HIV Epidemic in Asia

Implications for HIV vaccine efficacy trials

Pediatric Infectious Disease Society of the Philippines
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Head of Clinical Development and Regulatory

International Vaccine Institute

Outlines

- HIV prevention and HIV vaccines
- RV144 next steps
- HIV epidemiological data in Asia
- Asia country-specific data in MSM
- Conclusions

Toward Ending the HIV/AIDS Pandemic

Non-vaccine prevention modalities

+

An effective HIV vaccine

AIDS-Free Generation

What have learned?

- **Proven methods of partially effective prevention**
  - Medical male circumcision
  - Pre-exposure prophylaxis (PrEP)
  - Treatment as Prevention

- **HIV therapy is amazingly effective**
  - Adherence is essential
  - All HIV positive people should be offered therapy as soon as diagnosed

- **New advances in prevention and treatment are needed to help end the epidemic**

- **To make further progress we must integrate biomedical with behavioral and social science research**

Promise and pitfalls of PrEP

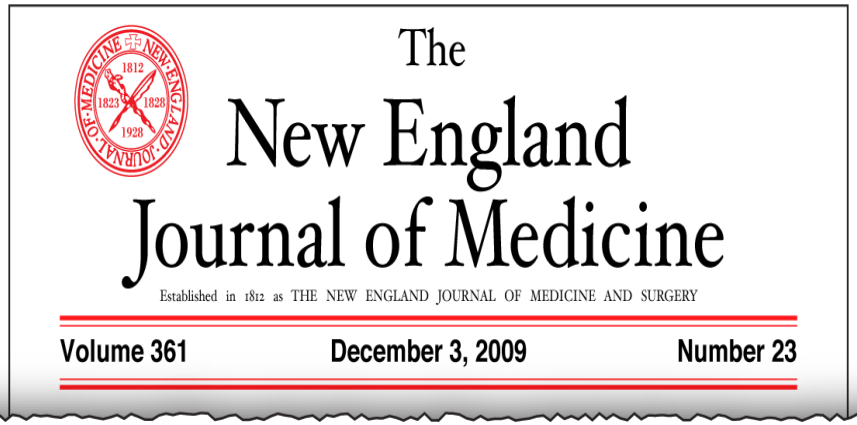
- PrEP, as defined as a daily pill containing FTC/TDF, is the U.S. FDA approved biomedical prevention modality PrEP
- PrEP is amazingly effective, **IF** the PrEP user adheres
- PrEP is not a magic bullet, must be delivered in the context of comprehensive prevention packages
- Need to address the access and adherence issues
- Next generation of PrEP agents beginning evaluation
  - Injectable (may circumvent issues linked to adherence)
  - Long-acting, easier to use, safer, more accessible due to lower cost

HIV-1 Vaccine Efficacy Trials

Vaccine regimen	Location/risk population	Overall vaccine efficacy	Increased risk of infection	Immune correlates of decreased vaccine efficacy[a]	Immune correlates of decreased HIV risk	Immune correlates of immune control post infection	Virus sieve	Host genetic correlates
VAX003 (Phase III) Protein/ Alum (CRF01_AE/Clade B Env)[52]	Thailand/injection drug users	No efficacy	No	No	No[52]	No	No[118,b]	n/d
VAX004 (Phase III) Protein/ Alum (Clade B Envs)[53]	USA/MSM/high risk women	No efficacy	No	No	Yes ADCVI, CD4 Blocking, Tier 1 NAb	n/d	No[160,161]	Yes Fcγ receptor IIIa genotype (VV genotype)[125]
STEP HVTN502 (Phase IIb) Ad5 Vector (Clade B Gag/Pol Nef)[54]	North/South America, Australia, Caribbean/MSM and High Risk Hetero-sexual Men and Women	No efficacy[c]	Yes	n/d	No	Yes T cell breadth/ magnitude, Lower VL	Yes[67]	Yes HLA alleles (B*27, B*57, B*58:01), Lower viral load
Phambili HVTN503 (Phase IIb) Ad5 Vector (Clade B Gag/Pol Nef)[57]	South Africa/Hetero-sexual Men and Women	No efficacy[d]	n/d	n/d	n/d	n/d	n/d	n/d
RV144 (Phase III) ALVAC vector (Clade B Gag/Pro + CRF01_ A/E Env) + Protein/ Alum (CRF01_AE/B Env)[50]	Thailand/Community	31% efficacy	No	Yes Plasma Env IgA[71,74]	Yes V1V2 IgG, Linear V2, V1V2 IgG3, Interactions (ADCC, Avidity, Tier 1 NAb, IgA), $CD4^+$ T cell Polyfunction, Cytokines[71-73,75,111]	n/d	Yes[85,162]	Yes HLA A*02 allele[126]: FcγRIIC -118 L allele[114]: DQB1*06[113]
HVTN505 (Phase IIb) DNA/ Ad5 (Clade A, B, C Env, *Clade BGag/Pol*)[60]	USA/MSM and TG, Ad5 seronegative, Circumcised	No efficacy[c]	No	No	Yes $CD8^+$ Env T-cell Polyfunction[e]	n/d	Yes[66]	n/d

Tomaras, Plotkin Immunological Reviews 2017, *275:245-261*

First Signal of Efficacy (31%) in an HIV Vaccine Clinical Trial – RV144



The New England Journal of Medicine

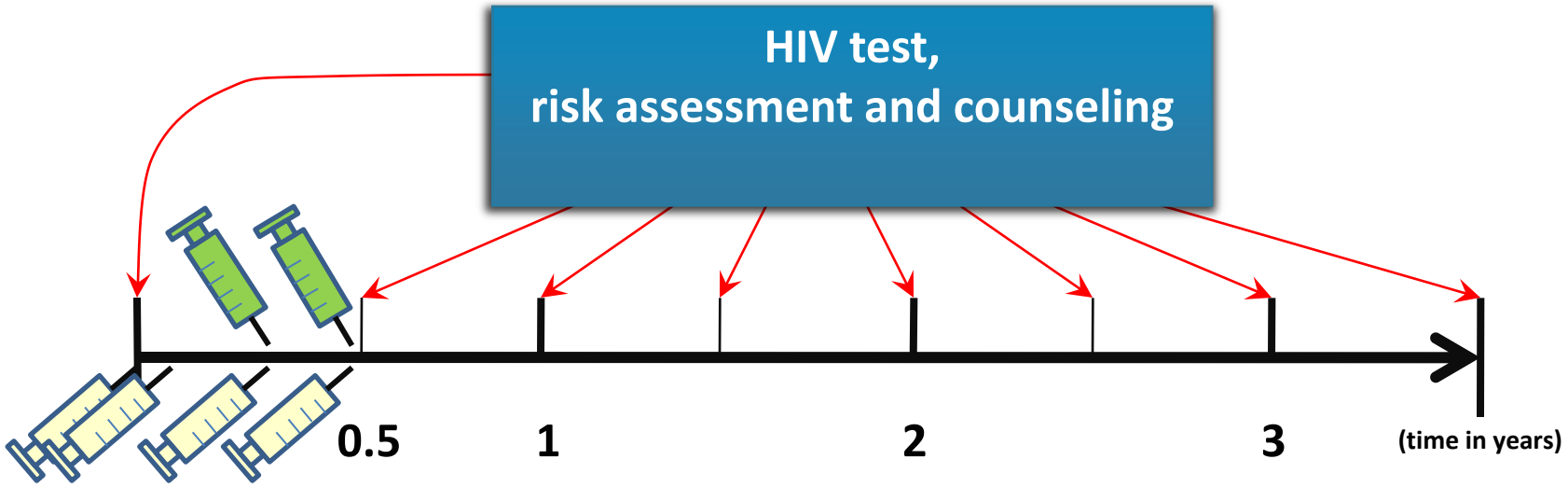
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 361 December 3, 2009 Number 23

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim, NL Michael, et al. for the MOPH–TAVEG Investigators

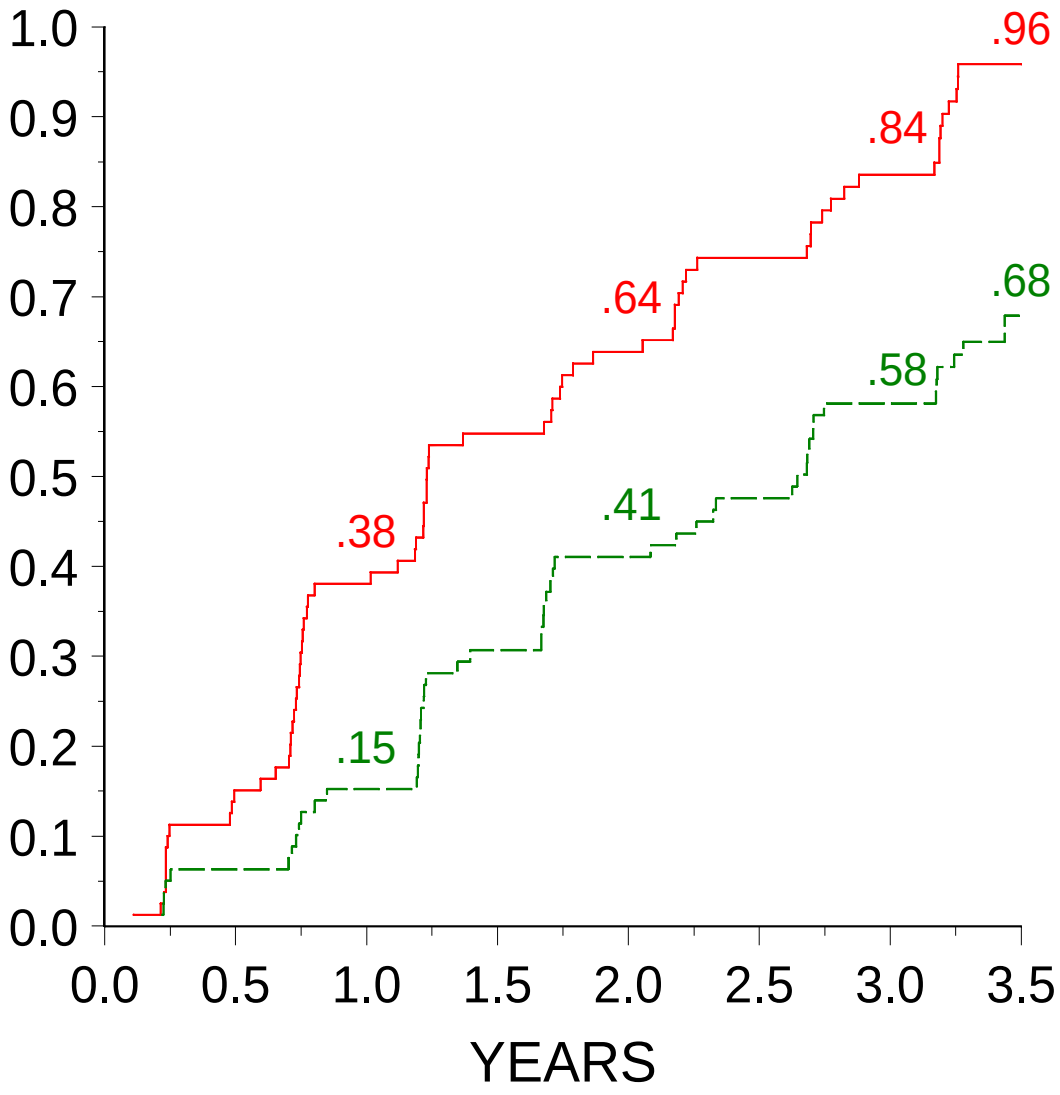
RV144 Vaccination and Follow-up Schedule



ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24

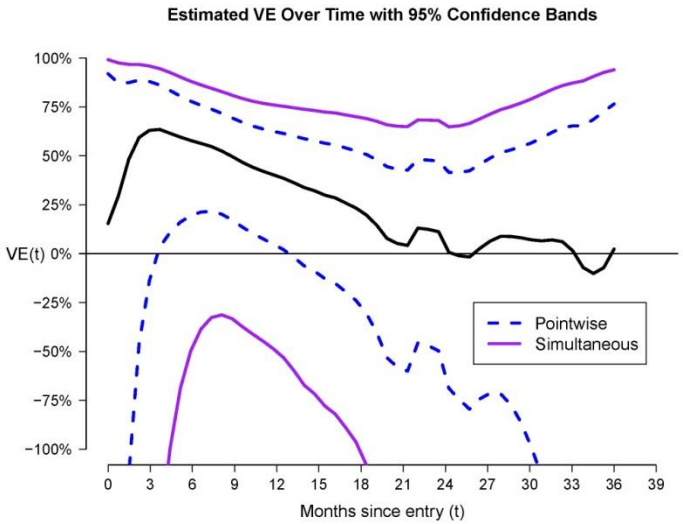
RV144
Acquisition Endpoint: Modified Intent-to-Treat (mITT)



Vaccine infections: 51
Placebo infections: 74
p = 0.04
Efficacy: 31.2%
95% CI (OBF): 1.1, 51.2

Thai Phase III HIV Vaccine Trial (RV144) Summary

Early (VE = 60%) effect wanes
(Robb et al, Lancet ID 2012)



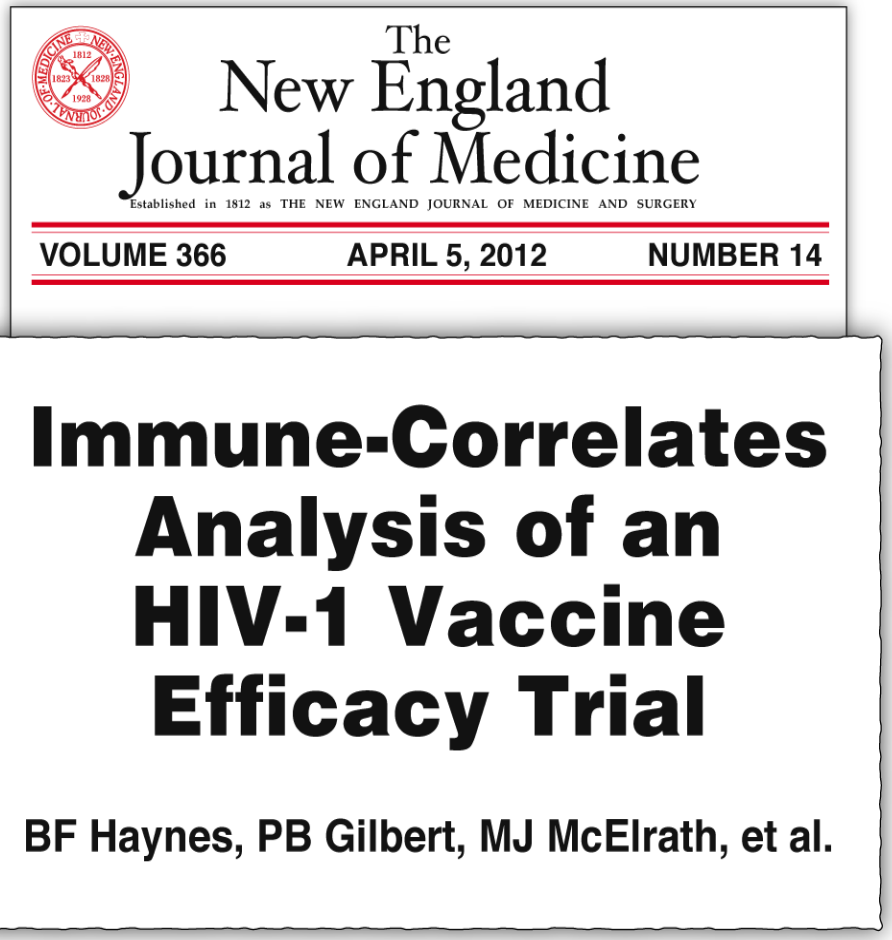
bAb decreases rapidly
Rerks-Ngarm et al, NEJM, 2009.

Antigen	Reciprocal GMT (Range)	
	2 weeks	24 weeks
B gp120	31207 (800-204800) (99% responders)	1758 (200-25600)* (99% responders)
E gp120	14558 (200-204800) (99% responders)	1000 (100-12800)* (99% responders)
B p24	205 (100-1600) (52% responders)	149 (100-200)* (18% responders)

P<0.0001 compared to placebo group - all Antigens
***: P<0.001 compared to 2 week time-point**

Dr. Mark de Souza

Immune Correlates Analysis from RV144



- IgG antibodies against the V1V2 region of the HIV-1 envelope protein associated with reduced infection
- Non-neutralizing antibodies mediate ADCC activity
- IgA antibodies correlated with increased infection

Immune Correlates of HIV Risk in RV144

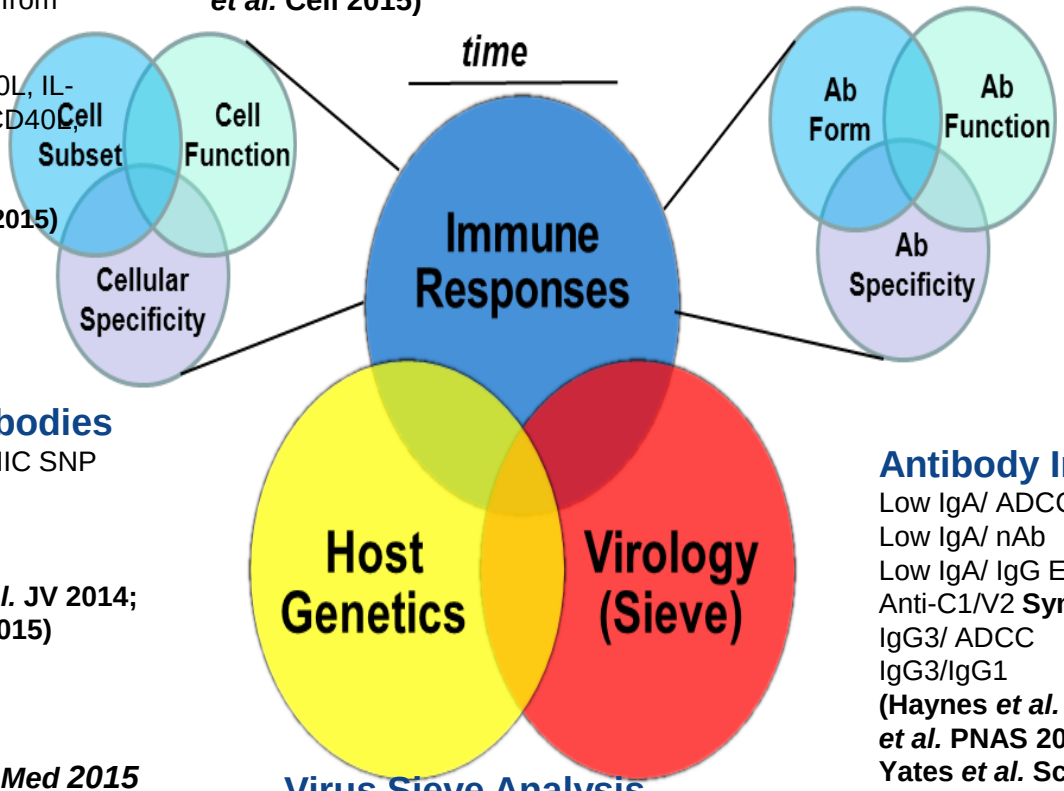
V2 Correlate

V1V2 IgG, V1V2 IgG Breadth, V2 Linear AE hotspot
V1V2 IgG3
Structure Function of V2 Mabs and Sieve Analysis
(Haynes *et al.* NEJM 2012; Liao *et al.* Immunity 2012 Gottardo *et al.* Plos One 2013; Zolla-Pazner *et al.* Plos One 2014; Yates, Tomaras *et al.* Sci. Trans. Med 2014; Chung *et al.* Cell 2015)

T Cell Correlate

Cytokine response (IL-10, IL-13) from Env stimulated PBMC

Polyfunctional CD4+ T cell (CD40L, IL-2, IL-4, IFN-γ and TNF-α) and (CD40L, IL-2 and IL-4)
**(Haynes *et al.* NEJM 2012;
Lin *et al.* Nature Biotechnology 2015)**



IgA Correlate

IgA Env Score
IgA A. OOMSA gp140 CF
IgA. A1 Congp140
IgA C1
IgA Non-Vaccine Strains
IgA/IgG ratio
(Haynes *et al.* NEJM 2012; Tomaras, Ferrari *et al.* PNAS 2013)

