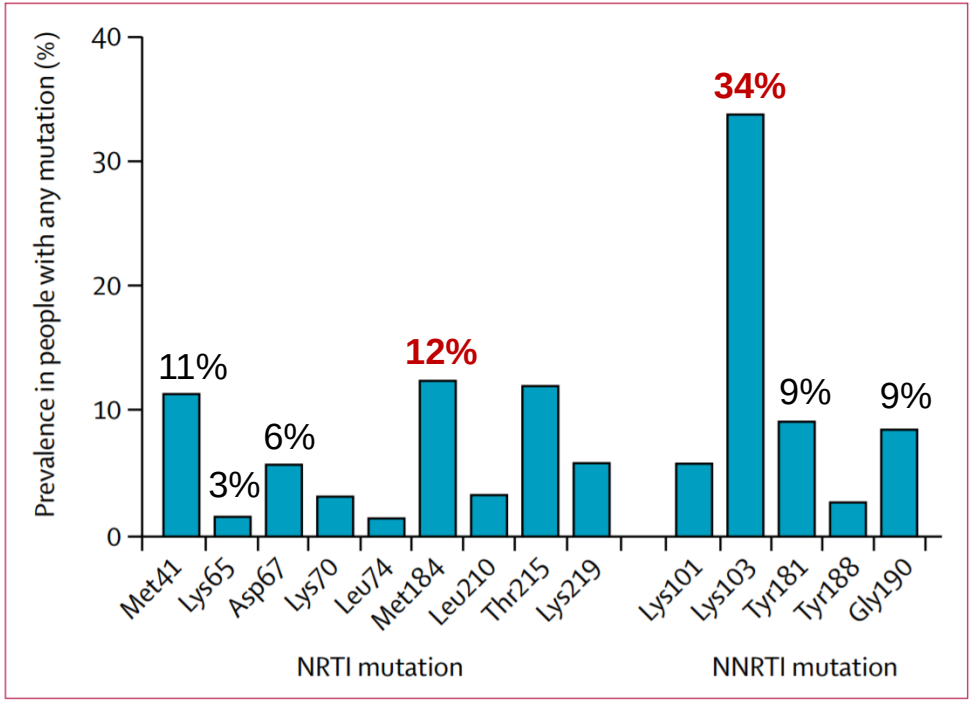
- 98 studies; 16,088 genotypes
- Sampling year 2009 (2006-2010)
- Yearly increases in the odds of PDR were 11% (95% CI 2%-20%)
- Compared prevalence of PDR among those reporting prior ARV exposure vs ART-naive individuals
  - Any resistance OR 6.35 (95% CI 2.15-18.76)
  - NNRTI resistance OR 8.05 (95% CI 4.25-15.26)
  - NRTI resistance OR 13.29 (95% CI 2.29-77.03)
- Association between MSM and overall HIVDR (p=0.047)



Gupta RK, et al. Lancet Infect Dis 2018;18:346-55.

PDR in Asia: A Systematic Review and Meta-regression Analysis

- 16,088 of 56,044 genotypes (28.7%) from Asia
- Most common mutation
  - NNRTI: Lys103Asn
  - NRTI: Met184Ile/Val
- Prevalence of DR to PIs was universally very low (<1%)

