HIV Epidemic in Asia: Implications for HIV Vaccine and Other Prevention Trials

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Abstract

An overall decrease of HIV prevalence is now observed in several key Asian countries due to effective prevention programs. The decrease in HIV prevalence and incidence may further improve with the scale-up of combination prevention interventions. The implementation of future prevention trials then faces important challenges. The opportunity to identify heterosexual populations at high risk such as female sex workers may rapidly wane. With unabating HIV epidemics among men who have sex with men (MSM) and transgender (TG) populations, an effective vaccine would likely be the only option to turn the epidemic. It is more likely that efficacy trials will occur among MSM and TG because their higher HIV incidence permits smaller and less costly trials. The constantly evolving patterns of HIV-1 diversity in the region suggest close monitoring of the molecular HIV epidemic in potential target populations for HIV vaccine efficacy trials. CRF01_AE remains predominant in southeast Asian countries and MSM populations in China. This relatively steady pattern is conducive to regional efficacy trials, and as efficacy warrants, to regional licensure. While vaccines inducing nonneutralizing antibodies have promise against HIV acquisition, vaccines designed to induce broadly neutralizing antibodies and cell-mediated immune responses of greater breadth and depth in the mucosal compartments should be considered for testing in MSM and TG. The rationale and design of efficacy trials of combination prevention modalities such as HIV vaccine and preexposure prophylaxis (PrEP) remain hypothetical, require high adherence to PrEP, are more costly, and present new regulatory challenges. The prioritization of prevention interventions should be driven by the HIV epidemic and decided by the country-specific health and regulatory authorities. Modeling the impact and cost-benefit may help this decision process.

Introduction

IN 2012, THERE WERE 4.3 BILLION PEOPLE living in Asia, about 60% of the global population, 2.9 billion people in the economically productive age band between 15 and 64 years and 750 million young women and men aged 15 to 24 years.¹ The Asia Pacific region is economically dynamic.¹ Trade and tourism in Asia are thriving and are expected to expand over the next decade. The further development of roads, communication, and other major infrastructure promises to intensify the

interchange between China, India, and southeast Asia (SEA), and the emergence of Myanmar after long isolation will generate new economic activity. These elements may influence the evolution of the HIV epidemic patterns, HIV prevention programs, and, consequently, the feasibility and design of prevention trials in Asia. Despite its early prominence in the epidemic (Thailand and Cambodia), HIV-1 prevalence remains under 1% of the population in most countries.

The HIV epidemic in Asia remains concentrated in nature, affecting mostly higher risk subgroups, including men who

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have sex with men (MSM) and transgender women (TG), people who inject drugs (PWID), and female sex workers (FSW).² These epidemiological features have considerable implications for the implementation of prevention intervention trials and further implementation of prevention policies in the region.

The data presented in this review were retrieved from several sources: 180 regional or country-specific articles listed on PubMed, 10 UNAIDS and WHO reports, and 7 country-specific reports from national health authorities. The HIV molecular epidemiology data were retrieved from published articles and from our original work. Specifically, the partial and full genome of HIV-1 sequences obtained from the Los Alamos National Laboratory HIV database (www.hiv.lanl.gov), from the U.S. Military HIV Research Program (MHRP), and from HIV-1 subtyping data from MHRP (unpublished data) were used to compile circulating subtype distributions by country from 2000 to 2007 and from 2008 to 2014. Although part of the Russian Federation is geographically located in Asia, most of the HIV epidemic is located in the eastern part of Russia.³ We therefore did not include the Russian Federation in our review.

We describe the current features of the HIV epidemic in high-risk populations of countries already engaged in prevention trials including HIV vaccine, preexposure prophylaxis (PrEP), and treatment as prevention (TasP) and discuss the implications for prevention trial design and implementation.

HIV Epidemic in Asia

Regional patterns and most at-risk populations

According to UNAIDS, at the end of 2013, in Asia and the Pacific there were 4.8 million people living with HIV, with China, India, Indonesia, Myanmar, Thailand, and Vietnam accounting for more than 90% of the people living with HIV in the region. Low national prevalence masks higher HIV prevalence and incidence rates in certain key populations with mixed pictures between and within countries. Figure 1

shows the percentage of people living with HIV and of new HIV infections by country.³ New infections declined by 58% in Myanmar, by 46% in Thailand, by 43% in Vietnam, and by 19% in India. New epidemics are emerging in the Philippines where, between 2001 and 2012, new HIV infections more than doubled, and in Indonesia with a 48% increase. The number of AIDS-related deaths in Asia fell by 37% between 2005 and 2013. For infected persons with access to antiretroviral therapy (ART), HIV infection has become a manageable chronic condition. Under the 2010 World Health Organization (WHO) guidelines, the overall treatment coverage is approximately 30% in Asia and the Pacific.⁴