Host Genetics and Antibodies

IgG, IgG3, nAb, Avidity and FcγRIIC SNP
IgA/ HLA A*02 allele
IgA/ HLA II DQB1*06
IgG/ HLA II DPB1*13
(Li *et al.* JCI 2014; Gartland *et al.* JV 2014; Prentice *et al*. Sci.Trans Med. 2015)

Antibody Interactions

Low IgA/ ADCC (**Blocking** ADCC)
Low IgA/ nAb
Low IgA/ IgG Env Avidity
Anti-C1/V2 **Synergy**
IgG3/ ADCC
IgG3/IgG1
(Haynes *et al.* NEJM 2012; Tomaras, Ferrari *et al.* PNAS 2013; Pollara *et al* JVI 2014; Yates *et al.* Sci. Trans. Med 2014; Chung *et al.* Cell 2015)

Virus Sieve Analysis

V2 Sieve (and V2 mAbs dependent on 169K)
Genetic distance from Vaccine strain /IgG and IgG3 V1V2 correlates
(Rolland *et al.* Nature 2012; Liao *et al.* Immunity 2012; Gilbert *et al.* Statistics in Biosciences 2016)

Kim, Excler, Michael *Annu Rev Med 2015*
Tomaras, Haynes *Vaccines* 2014, *2(1),15-35.*
Tomaras, Plotkin Immunological Reviews 2017, *275:245-261*

Sreategies to amplify RV144 responses

MORE, BETTER, LONGER

- Strength
- Breadth
- Durability

HOW

- New proteins
- Potent adjuvants
- Additional boosts
- Longer intervals
- New vectors

South Africa Strategy

- The RV144 regimen tested in South Africa showed same safety and immunogenicity patterns (HVTN 100)

- A similar prime-boost regimen using ALVAC-HIV and gp120 subtype C formulated with MF59 (HVTN 107)
  - South Africa
  - Lower V1V2 antibody response than in RV144
  - Limited cross-reaction with other HIV-1 subtypes

- The subtype C regimen has now entered a Phase IIb trial (HVTN 702) in South Africa in heterosexual populations. However, a fraction of this population appears to also practice anal intercourse, a possible confounding factor for efficacy.

Public Health Impact and Regional Relevance

Precedent for vaccine efficacy

Focus on regional public health impact

RV144

THAILAND
High-risk MSM

Southern Africa
High-risk Heterosexual

Mutually reinforcing studies strengthen and support public health benefit in target populations and the translation of the platform globally.

Future amplification of global reach

Regional Strategy for Asia

- The initial follow-up clinical development strategy with the RV144 regimen was to conduct a Phase IIb in men having sex with men (MSM) in Thailand. However, for various reasons this strategy did not materialize.
- Clinical trial data suggest that that gp120 A244 Δ11 (CRF01_AE component of AIDSVAX B/E) has special characteristics unmatched by other envelope proteins.
- Another prime-boost strategy in clinical trial is using two viral vectors expressing HIV-1 mosaic antigens (Ad26 and Modified Vaccinia Ankara (MVA))
- This triggered a renewed interest of donors and Pharma industry in considering a Phase IIb trial in MSM in Asia where HIV incidence remains high in several countries.

GENERAL HIV EPIDEMIOLOGICAL PATTERNS IN ASIA

Epidemiological Patterns of HIV Infection

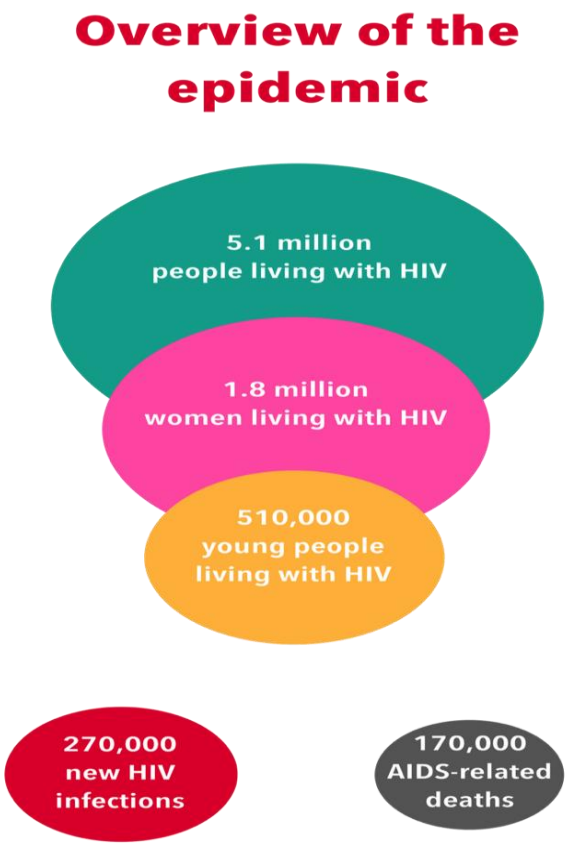
Africa

- Mostly **heterosexual** transmission
- Unveiled and expanding MSM transmission
- Mother-to-child transmission

Asia

- Heterosexual
- Mostly **MSM**, expanding
- IDU, decreasing

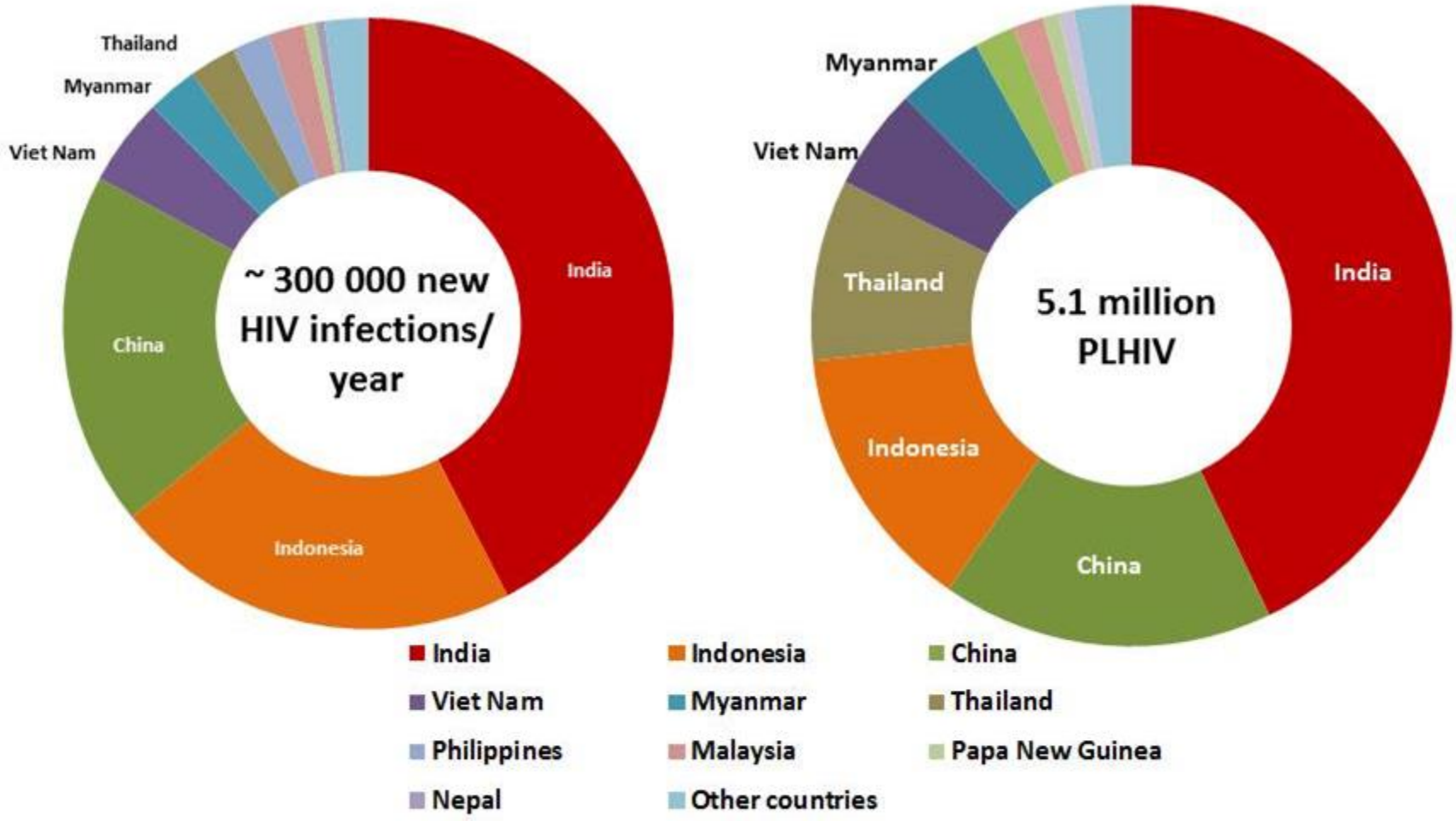
HIV and AIDS in Asia and the Pacific 2017