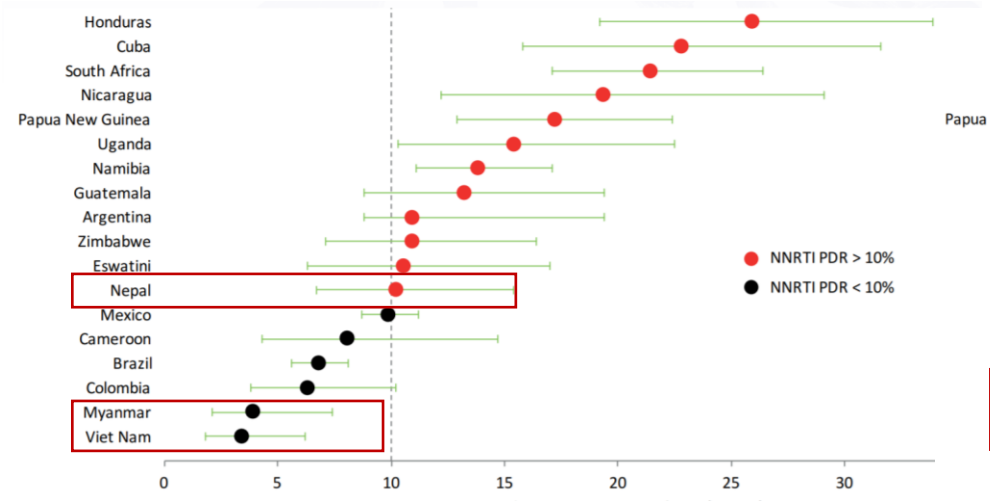


Gupta RK, et al. Lancet Infect Dis 2018;18:346-55.