New HIV infections are concentrated among key populations at higher risk, more difficult to reach due to stigma and legal barriers. These key populations include PWID, FSW and their clients, MSM, and TG,^{5–8} and are mostly concentrated in major cities. In a recent meta-analysis of the HIV mode of transmission model (based on published data and UNAIDS reports from generalized and concentrated epidemics from 29 countries between 2003 and 2012), the estimated annual fraction of new HIV infections (FNI) among FSW remained low, with little variability by region and epidemic type despite variability in sexual behavior. In India and Thailand for example, the FNI among FSW was 2% and 4%, respectively. In contrast, the FNI among MSM was higher than in FSW, varied with countries, and increased with MSM population size.⁹

In a systematic review in low- and middle-income countries, the burden of HIV infection was disproportionately high among FSW in Asia and the Pacific, with a 29-fold increase in odds of living with HIV compared with women of reproductive age.¹⁰ As observed with other key populations, some geographic areas exhibit a higher HIV prevalence, e.g., in 2012, 22.5% in Hanoi,¹⁰ 25% in Jayawijaya, Indonesia,¹¹ and 15% in Patheingyi, Myanmar.¹² In 2007, street-based FSW in Thailand had an especially high HIV prevalence (22.7%), 10 times higher than among venue-based FSW (2.5%).¹³ Table 1 shows available HIV prevalence and incidence figures among key populations in selected countries.

FIG. 1. HIV epidemic in Asia and the Pacific, 2013. Proportion by country of people living with HIV and of new HIV infections. UNAIDS Gap Report 2014.³

TABLE 1. HIV PREVALENCE AND INCIDENCE IN KEY POPULATIONS IN THAILAND, CHINA, MYANMAR, AND INDIA

	HIV prevalence			HIV incidence			References
	MSM	TG	PWID	FSW	MSM	TG	FSW
Thailand							
Nationwide	5.5–28.3% (2003–2007)	12.5% (2000–2011)		11.9% (2007–2011)	8.2% (2006–2008)		6,8,10,75
Bangkok	30.8% (2007)		23.6% (2013)	22.7% street based; 2.5% venue based (2007)	6.4% (2005) 1.95% (2008–2009)	0.68% (2010)	6,13,143,175
	21.3% (2011)				7.7% (2007) 5.9% (2011) 2.7% (60% were MSM) 2006–2007		7
Chiang Mai	16.9% (2007)	9.30% (2011)	10.9% (2013)		8.2% (2011)		23
Bangkok, Ubon, Ratchathani, Lampang, Mahasarakam Pattaya	16.5–6.9% in bisexuals (2011)				6.3% (2014)		75,175 75
					7.4% (2014)	5% (2014)	Nittaya Phanuphak, unpublished data
Myanmar							
Nationwide	7.8% (2011)			18.4% (2008) 9.4% (2012)			12,77
Yangon	5% (2011)						
Mandalay	9% (2011)						
Patheingyi				15% (2012)			10,12
China							
Nationwide	7.4% (2.3–11.4) (2009)						84
	6% (2010)		9% (2010)	0.36% (2010)			81
	4.9–18% (2008–2009)						85
Beijing	7.8% (2010)				1.7% (2010)		96
Study in 16 cities	5.3% (2009)						94
India							
Nationwide	4.4% (2011)	19% (2012)	7.1% (2011)	2.7% (2011)			12
Maharashtra							15
Study in 12 cities	7% (2012–2013)				0.87% (2012–2013)		105
Study in 15 cities			18.1% (2013)			2.9% (2013)	100

This table focuses on the most recent available data in selected countries and key populations where prevention intervention efficacy trials might be considered. Empty cells correspond to no data available. Data in *italics* correspond to potential target populations suitable for HIV vaccine trials.

Estimates based on country information indicate that the regional population of MSM and TG that is at risk for HIV infection ranges from 10.5 to 27 million. TG women are 50 times more likely to acquire HIV than adult males or females of reproductive age. For example, 18% of surveyed male sex workers in Indonesia and Thailand tested HIV positive, 31% of TG sex workers in Jakarta, and 19% in Maharashtra.¹⁴

An estimated 3–4 million people living in Asia are PWID. In Indonesia and the Philippines, injecting drug use has been a significant factor in the spread of HIV. In 2012, HIV prevalence among PWID was 36.4% in Indonesia,¹⁴ 13.6% in the Philippines,¹⁵ with an explosive epidemic in Cebu (53.8%), and 11.6% in Vietnam,¹⁶ with considerable geographic variations within countries. In contrast to previous figures on HIV prevalence in PWID,^{17,18} harm reduction programs have demonstrated a dramatic and beneficial impact on the epidemic in these populations.¹⁹

Little is known about the relative contribution of acute phase to HIV transmission in Asia. Individuals with acute HIV infection have an 8- to 26-fold greater risk for transmitting HIV compared to those with chronic infection because of their high viral load^{20–22} while they may remain undiagnosed by routine antibody tests.²³ Phylogenetic clustering of new HIV infections in MSM supports acute HIV infection as one of the main drivers of ongoing HIV transmission in MSM in rising and ongoing HIV epidemics.^{24–26}