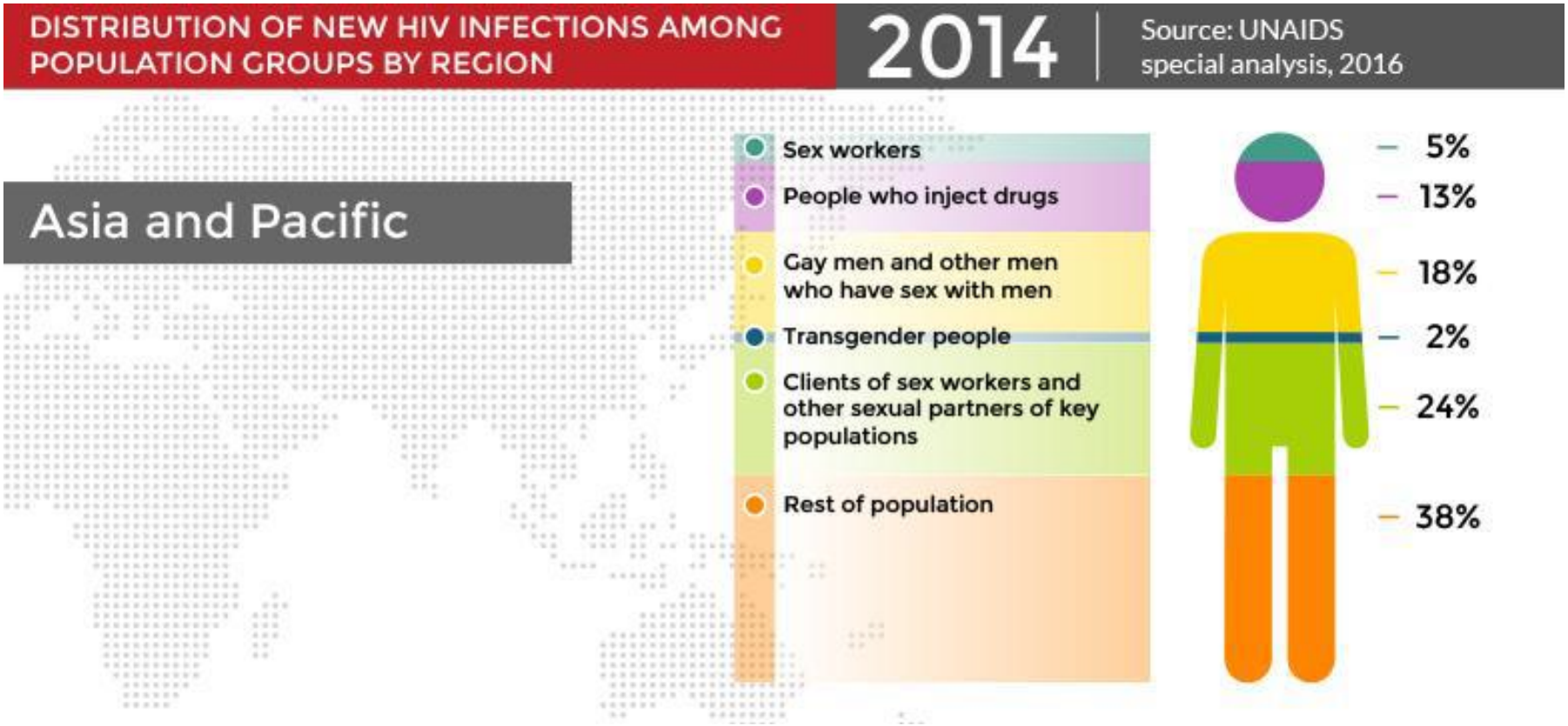
General HIV epidemiological data in Asia 1

- Globally, HIV incidence decreased by 35% since 2000 and AIDS-related deaths dropped by 42% since 2004. New HIV infections declined in some countries in the region (India, Myanmar, Thailand, Cambodia, and Viet Nam) but increased in others (Pakistan, Philippines, and Indonesia).

The majority of estimated new HIV infections (on the left) and people living with HIV (on the right) are in India, **China**, Indonesia, **Thailand and Viet Nam**/ Myanmar. HIV is concentrated among key populations: MSM, TGW, FSW and PWID.



New HIV infections in key affected populations



General HIV epidemiological data in Asia 2

- Epidemics in the region can be characterised as being **concentrated and growing in key populations, mainly among MSM, particularly young MSM, or shifting towards MSM as the main mode of transmission.**

- **HIV prevalence is 5-15 times higher among MSM** compared to the general population in South and South-East Asia. Infections among female sex workers (FSW) have slowed but remain important contributors to HIV transmission in the region.

- **Limited data are available about the HIV epidemics in transgender people (TG)**, estimated to be 9–9.5 million in the region, and small-scale research is mostly limited to TG women who have sex with men. In several cities HIV prevalence in this group was substantially higher than in general population of reproductive age, and even higher than in MSM.

General HIV epidemiological data in Asia 3

- While disproportionately affected by HIV, the key risk populations are mostly underserved by HIV prevention programs.

- **Throughout Asia, less than 60% of MSM and FSW know where to get tested for HIV or have received condoms through distribution programs** (level of condom use > 80% is considered to have an impact on HIV epidemic). Condom promotion programs are not reaching men at a sufficiently high level: rates of condom use at last sex among MSM are half of the rate in FSW (two thirds among male sex workers (MSW)).

- Studies in MSM have provided evidence of the safety and efficacy of daily tenofovir, alone or in combination with emtricitabine for HIV pre-exposure prophylaxis (PrEP). No studies were conducted to evaluate PrEP efficacy specifically in TG people, but TG participants of the iPrEx trial were protected from HIV if they had taken PrEP.

HIV-1 molecular epidemiology patterns

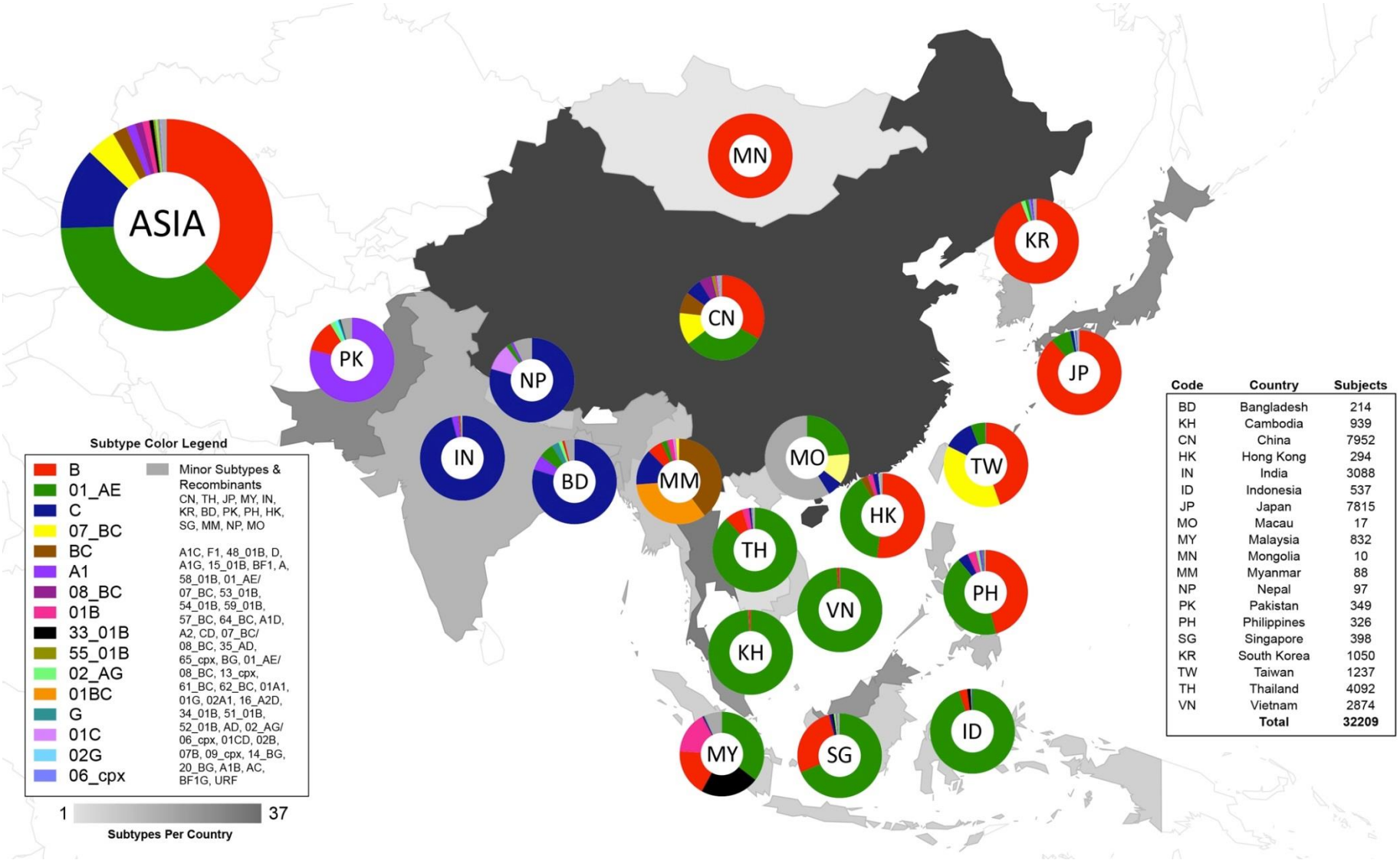
- CRF01_AE remains predominant in South East Asia with a growing presence in China and an increasing number of recombinant forms containing CRF01_AE, B and C subtypes. **CRF01_AE dominates** in Thailand, Cambodia, Indonesia, Laos, Myanmar, and Viet Nam.

- In Malaysia, co-circulation of CRF01_AE and subtype B has resulted in the emergence of CRF33_01B in approximately 20% of HIV-1 infected individuals, now also described in Indonesia.

- Co-circulation of CRF01_AE and subtype B in the Philippines

Phanuphak N, et al. ARHR 2015

HIV-1 molecular epidemiology in Asia (2000-2014)

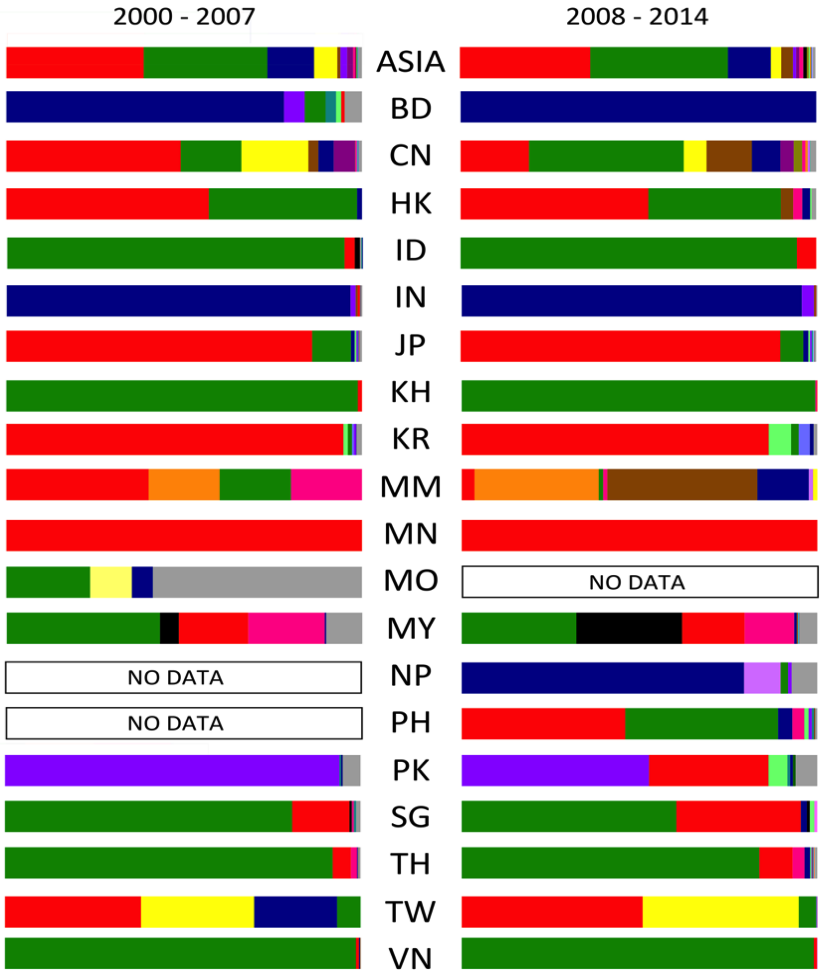


Code	Country	Subjects
BD	Bangladesh	214
KH	Cambodia	939
CN	China	7952
HK	Hong Kong	294
IN	India	3088
ID	Indonesia	537
JP	Japan	7815
MO	Macau	17
MY	Malaysia	832
MN	Mongolia	10
MM	Myanmar	88
NP	Nepal	97
PK	Pakistan	349
PH	Philippines	326
SG	Singapore	398
KR	South Korea	1050
TW	Taiwan	1237
TH	Thailand	4092
VN	Vietnam	2874
	Total	**32209**