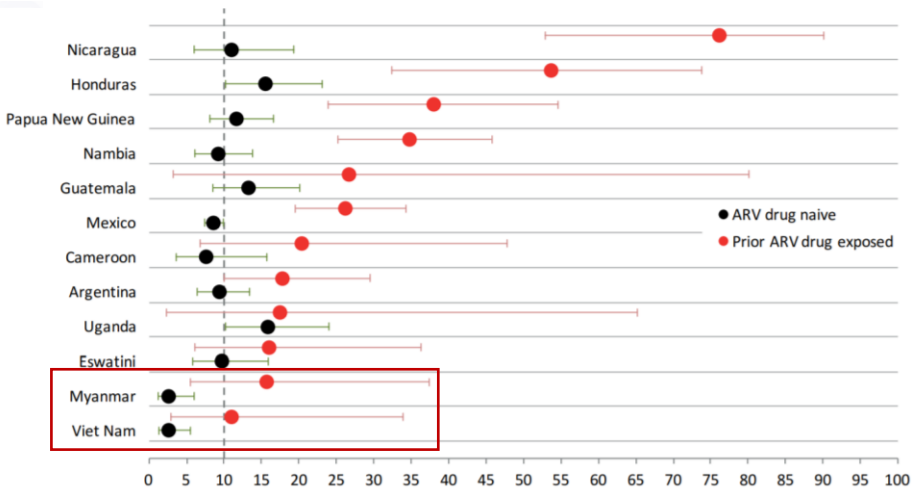
NNRTI (EFV and/or NVP) PDR Prevalence

World Health Organization

NNRTI PDR point prevalence between 2014 and 2018



NNRTI PDR (by previous ARV drug exposure) among first-line ART initiators



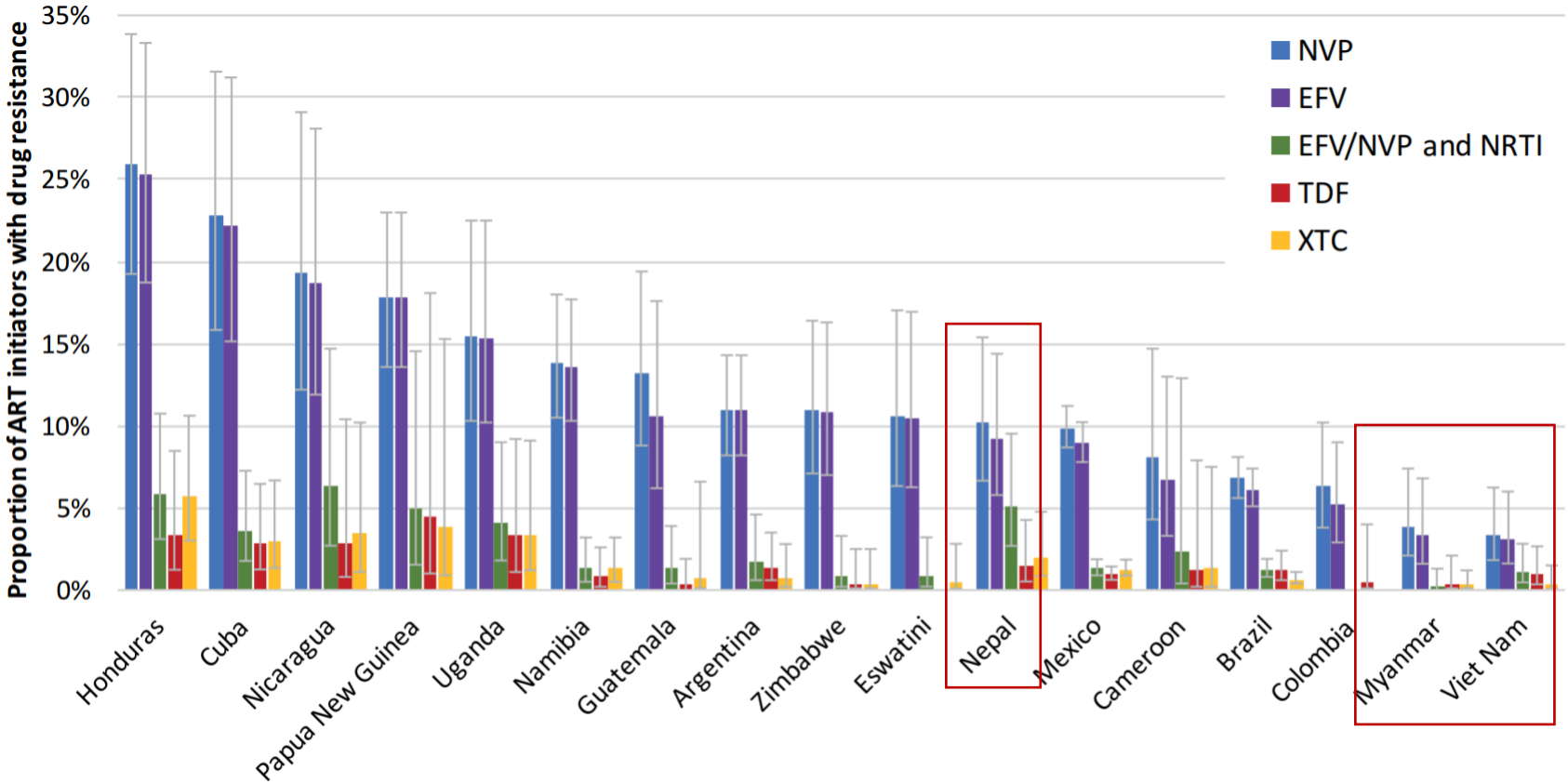
Prevalence of NNRTI PDR was nearly twice as high among women than men initiating ART: 11.8% (95%CI 9.4-14.8) vs 7.8% (95%CI 6.3-9.5), p=0.005

People reinitiating ART reporting previous exposure to ARV drugs had a significantly higher NNRTI PDR prevalence: 21.1% (95%CI 15.0-28.9) vs 7.8 (6.3-9.6), p ≤0.0001

https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

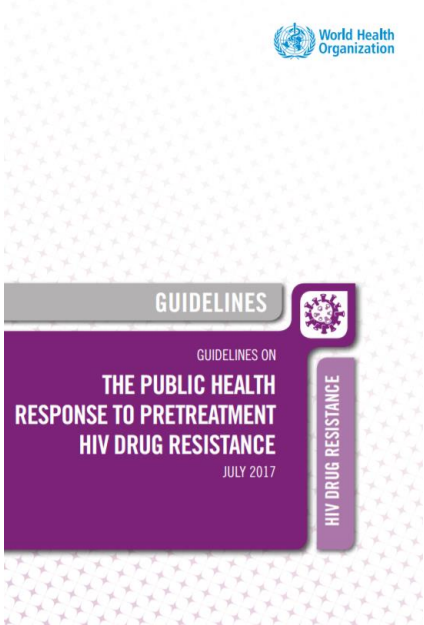
PDR to Drugs Used in First-line Regimens