HIV-1 molecular epidemiology

The geographic and temporal distribution of circulating HIV-1 subtypes by country from 2000 to 2007 and from 2008 to 2014 is shown in Fig. 2A. The relative percentage changes in HIV-1 subtype prevalence for selected countries is shown in Fig. 2B. CRF01_AE remains predominant in southeast Asia with a growing presence in China and an increasing number of recombinant forms containing CRF01_AE, B, and C subtypes.^{27–29} CRF01_AE dominates in Thailand (developed below), Cambodia,³⁰ Indonesia,³¹ Laos, Myanmar,²⁷ and Vietnam.^{32,33} In Malaysia, cocirculation of CRF01_AE and subtype B³⁴ has resulted in the emergence of CRF33_01B in approximately 20% of HIV-1-infected individuals,³⁵ now also described in Indonesia.³⁶

In Thailand, among 390 volunteers who were deferred from enrollment in the RV144 HIV vaccine trial due to preexisting HIV-1 infection molecular analyses showed the following subtype distribution: CRF01_AE: 91.7%, subtype B: 3.5%, B/CRF01_AE recombinants: 4.3%, and dual infections: 0.5%. CRF01_AE strains were 31% more diverse than those from the 1990s Thai epidemic that informed vaccine immunogen design, which represents a clear example of viral evolution that occurred between immunogen design and subsequent efficacy trial.³⁷ The impact on vaccine efficacy is unknown. While sequence diversity of HIV remains a challenge for HIV vaccine development, the rate of diversification can present a problem given the timelines for efficacy testing.

In China, in a comprehensive mapping of HIV genotypes in various risk groups using samples collected between 2006 and 2008, CRF07_BC (35.5%), CRF01_AE (27.6%), CRF08_BC (20.1%), and Chinese/Thai subtype B or B' (9.6%) were the four main HIV-1 strains. CRF07_BC and CRF08_BC were the primary drivers of infection among

PWID. Recently, however, MSM is the risk group associated with the most rapid increases in HIV infections within China, and studies note HIV-1 strains of different subtypes and CRFs.^{38–42} In cities in northern China CRF01_AE infection in MSM is more common than subtype B,^{24,43–45} with similar trends in Beijing, Fujian, Guizho, Guandong, Guanxi, Hebei, Hong Kong, Hunan, Jiangsu, Jianxi, Shanghai, and Yunnan. CRF07_BC has recently been identified in young MSM and in some cities exceeds the prevalence of CRF01_AE infection (unpublished data).

The HIV epidemic among MSM is expanding to Japan and illustrates the ongoing mixing of CRF01_AE and subtype B lineages circulating among MSM populations in east Asia.^{46–48}

Western Yunnan, bordering with Myanmar, is a known hotspot of recombination with the identification of CRF07_BC^{49,50} and CRF08_BC.^{51,52} In 2006, CRF01_AE was found (40.5%, mostly acquired by sexual transmission) at the Yunnan–Myanmar border.⁵³ Recent data on HIV subtypes circulating in Myanmar are limited to the China–Myanmar border, mostly in PWID populations.^{54–56} A breakdown of HIV-1 in Yunnan includes CRF07_BC (18.9%), CRF08_BC (39.1%), and CRF01_AE (22.4%)⁵⁷; *pol* sequences in newly diagnosed HIV-infected individuals from Dehong county, Yunnan, showed that subtype C accounted for 43.1%, URF for 18.4%, CRF01_AE for 17.7%, B for 10.7%, CRF08_BC for 8.4%, and CRF07_BC for 1.7%⁵⁸; near-full-genome sequencing results show that many new CRFs have been generated in this region.^{59–62}

In India, subtype C is the predominant circulating subtype,^{63–66} irrespective of the route of transmission,^{67,68} and has been reported as one of the parental strains of CRF07_BC and CRF08_BC in China.⁶⁹ URFs of subtype C with B' are increasing, especially in the northeastern states.^{27,70}

Thailand

The Thai HIV epidemic is a very mature one. At its peak in 1991 Thailand had approximately 168,000 new adult HIV infections per year.⁷¹ Among other campaigns, the 100% condom program addressing the client–sex worker relationship and the reduction in the number of partners have brought a dramatic reduction in incidence, down to 8,135 new infections per year in 2013.^{72,73} The declining trend in HIV transmission rates despite an ever-growing prevalence indicates prevention success correlated with the national HIV/AIDS program.⁷⁴

In 2007, HIV prevalence among MSM was 30.7% in Bangkok and 16.9% in Chiang Mai, essentially unchanged since 2005.⁶ The HIV prevalence found in subsequent studies ranged from 5.5% to 28.3% with an incidence rate of 8.2% in Chiang Mai^{6,75} and 6% in Bangkok between 2006 and 2008.⁷ The HIV prevalence in transgender women was estimated at 12.5% (5.1–19.9%) for the period 2000–2011.⁸ Another study conducted in Bangkok between 2008 and 2009 showed a much lower HIV incidence (1.95 per 100 person-years) among MSM recruited at the Thai Red Cross Anonymous Clinic through routine HIV counseling and testing activities.⁷⁶ In 2013, 64% of new HIV infections occurred among key populations, 42% among MSM, while only 12% for FSW and clients and 10% for PWID.⁷¹ In a recent cohort study conducted in Pattaya, HIV incidence was 7.4 and 5.5 per 100 person-years among MSM and TG sex workers, respectively