David Chang, Sodsai Tovanabutra, Gustavi Kijak, Jean-Louis Excler, Jerome Kim, MHRP

Geographical and temporal distribution of circulating HIV-1 subtypes by country: 2000-2007 and 2008-2014

Phanuphak et al.
ARHR 2015



Subtype Color Legend

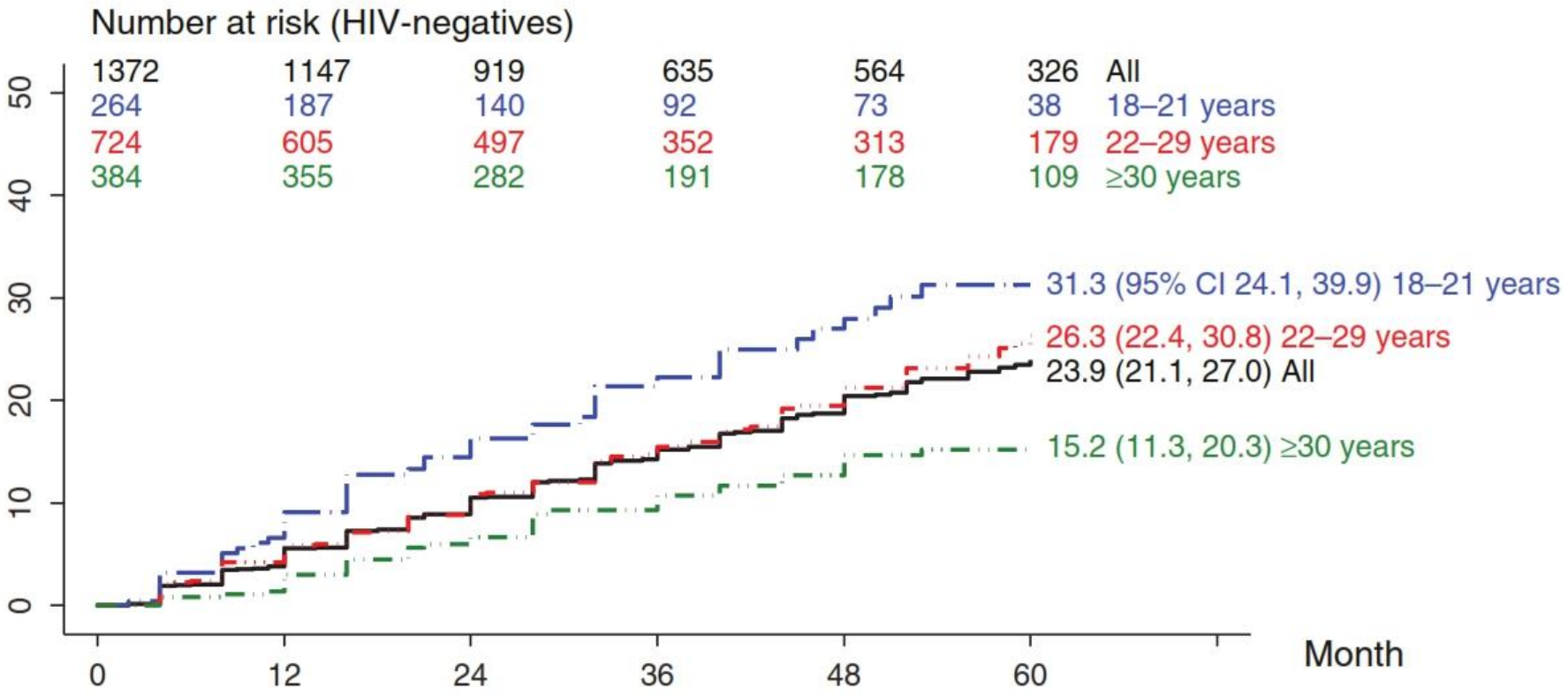
- B
- 01_AE
- C
- 07_BC
- BC
- A1
- 08_BC
- 01B
- 33_01B
- 55_01B
- 02_AG
- 01BC
- G
- 01C
- 02G
- 06_cpx
- Minor Subtypes & Recombinants: CN, TH, JP, MY, IN, KR, BD, PK, PH, HK, SG, MM, NP, MO

A1C, F1, 48_01B, D, A1G, 15_01B, BF1, A, 58_01B, 01_AE/07_BC, 53_01B, 54_01B, 59_01B, 57_BC, 64_BC, A1D, A2, CD, 07_BC/08_BC, 35_AD, 65_cpx, BG, 01_AE/08_BC, 13_cpx, 61_BC, 62_BC, 01A1, 01G, 02A1, 16_A2D, 34_01B, 51_01B, 52_01B, AD, 02_AG/06_cpx, 01CD, 02B, 07B, 09_cpx, 14_BG, 20_BG, A1B, AC, BF1G, URF

Code	Country	Subjects 2000-2007	Subjects 2008-2014
BD	Bangladesh	205	9
CN	China	3712	4240
HK	Hong Kong	72	222
ID	Indonesia	482	55
IN	India	1344	1744
JP	Japan	2399	5416
KH	Cambodia	415	524
KR	South Korea	955	95
MM	Myanmar	5	83
MN	Mongolia	7	3
MO	Macau	17	0
MY	Malaysia	246	586
NP	Nepal	0	97
PH	Philippines	0	326
PK	Pakistan	219	130
SG	Singapore	161	237
TH	Thailand	2163	1929
TW	Taiwan	622	615
VN	Vietnam	684	2190
ASIA	**Total**	**13708**	**18501**

THAILAND

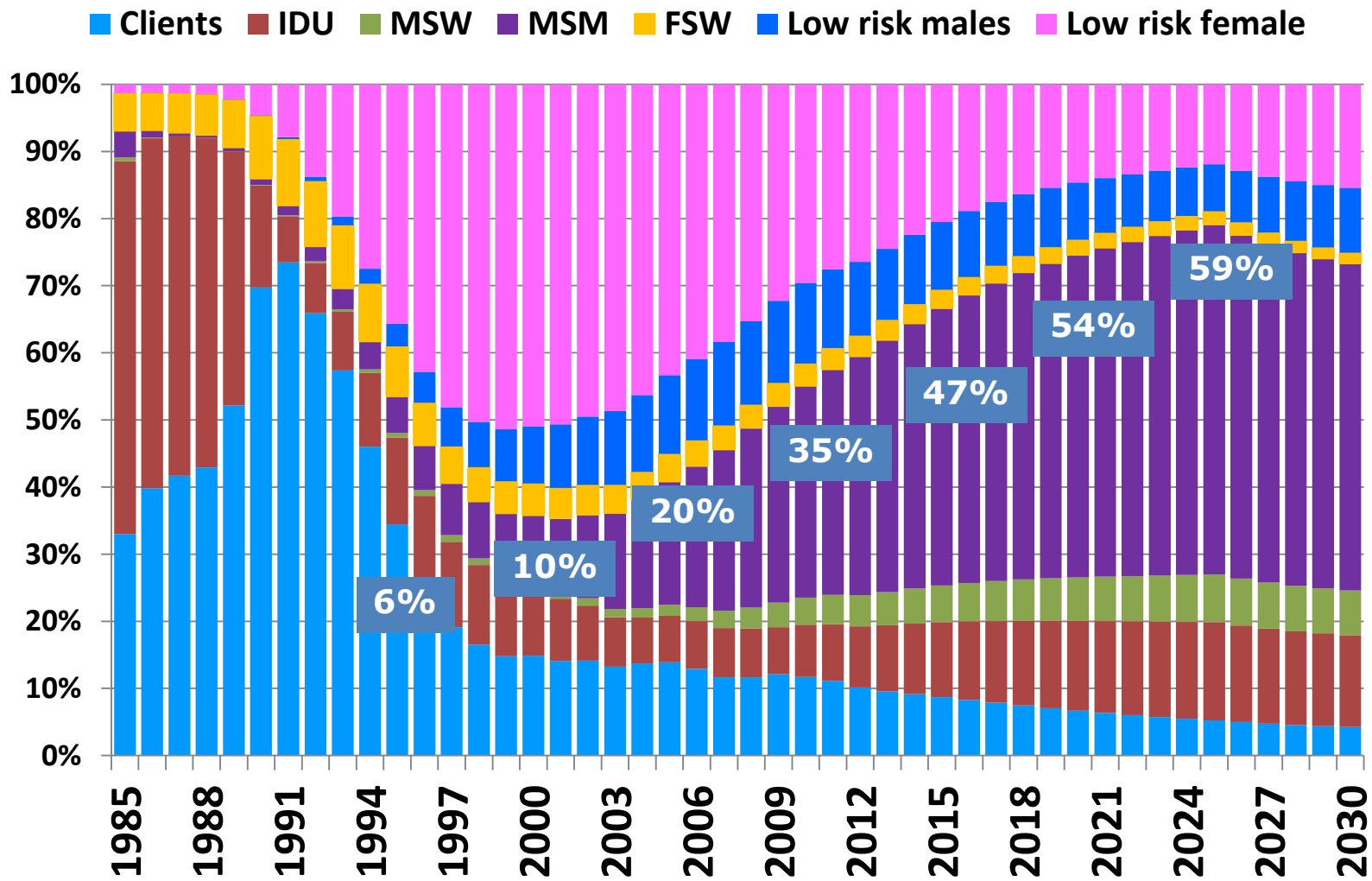
“Explosive HIV epidemic”among MSM in Bangkok