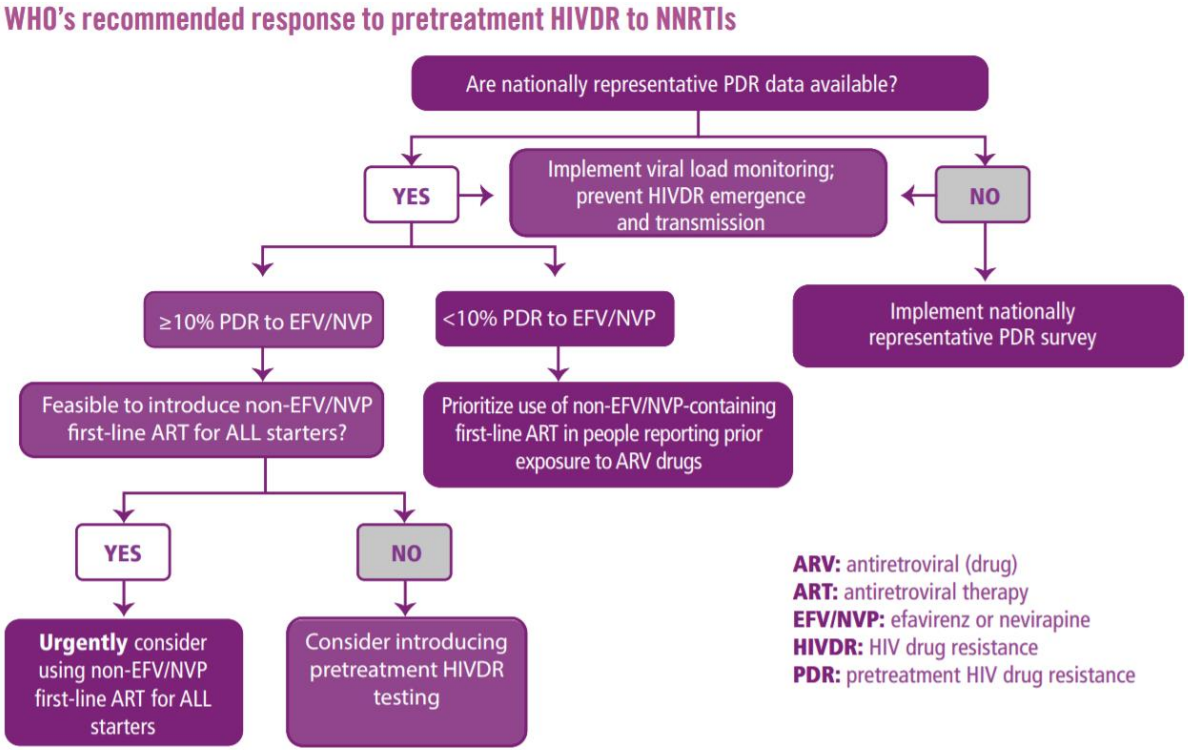
World Health Organization



https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

WHO's Recommended Response to PDR to NNRTIs

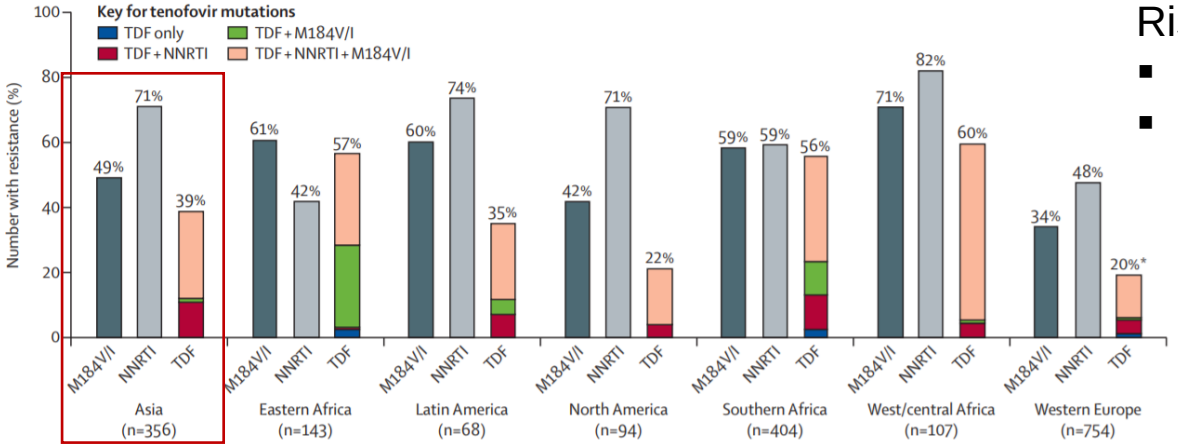




WHO Guidelines. July 2017.