FIG. 2. HIV-1 molecular epidemiology in Asia. Partial and full genome of HIV-1 sequences obtained from the Los Alamos National Laboratory HIV database (www.hiv.lanl.gov) and the U.S. Military HIV Research Program (MHRP); HIV-1 subtyping data from the MHRP (personal communication, unpublished data) were used to compile circulating subtype distributions by country. (A) Geographic and temporal distribution of circulating HIV-1 subtypes by country for 2000–2007 and 2008–2014. Bangladesh, Myanmar, Mongolia, Macau, Nepal, and Philippines are omitted due to insufficient data.

FIG. 3. Proportion of new HIV infections by mode of transmission, Thailand, 1985–2030. Thailand Working Group on HIV/AIDS Projection.⁷¹

(Merlin Robb, personal communication). An ongoing “Test and Treat” cohort among MSM and TG in Bangkok, Ubon Ratchathani, Lampang, and Mahasarakham found a preliminary HIV incidence of 6.3% (Nittaya Phanuphak, unpublished data). The national projections show that MSM will remain the dominant key population for new HIV infections over the next 15 years (Fig. 3).⁷¹

Myanmar

Data on the HIV-1 epidemic in Myanmar remain scarce and of questionable representativeness. No HIV incidence data are available. In 2011, over 60% of new HIV infections occurred among FSW and their clients, PWID, and MSM. It is estimated that by the year 2015, these groups will constitute over 70% of new infections. According to the 2011 HIV sentinel serosurveillance, HIV prevalence rates among FSW dropped from 18.4% in 2008 to 9.4% in 2012.⁷⁷ It is estimated that there are 40,000 to 80,000 FSW in Myanmar. The number of MSM is estimated at 240,000, mostly in Yangon and Mandalay, with an overall HIV prevalence of 7.8% (Mandalay 9%, Yangon 5%), with more than 81% having used a condom at last sex.¹²

Importantly, the current HIV epidemic figures in FSW may offer a unique, and perhaps the last, opportunity to access high-risk heterosexual populations for an HIV vaccine efficacy trial in SEA. However, this window of opportunity may quickly narrow as increased access to prevention services improve.⁷⁸

China

Figure 4 shows the geographic distribution of cumulative HIV/AIDS cases at the end of 2011.⁷⁹ Several HIV epidemic clusters have been described, illustrating the diversity of the epidemic.⁸⁰ Zhang *et al.*⁸¹ used the public health data system

of the Chinese Center for Disease Control and Prevention (China CDC) to characterize trends and prevalence for HIV from all 31 provinces. At the end of 2011, 780,000 people were living with HIV/AIDS in China, with 48,000 new infections. The routes of infection were predominately through heterosexual (52.2%) and homosexual (29.4%) transmission and through injecting drug use (18.0%). The HIV epidemic among PWID is decreasing in all regions outside southwest China and has stabilized at a high level in northwest China. Comparatively, HIV prevalence in FSW is much lower and stabilized at low levels in all regions except in the southwest. In 2010, the national HIV prevalence was 9.08% in PWID and 0.36% in FSW, with low incidence in both populations (0.57% and 0.02%, respectively).⁸¹

In contrast, HIV prevalence among Chinese MSM increased rapidly in all Chinese regions in the past decade and disproportionately affected southwest China where overlapping bisexual, commercial, and drug use behaviors are commonly observed.⁸² HIV prevalence in MSM increased from 1.77% in 2000 to 5.98% in 2010, with a national incidence of 0.98% in 2010.⁸¹ Several other studies confirm this trend.⁸³ In a meta-analysis, the pooled HIV prevalence among MSM increased from 0.6% in 2003 to 7.4% in 2009 with a yearly increase of 1.1%. The pooled regional HIV prevalence ranged from 2.3% in east China to 11.4% in southwest China. The proportion of MSM in the annually reported HIV cases increased from 12% in 2007 to 33% in 2009.⁸⁴ In 2008–2009, the overall HIV prevalence in 61 cities was 4.9%, with considerable heterogeneity between provinces. The highest prevalence was up to 18% in southwestern provinces.⁸⁵

In the absence of interventions, HIV will spread very quickly in the MSM population⁸⁶ with an estimated reproductive ratio of 3.9.⁸⁷ Risk reduction interventions on HIV knowledge, attitudes, and behaviors were effective in