60-month cumulative HIV-incidence among MSM in Bangkok, 2006–2012.
MSM=men who have sex with men

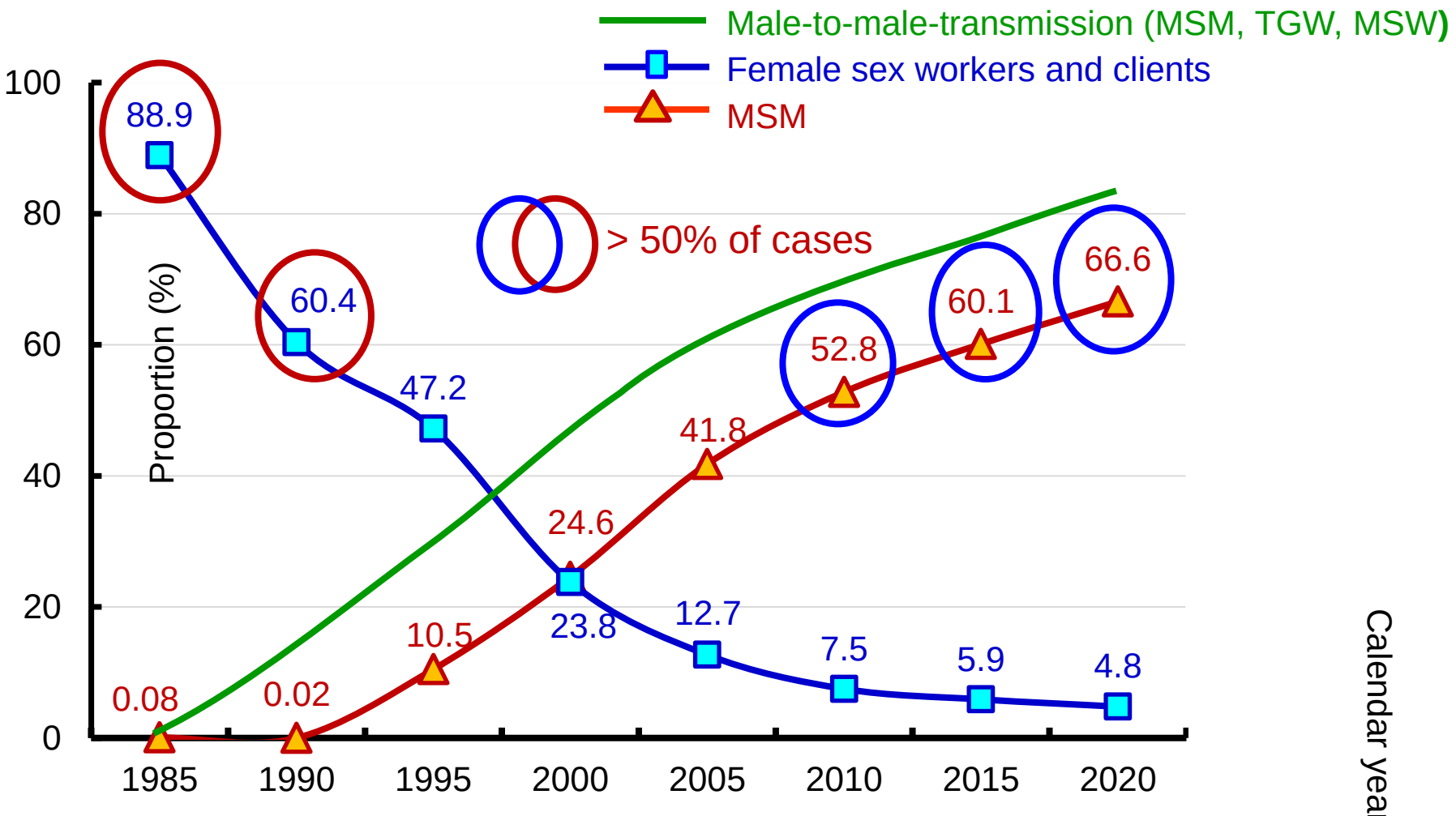
van Griensven F, et al. AIDS, 2013 Mar 13;27(5):825-32.

Increasing proportion of new HIV infections in Thailand from MSM over time



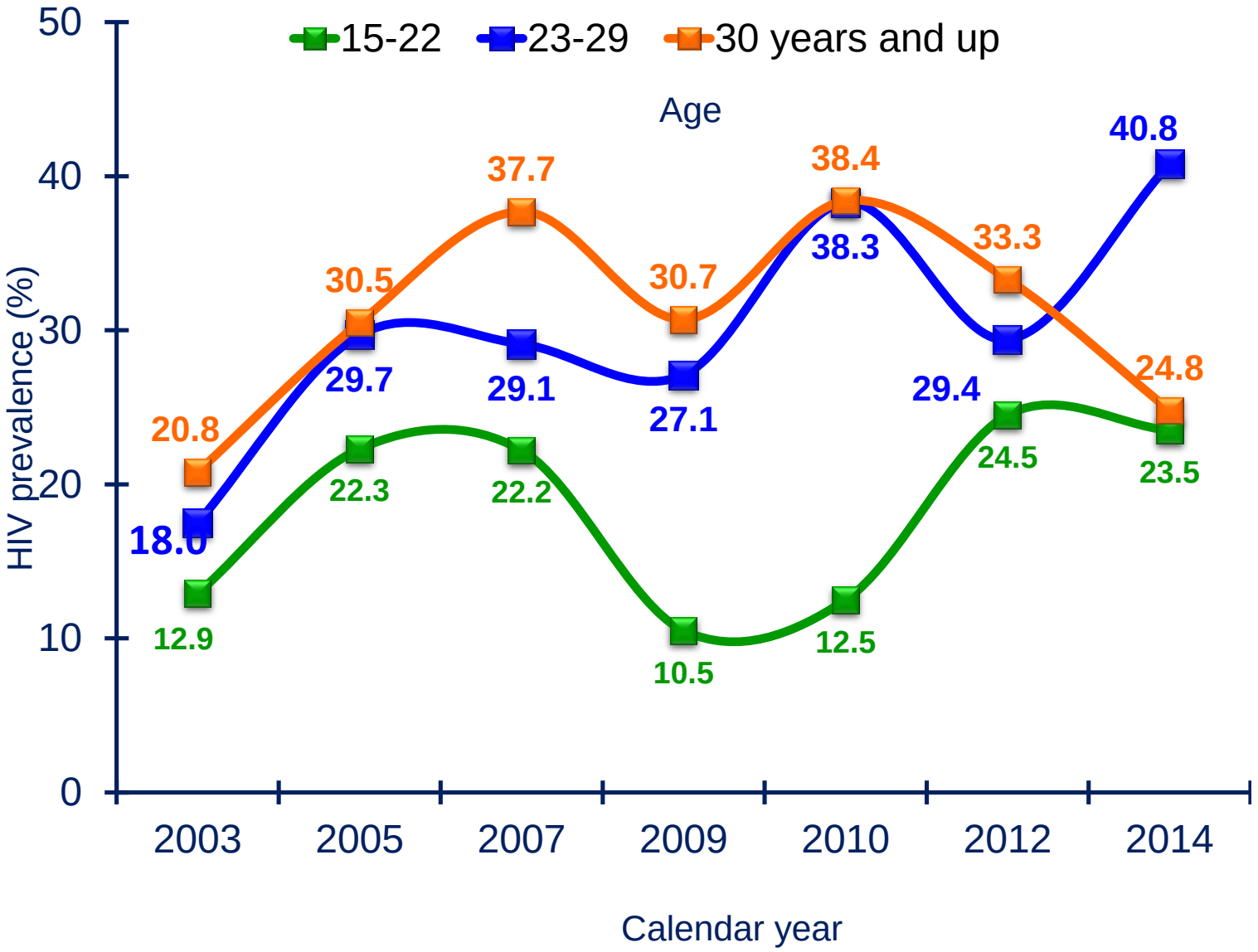
AIDS Epidemic Model Projections for HIV/AIDS in Thailand: 2010-2030.

Estimated proportion of annual new HIV infections in MSM, from male-to-male sex and FSW and clients, Bangkok, 1985-2020



Source: Projections of HIV/AIDS in the Bangkok Metropolitan Administration area , 2014

HIV prevalence in MSM, IBBS, Bangkok, 2003-2014 by age group



HIV incidence among MSM in Thailand

- In a recent cohort study conducted in Pattaya, HIV incidence was **8.2 and 4.28 per 100 PY** among MSM and TGW sex workers, respectively.
- An ongoing 'Test and Treat' cohort among MSM and TGW in Bangkok, Ubon Ratchathani, Lampang and Mahasarakam found a preliminary HIV incidence of **6.12-7.05/100 PY** between November 2012 and September 2014 (Nittaya Phanuphak, unpublished data).