Drug Resistance After Failure of WHO Recommended First-line Regimens: TenoRes

- A multicenter retrospective cohort study
  - Patients with virological failure with a first-line regimen containing TDF + 3TC/FTC + EFV/NVP
- 1,926 patients, 36 countries, 1998-2015
  - Asia (n=356), 4 countries, 5 studies

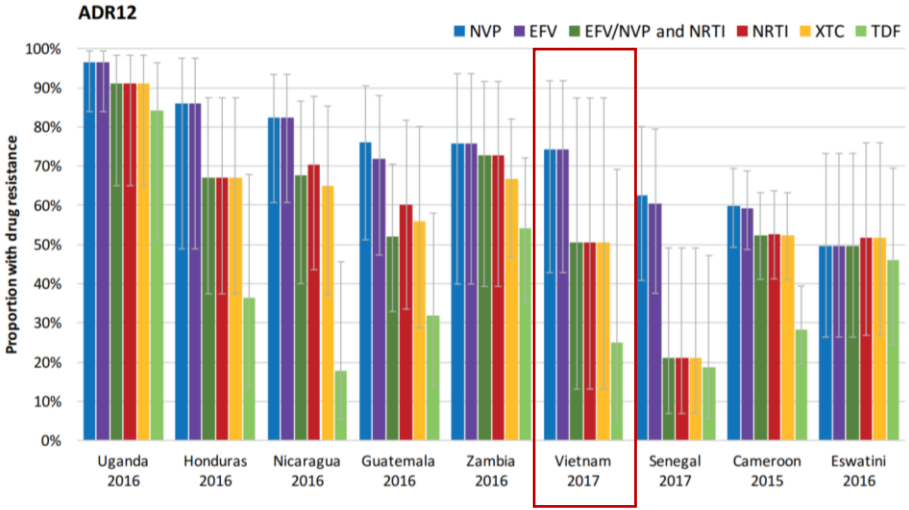


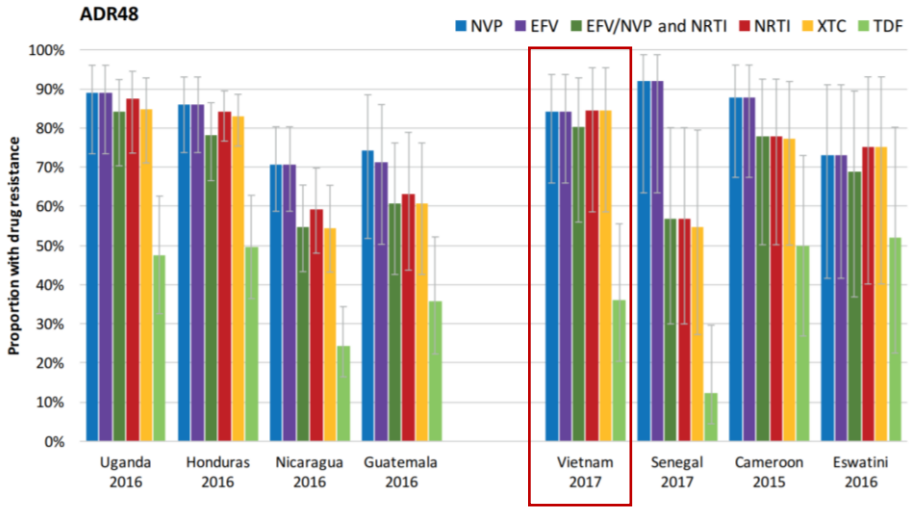
Risk factors for resistance to TDF:

- Pre-treatment CD4 count
- Co-administered ARVs

TenoRes Study Group. Lancet Infect Dis 2016;16:565-75.