FIG. 4. Geographic distribution of cumulative HIV/AIDS cases in China. China AIDS Response Progress Report, Ministry of Health of the People's Republic of China, UNAIDS, 2012.⁷⁹

reducing risk behaviors and improving knowledge and attitudes among Chinese MSM, but were not associated with a change in HIV prevalence.⁸⁸ Approximately 25% of Chinese MSM are married,⁸⁹ and 30% of these individuals have sex with a steady female partner, but with a low rate of condom use,⁹⁰ constituting a dangerous bridge of HIV transmission from high-risk groups to the general population.^{91,92}

Aggressive prevention interventions deployed by China over the past decade were unable to stem the HIV epidemic in MSM.^{93,94} A 4-fold increase in testing rates may prevent 42,000 new HIV infections among all at-risk groups in China over 5 years.⁹⁵ Even enhanced levels of HIV testing and linkage to care including ART will not interrupt the expansion of the epidemic. Promoting condom use remains a crucial component of combination interventions in MSM.⁹⁶

India

In 2011, the national adult HIV prevalence in India was 0.27% with a total number of people living with HIV/AIDS estimated at around 2.09 million, 39% among women, and 116,000 new infections, representing an overall reduction of 57% since 2000. Four states of south India (Andhra Pradesh, Karnataka, Maharashtra, and Tamil Nadu) account for 53% of all the HIV-infected population. India continues to portray a concentrated epidemic. The HIV prevalence among high-risk groups, i.e., FSW, PWID, MSM, and TG, is about 20 times higher than the general population (Fig. 5). The highest HIV prevalence is observed in PWID (7.1%), MSM (4.4%), FSW (2.7%), and STI clinic attendees (2.5%).⁹⁷⁻⁹⁹ A recent study conducted in 2013 among PWID from 15 cities showed

that estimated HIV prevalence and incidence were 18.1% and 2.9 per 100 person-years, respectively.¹⁰⁰ Sex work continues to be the most important source of HIV infection in India due to the large number of clients of sex workers (in particular single male migrants) who further transmit HIV infection to the general population.^{101,102}

MSM remain hidden because anal intercourse is criminalized and marriage is socially required, with the current estimated HIV prevalence among MSM ranging between 7% and 16.5%.¹⁰³ HIV prevalence was characterized among MSM in eight cities from Tamil Nadu where 34% were married and 40% self-identified as homosexual. HIV prevalence was 9%, and was higher among married men, 14%.¹⁰⁴ A recent study (2012–2013) conducted among MSM from 12 cities across India confirms a relatively high HIV prevalence of 7% and a low HIV incidence of 0.87% (0–2.2%).¹⁰⁵ MSM who reported injection drug use were 6.7 times more likely to be HIV infected. In another study in MSM who attended voluntary counseling and testing in Mumbai, HIV prevalence was 12.5%.¹⁰⁶ Interestingly, heterosexual anal sex was reported by 11.9% of FSW in four high prevalence states in India.¹⁰⁷ Meta-analysis of studies from developed countries has shown that the probability of HIV transmission is higher per act of receptive anal sex (1.7%) as compared to peno-vaginal sex (0.8%).^{108,109}

Prevention Trials and Breakthrough Results

HIV vaccine clinical development

Table 2 provides the prevention efficacy trials conducted in Asia between 1995 and 2010. Considerable efforts at HIV

FIG. 5. HIV prevalence and incidence in men who have sex with men (MSM) and people who inject drugs (PWID), India, 2012–2013. The MSM study was conducted in 12 cities¹⁰⁵ and the PWID study was conducted in 15 cities.¹⁰⁰

vaccine clinical development have been deployed in the region since the mid-1990s.¹¹⁰ The first Phase III trial in a middle-income country (Vax003) tested a bivalent recombinant gp120 B/E (MN and A244 CRF01_AE) in alum (AIDSVAX B/E) in PWID in Bangkok, Thailand.¹¹¹ The vaccine showed no efficacy against HIV acquisition or progression to disease.

A community-based Phase III trial (RV144) provided the first evidence that an HIV-1 vaccine might prevent HIV infection.^{112,113} The prime-boost vaccine regimen consisted of a recombinant canarypox vector, ALVAC-HIV (vCP1521) prime and AIDSVAX B/E boost. The vaccine regimen was safe and generally well tolerated.¹¹⁴ The modified intent-to-treat analysis showed 31.2% efficacy after 42 months of follow-up. There was no effect on early postinfection HIV-1 RNA viral load or CD4⁺ T cell count or on clinical outcomes in longer-term follow-up. In a post-hoc analysis, vaccine efficacy was significantly higher (60%) at 12 months post-vaccination, suggesting an early, but nondurable, vaccine effect.¹¹⁵ Although RV144 was not powered to assess the interaction of vaccine efficacy and risk behavior, post-hoc analysis suggested greater benefit in low-risk individuals.