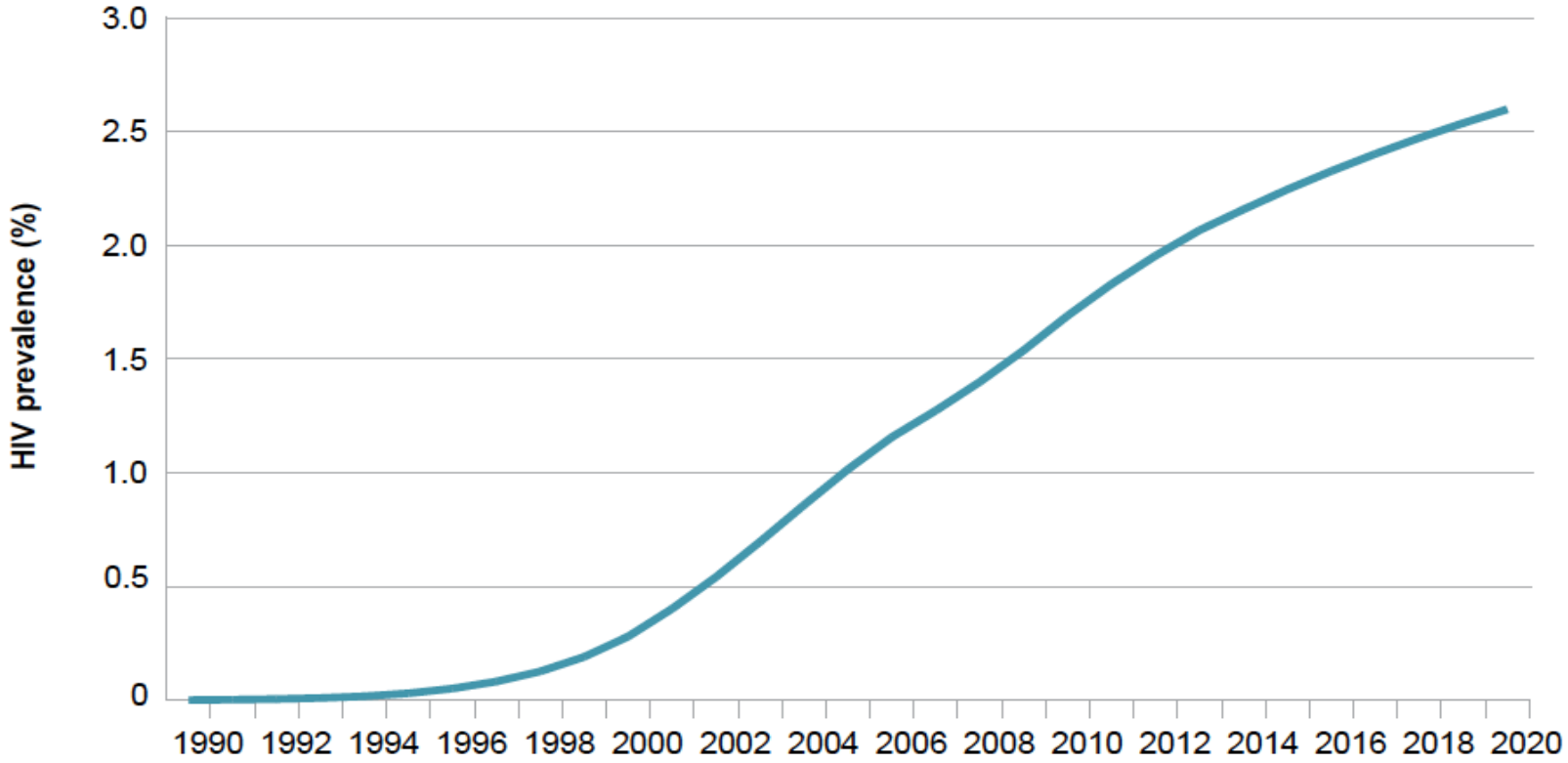
Robb M, et al. NEJM 2016; 374:2120-2130.

Thailand Working Group on HIV/AIDS Projection. AIDS Epidemic Model - Projection for HIV/AIDS in Thailand. 2010-2030. Summary Report Bangkok: Ministry of Public Health, 2012.

VIETNAM

Estimated HIV prevalence in MSM - Vietnam 1990-2020

Fig. 7: Estimated HIV prevalence among MSM in Viet Nam, 1990–2020: national prevalence



Source: Asian Epidemic Model, baseline scenario, VAAC, 2014

HIV epidemic in MSM in Vietnam 2

- The population of MSM in HCMC was estimated to be 37,238, which is 1.35% of the male population.
  - *Safarnejad J Urban Health 2017*

- The overall HIV prevalence trend among MSM in HCMC increased between 2005 and 2013.

- **In 2013, 12% of MSM in HCMC were infected with HIV, and estimated to 14.2% in 2014.**
  - *Joint Review of the Health Sector Response to HIV in Viet Nam 2014, WHO WPRO*

- Overall MSM population not clearly known in Hanoi (likely in the range of 10,000).

- **HIV prevalence in Hanoi was 6.4% (late 2014).**
  - *Vu Front. Public Health 2016*
  - *Nguyen AIDS Behav 2016*

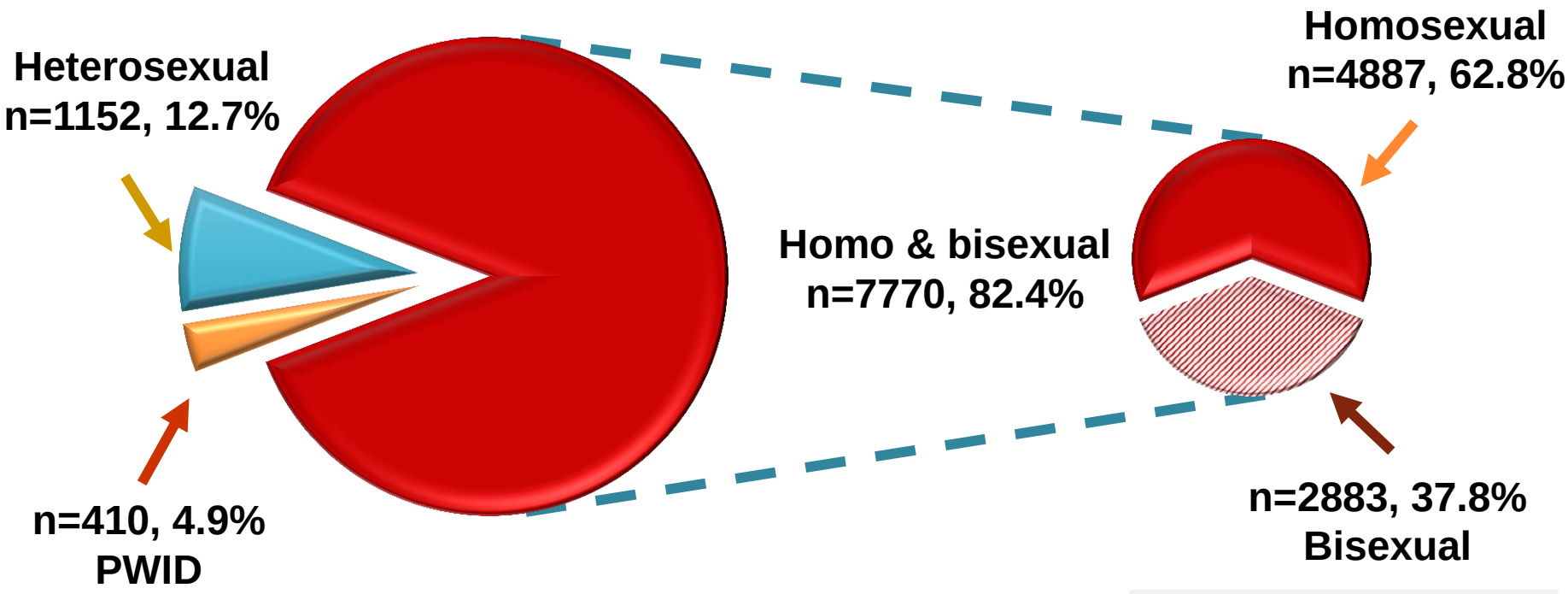
- **No HIV incidence data available in MSM in Vietnam**

PHILIPPINES

Majority of new HIV infections are among MSM 2015, Philippines

Cumulative reported number of newly diagnosed HIV infections in youth (15 - 24 years), 1984-2016[1], the Philippines, by transmission category

[1]up to and including June 2016



Source: Department of Health, Manila, the Philippines, 2016

LoveYourself (LYS) Foundation, Metro Manila

HIV incidence among MSM and transgender re-testers at Clinic in Manila (2012-2015)

6 per 100 person years

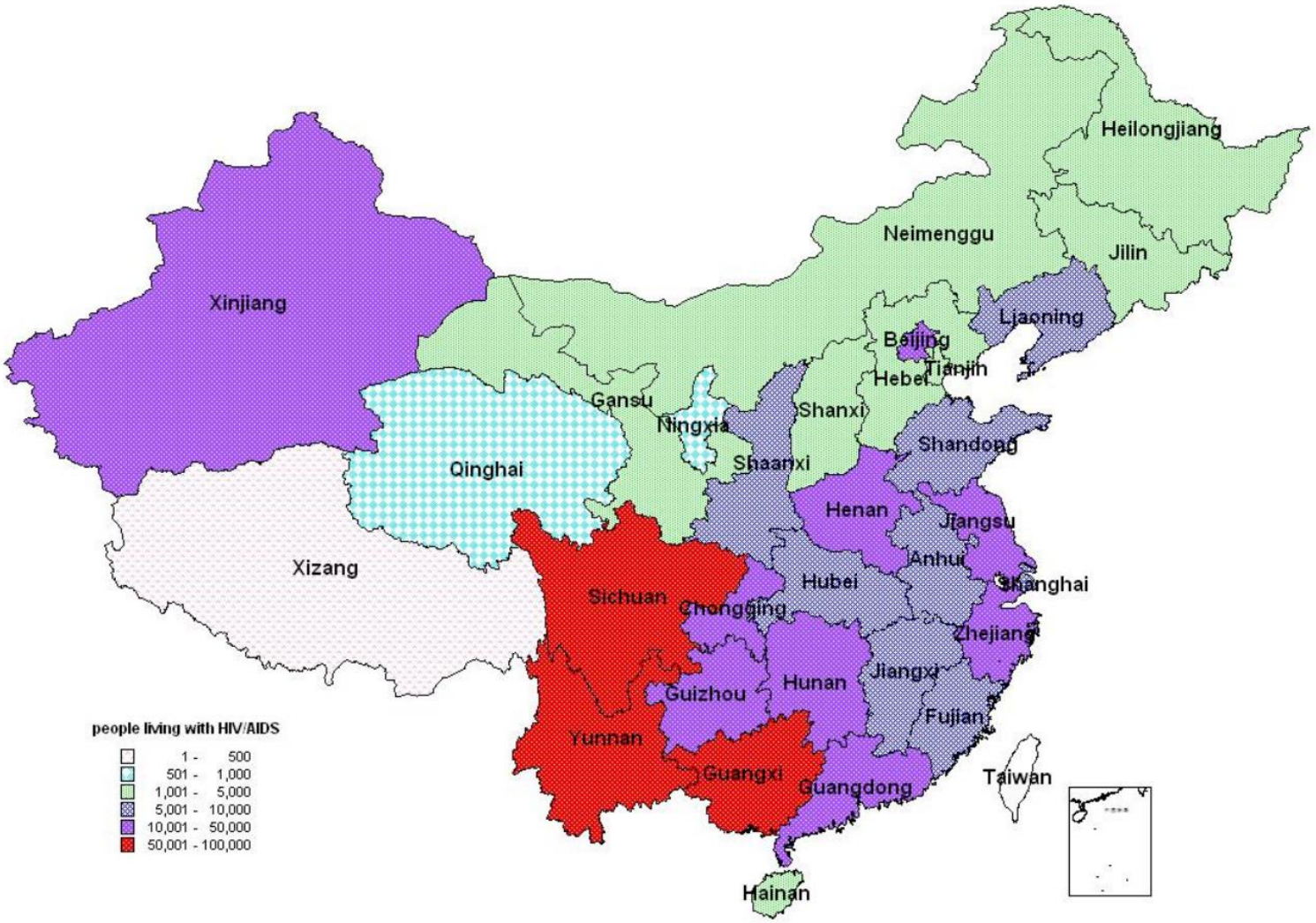
9 per 100 person years among ≤ 21 year old