Prevalence of Acquired HIV Drug Resistance





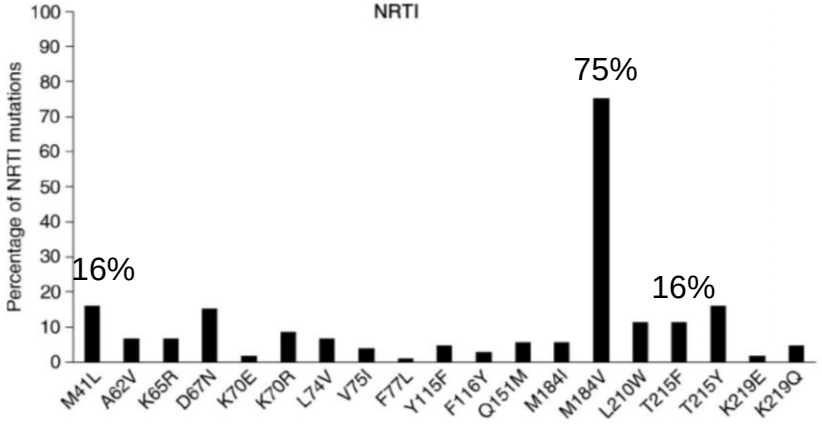
- Prevalence of any ADR among people receiving ART: 3% to 29%
- In Vietnam at 12 and 24 months after ART, respectively
  - 50% and 80% had resistance to EFV/NVP and NRTI
  - 25% and 35% had resistance to TDF

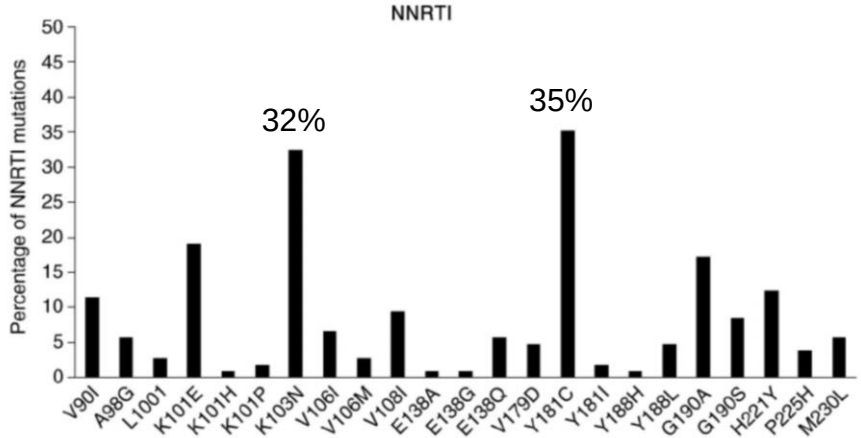
https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

HIVDR at First-line Antiretroviral Failure

Therapeutics Research • Education • AIDS Training
TREATASIA

- 10 sites in Thailand, Hong Kong, Indonesia, Malaysia and Philippines
- N=105: 92% harboring ≥1 RAMs, 37% with multi-NRTI RAMs





- Factors associated with multi-NRTI RAMs
  - CD4 ≤200 cells/μL at genotyping and ART duration >2 years
- Virological suppression was achieved in 85% at 12 months after switch to second-line ART

Jiamsakul A, et al. J Int AIDS Soc 2014;17:19053.

Conclusions: HIVDR in Asia

- PDR in some countries exceed 10%, especially NNRTI resistance
- Need to characterize the shift of sexual transmission within the MSM population and use of PrEP
- If HIVDR testing is not feasible at individuals' level, countries are encouraged to conduct national-level studies to determine the level of PDR and define further actions
- HIVDR after treatment failure is also a problem
- Actions to prevent HIVDR should be urgently implemented
  - Viral load testing coverage, retention in ART, minimize loss to follow-up, ARVs dispensing practices, timely management to individuals with HIVDR and transition from NNRTIs to more robust drug classes

Thank You for Your Attention