RV144 provided an opportunity to perform a correlates of risk analysis,¹¹⁶ and a case-control study showed that IgG antibodies to the scaffolded V1V2 region of gp120 Env correlated with a decreased risk of infection while the presence of IgA antibodies to Env was directly associated with infection risk.^{117–119} There was no enhancement of HIV-1

infection risk when compared to the placebo group. A subsequent analysis showed that RV144 antibodies to subtype A, C, and CRF01_AE gp70 V1V2 scaffolded proteins also correlated inversely with risk,¹²⁰ suggesting that the RV144 regimen might protect against HIV strains heterologous (A and C) to the vaccine components.

The Env IgG/IgA ratio significantly correlated with increased risk of infection (decreased vaccine efficacy).¹²¹ In the presence of low vaccine-elicited IgA responses, both antibody-dependent cellular cytotoxicity (ADCC) and neutralizing antibody (Nab) responses correlated with decreased risk of infection. ADCC responses were predominantly directed to the C1 conformational region of gp120.¹²² IgA antibodies elicited by RV144 could block anti-C1 IgG-mediated ADCC.¹²¹ It is suggested that nonneutralizing antibodies mediating ADCC are directed against viral entry epitopes including the CD4-inducible A32 epitope of a highly conserved region of gp120 at the gp120–gp41 interface,¹²³ and there is evidence of synergy between the anti-C1 and anti-V2 activities, with increased anti-V1V2 binding in the presence of vaccine-induced anti-C1 antibody.¹²⁴ IgGs to linear epitopes in the V2 and V3 regions of gp120 are part of a complex interplay of immune responses that contributed to protection in RV144.¹²⁵ These correlates were supported by corresponding V2 mutations in a "sieve" analysis of breakthrough viruses suggesting that genetic mutations away from V2 sequences found in the vaccine (positions 169K and 181I) were associated with altered efficacy.¹²⁶

TABLE 2. HIV-1 PREVENTION EFFICACY TRIALS CONDUCTED IN ASIA BETWEEN 1995 AND 2010

Study	Years of implementation	Vaccines/drugs	Phase	Volunteers' risk	Location	HIV incidence per 100 person years	Result	References
Vax003	1995–1998	AIDSVAX B/E	III	People who inject drugs	Bangkok, Thailand	3.4%	No efficacy	111
RV144	2003–2009	ALVAC-HIV vCP1521 and AIDSVAX B/E rgp120 in alum	III	Community risk	Rayong and Chonburi provinces, Thailand	0.28%	31.2% efficacy at 42 months, 60% at 12 months against HIV acquisition; no effect on plasma viral load and CD4 count	112–115
iPrEx	2007–2009	Daily oral emtricitabine and tenofovir disoproxil fumarate	III	Men who have sex with men	Chiang Mai, Thailand (and 5 other countries) ^a	3.9% overall	44% in reduction of HIV incidence (global)	144
PrEP	2005–2010	Same as above	III	People who inject drugs	Bangkok, Thailand	0.68%	48.9% in reduction of HIV incidence	143
HPTN 052 (TasP)	2007–2010	Various combinations of antiretroviral drugs ^b	III	HIV-1 serodiscordant couples	Thailand, India (and 7 other countries) ^c	1.2% overall	Relative reduction of 96% of linked HIV-1 transmissions after early ART initiation	161,162
TasP	2003–2011	Antiretroviral therapy		Retrospective observational cohort of HIV-1 serodiscordant couples	China	2.6%	Relative reduction of 26% of HIV-1 transmission	170

^aPeru, Ecuador, South Africa, Brazil, United States.^bCombination of lamivudine and zidovudine (Combivir), efavirenz, atazanavir, nevirapine, tenofovir, lamivudine, zidovudine, didanosine, stavudine, combination of lopinavir and ritonavir (Kaletra and Aluvia), ritonavir, and combination of emtricitabine and tenofovir (Truvada).^cBotswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, United States.

ALVAC-HIV (vCP1521), recombinant canarypox vector expressing Gag and protease subtype B (MN) and CRF01_AE (A244); iPrEx and PrEP, preexposure prophylaxis; TasP, treatment as prevention; subtype B gp41 (LAI) genes; AIDSVAX B/E, bivalent recombinant gp120 proteins subtype B (MN) and CRF01_AE (A244);

Follow-up trials are continuing¹²⁷ to explore systemic and mucosal immune responses elicited by late boosts (7–8 years post) administered to RV144 vaccine recipients, the value of additional boosts at 12, 15, and 18 months to the RV144 regimen, the immune responses in mucosal compartments and memory B cells, and new adjuvant formulations.

One of the main objectives for future vaccines is to counter HIV-1 variability, between subtypes and intrasubtype, as diversity within geographically circumscribed epidemics increases with time.¹²⁸ Whether various envelope immunogens eliciting V2 antibodies are functionally strain-specific, region-specific, or universal in a cross-clade manner and universal correlates of risk in populations with various modes of transmission remains to be demonstrated in future efficacy trials.

Other vaccine approaches including immunogens derived from conserved sequences or mosaics expressed by various vectors (Ad26, MVA) have recently been reviewed.^{127,129} Our current understanding of the immune correlates of protection suggests that no specific vaccine approach should be privileged over the other and that all reasonable vaccine approaches deserve to be pursued.^{130,131} At least for the pox-protein prime-boost strategy, the analysis of the correlates of risk raises hypotheses that might be used to down-select products in advance of efficacy testing.