3 per 100 person years among > 21 year old

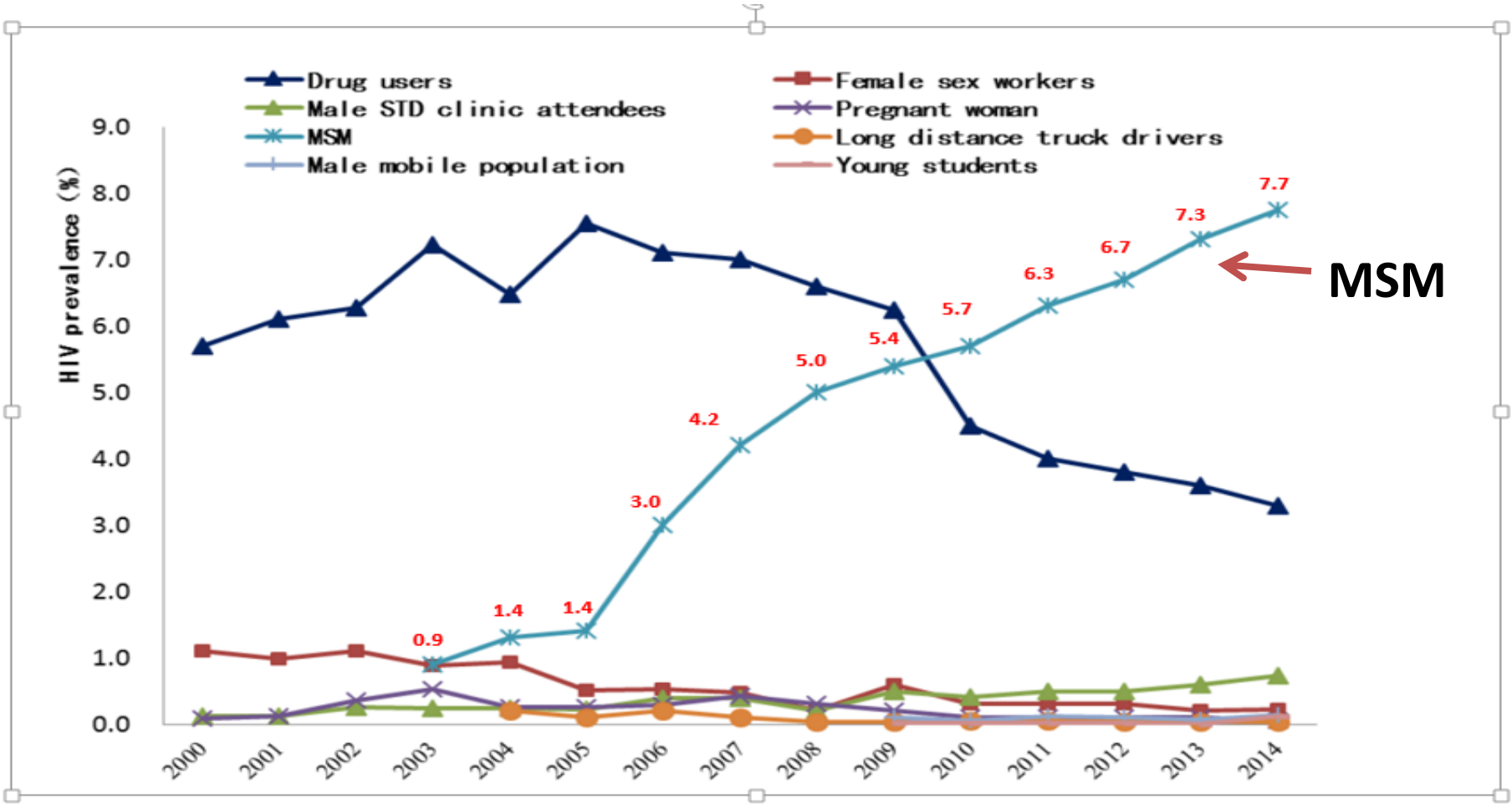
Source: Clinic Anglo

PEOPLE'S REPUBLIC OF CHINA

Total number of reported persons living with HIV by province, China, 2014



HIV prevalence among 8 populations in China's HIV Sentinel Surveillance Surveys (2000-2014)



China UNAIDS HIV Annual Report 2014

Estimating HIV incidence in China

- Several HIV incidence studies have been conducted in MSM across Chinese cities.

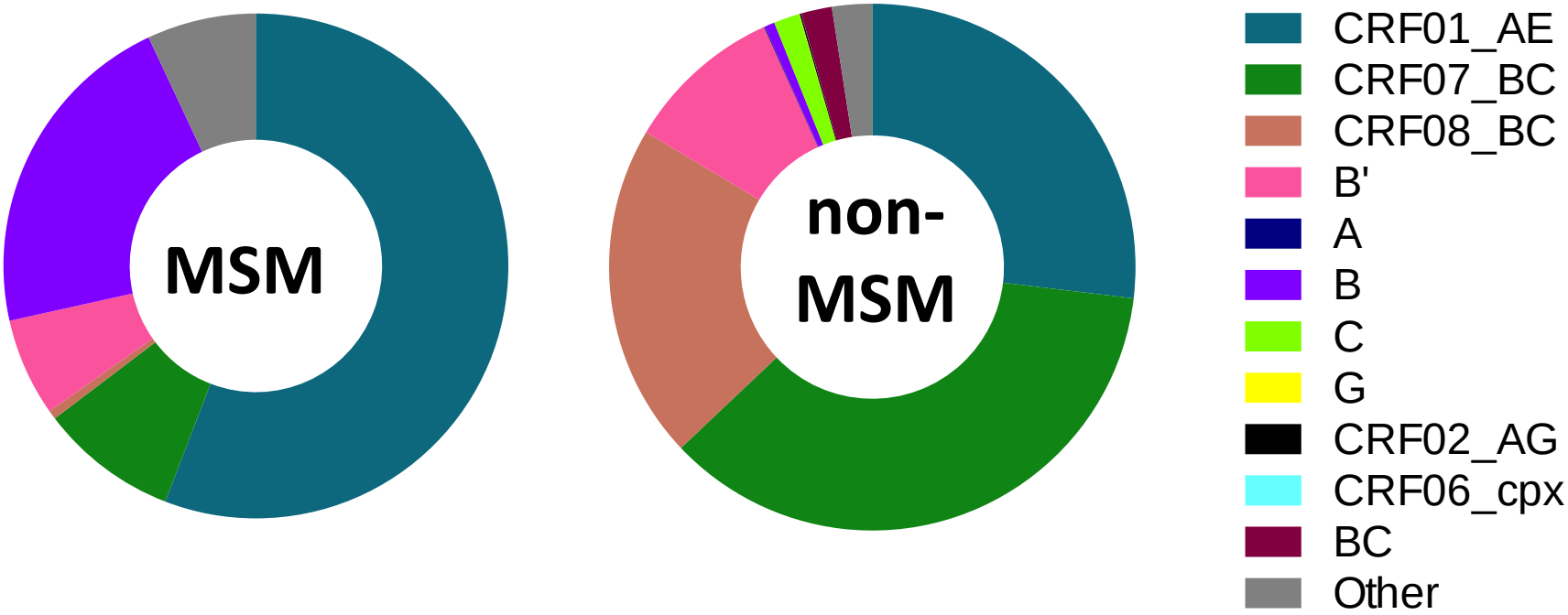
Cui Y et al. JIAS 2016, 19:20609

Li D, et al. PLoS ONE 2016; 11(1): e0147422

Xu et al. Infectious Diseases of Poverty (2016) 5:82

- The most recent data (some unpublished and under embargo) indicate **very high HIV incidence in MSM in the range of 7-10/100 PY.**

Estimated HIV subtype distribution MSM vs non-MSM in China



Adapted by David Chang, Sodsai Tovanabutra, Gustavi Kijak, Jean-Louis Excler, Jerome Kim, MHRP 2015 from: *He, et al. A Comprehensive Mapping of HIV-1 Genotypes in Various Risk Groups and Regions across China Based on Nationwide Molecular Epidemiologic Survey. Plos One. 2012*.

CONCLUSIONS 1

- Considerable progress has been achieved in reducing the HIV/AIDS epidemic in Asia over the past decade
- More remains to be done in particular in key populations such as MSM and TGW where the highest prevalence and incidence are found
- Combination of behavioral and biomedical prevention modalities is the only way to go.

CONCLUSIONS 2

- RV144 pave the way to new efficacy trials in both Africa and Asia
- Improvements of the RV144 regimen are on going in Thailand and South Africa
- New vaccine approaches such as Ad26 and MVA mosaic constructs will soon enter into efficacy trial in Thailand, EU, Americas and Africa
- **Unique opportunity to test a vaccine among mostly CRF01_AE-infected MSM and TGW populations in Asia**

CONCLUSIONS 3

- **Continue focusing efforts in Thailand:**
  - ✓ Possible challenges:
    - WHO consolidated guidelines on HIV testing, treatment and prevention call for an expanded access to PrEP worldwide and have provided guidance on PrEP implementation in the region
    - Several PrEP studies on going and scaled up intervention planned
    - PrEP will likely needed to be implemented in the context of HIV vaccine efficacy trials
    - HIV incidence may decline as a consequence and compromise the feasibility of an efficacy trial (insufficient endpoints)

Invest efforts and funds in other Asian countries

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