In China, a plasmid DNA and a replication-competent TianTan vaccinia HIV vaccine vector expressing HIV-1 CN54 CRF07_B'/C genes¹³² is now in Phase II. Preliminary results suggest that both vaccines are safe and immunogenic.¹³³ An efficacy trial in MSM populations might be envisaged with possibly an envelope protein boost.

India conducted three Phase I trials testing HIV-1 subtype C-derived vaccine candidates.^{134–137} HIV vaccine clinical development came to a halt and shifted to designing immunogens able to induce HIV-specific broadly neutralizing antibodies (www.iavi.org). The prioritization of trial-related financial and healthcare provisions, including access to an efficacious vaccine posttrial, among MSM in India indicates the importance of trials providing such services, as well as the value of formative research in identifying key concerns among participating communities in resource-limited settings.¹³⁸

Preexposure prophylaxis (PrEP) and microbicides

A meta-analysis of PrEP randomized controlled trials in high-risk populations defined as MSM, PWID, and HIV-discordant heterosexual couples demonstrated an overall risk reduction of 47%.¹³⁹ Early PrEP trials in Cambodia failed to launch due to ethical, political, and logistical concerns raised by civil society leaders during 2004,^{140–142} and initiation of the Bangkok Tenofovir PrEP study was delayed for several years.¹⁴⁵ Two clinical trials of oral PrEP for HIV-negative individuals conducted in Thailand showed a reduction in HIV acquisition in MSM¹⁴⁴ and in PWID¹⁴³ (Table 2). Daily oral Truvada was approved by the U.S. FDA for PrEP in 2012¹⁴⁵ and the WHO^{146–148} and CDC^{149,150} recommended PrEP for certain populations.

Results of the PROUD study and of the on-demand (before and after sexual intercourse) “Ipergay” PrEP study showed a relative reduction of 86% in the incidence of HIV acquisition among MSM.^{151,152} The results of the Ipergay trial also raise

hope that costs of a PrEP strategy among MSM could be considerably reduced. PrEP is still considered an individual prevention intervention for HIV-negative individuals at a time at which governments struggle to sustain funding for HIV treatment programs,¹⁵³ although the increasing HIV incidence among MSM is an argument to include PrEP for HIV prevention for this particular group.^{5,7} High-risk individuals in China^{154–156} and Thailand^{157,158} have signaled their acceptance of PrEP if offered. PrEP demonstration projects and effectiveness trials are ongoing in India and Thailand. Moreover, PrEP and male circumcision were recently recommended (although not reimbursed by national coverage scheme) in high-risk groups such as MSM and were included in the 2014 Thailand National Guidelines on HIV/AIDS Treatment and Prevention.¹⁵⁹

Treatment as Prevention (TasP)

The introduction of potent combination ART in 1996 and the public health approach to HIV treatment in resource-limited settings in 2002 have changed the course of the HIV epidemic.¹⁶⁰ HPTN 052,^{161,162} conducted in 13 sites in nine countries including India and Thailand, demonstrated that earlier ART reduces the risk of heterosexual HIV transmission by 96%¹⁶³ in discordant couples and confirmed results of observational and ecological studies.^{164–169} These results prompted a retrospective study of treated and untreated discordant couples in China,¹⁷⁰ which showed a relative reduction of 26% of HIV-1-linked transmission (Table 2).

In India, early ART was cost effective over a 5-year period and very cost effective over a lifetime (\$1,800 and \$530 per life-year saved, respectively).¹⁷¹ A recent modeling study in India suggests that in the presence of existing condom-based interventions, existing ART programs could avert 11–28% of the remaining HIV infections in FSW between 2014 and 2024.¹⁷² Several studies of TasP are ongoing in India, Vietnam, Thailand, China, and Indonesia. In China, a 10-fold increase in ART could decrease the number of HIV-related deaths by 58% and the number of new infections by 25% by 2015.⁹⁵ In Thailand, an additional \$100 million was invested in high-impact interventions focusing on key populations, and an estimated 20,000 people will escape HIV infection, 22,000 deaths will be averted, and \$300 million in projected savings and labor productivity gains will be accrued.¹⁷³

Implications for HIV Prevention Trials

HIV prevention trials in community-risk populations may be difficult in Asia.^{127,174} Despite undeniable gaps in HIV prevention and in access to care and treatment of key populations,¹⁴ an overall decrease of HIV prevalence is observed in the region due to effective prevention programs. Furthermore, with treatment programs starting at higher CD4 thresholds, HIV incidence may significantly decrease in all populations. The implementation of prevention trials then faces important challenges.

Although HIV prevalence still remains high in some cities (23.6% in Bangkok, 10.9% in Chiang Mai),¹⁷⁵ the success of harm reduction programs has yielded a decreasing HIV incidence in PWID.^{19,176} HIV vaccine efficacy trials in PWID are unlikely to proceed as illustrated in the HPTN 058 trial conducted in Xinjiang and Guangxi Provinces, China, and Chiang Mai, Thailand where only 7 of 1,157 HIV-uninfected

PWID acquired HIV over a 2-year follow-up.^{177,178} In Project Accept (HPTN 043) conducted in Africa and 14 sites in Thailand, Thailand was excluded from the analysis because of an unexpectedly low HIV prevalence.¹⁷⁹ In addition, a high proportion of new circulating recombinant forms is now found in PWID, as illustrated by CRF01_AE/B/C recombinants (42.6%) in northern Myanmar at the border with China^{54–56} and India.⁶⁵ Taken together the burden of multiple transmitted/founder variants in PWID¹⁸⁰ and rates of HIV superinfection¹⁸¹ represent major challenges for any HIV vaccine and would complicate trials in areas with higher proportions of CRF/URFs, such as China, India, and Myanmar.

Efficacy trials that target MSM and TG populations with current HIV incidence in these groups offer the benefit of being smaller and less costly. However, the recent results of the PROUD and Ipergay PrEP studies showing a reduction of 86% in the incidence of HIV acquisition along with the impact of TasP among MSM populations suggest that the expansion of these prevention strategies may rapidly lead to low HIV incidence among MSM populations. Circumcision rates among MSM remain low (<20%) in countries such as Thailand⁷⁶ or China.^{182,183} Although a recent study in India suggests that circumcised MSM who predominantly take the receptive role in anal intercourse may be at a lower risk of HIV infection,¹⁸⁴ evidence that circumcision reduces HIV among MSM remains weak and inconsistent.^{185,186} Despite the willingness to undergo circumcision among MSM populations,^{187,188} male circumcision is not promoted as a priority in Asian countries with concentrated epidemics and has not been recommended for MSM unless they also engage in vaginal sex.¹⁴⁸ It is therefore unlikely that male circumcision will significantly contribute to reducing the HIV incidence among MSM populations. A lower HIV incidence may make HIV vaccine trials in MSM populations infeasible.

The decision will be made on a country-by-country basis after careful analysis of the most recent epidemiological data and of the use of PrEP. It has also been argued that vaccine protection might be easier to achieve in high-risk populations with predominantly heterosexual transmission such as those found in Africa,^{108,174} in contrast to MSM populations with rectal transmission, with the highest risk mode of sexual HIV transmission at 1:20–1:300 infections per exposure.¹⁸⁹ This adds to the complexity of the decision as to which HIV vaccine strategy makes best scientific sense for efficacy testing among MSM populations.

The evolving patterns of HIV-1 diversity in the region illustrate the need to closely monitor the molecular HIV epidemic in potential target populations for HIV vaccine efficacy trials.^{28,29} CRF01_AE remains predominant in southeast Asian countries and MSM populations in China and may provide a rationale for regional efficacy trials, for example, Thailand and China.¹¹⁰ However, bivalent or trivalent subtype-specific vaccines targeting predominant circulating forms, such as CRF01_AE, subtype B, and, potentially, C seem more appropriate.¹²⁸ Other vaccine approaches such as prime-boost regimens using DNA and vectors (Ad26, MVA) expressing mosaic antigens^{190,191} or conserved sequences must also be seriously considered as global HIV vaccine strategies.^{192–195}

The rationale and design of efficacy trials of combination prevention modalities such as HIV vaccine and PrEP have

recently been explored.^{196,197} Such trials are complex, and the clinical and regulatory challenges remain hypothetical. Ultimately the prioritization of prevention interventions should be driven by the HIV epidemic and decided by the country-specific health and regulatory authorities. Modeling the impact and cost–benefits of combined interventions may help this decision process.

Conclusions

An overall decrease in HIV prevalence has been observed in several key Asian countries due to effective prevention programs. The decrease in HIV prevalence and HIV incidence may hopefully further improve with the scale-up of combination prevention interventions. The implementation of prevention trials then faces important challenges. The opportunity to identify heterosexual populations at high risk may rapidly wane. With unabating HIV epidemics among MSM and TG, an effective vaccine would likely be the only option to turn the epidemic. It is therefore more likely that efficacy trials will occur in the MSM and TG populations because their higher HIV incidence would allow smaller and less costly trials. The evolving patterns of HIV-1 diversity in the region suggest the need for close monitoring of the molecular HIV epidemic in potential target populations. However, CRF01_AE remains predominant in southeast Asian countries and among MSM populations in China. This would be conducive to regional efficacy trials, and as efficacy warrants, to regional licensure. The rationale and design of efficacy trials of combination prevention modalities such as HIV vaccine and PrEP remain for the moment hypothetical and would be more costly and challenging for the regulatory approval process to licensure. The prioritization of prevention interventions should be driven by the HIV epidemic and decided by the country-specific health and regulatory authorities. Modeling the impact and cost–benefit interventions may help this decision process.

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