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Review

Challenges and potential barriers to the uptake of antiretroviral-based prevention in Asia and the Pacific region

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Abstract. Evidence has emerged over the past few years on the effectiveness of antiretroviral-based prevention technologies to prevent (i) HIV transmission while decreasing morbidity and mortality in HIV-infected persons, and (ii) HIV acquisition in HIV-uninfected individuals through pre-exposure prophylaxis (PrEP). Only few of the planned studies on treatment as prevention (TasP) are conducted in Asia. TasP might be more feasible and effective in concentrated rather than in generalised epidemics, as resources for HIV testing and antiretroviral treatment could focus on confined and much smaller populations than in the generalised epidemics observed in sub-Saharan Africa. Several countries such as Cambodia, China, Thailand and Vietnam, are now paving the way to success. Similar challenges arise for both TasP and PrEP. However, the operational issues for PrEP are amplified by the need for frequent retesting and ensuring adherence. This paper describes challenges for the implementation of antiretroviral-based prevention and makes the case that TasP and PrEP implementation research in Asia is much needed to provide insights into the feasibility of these interventions in populations where firm evidence of 'real world' effectiveness is still lacking.

Additional keywords: Cambodia, China, pre-exposure prophylaxis, Thailand, treatment as prevention, Vietnam.

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Background

Thirty years after AIDS was first reported, we are still facing a significant HIV epidemic in Asia and the Pacific, where half of the world's population resides.[1] Asian countries are affected by low-level (HIV may have been present for many years but never spread to substantial levels in any subpopulation: prevalence is consistently <5% in any subpopulation) or concentrated HIV epidemics (the spread of HIV has occurred in a defined subpopulation with a prevalence that is consistently >5% in a defined subpopulation but is <1% in pregnant women in urban

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areas).[2] Predominantly affected subpopulations, usually referred to as key populations, are sex workers (SWs), injecting drug users (IDUs), men who have sex with men (MSM) and transgender people.[3,4] Although the 2012 estimates suggest that new HIV infections were down by 26% from 2001, HIV continues to spread, particularly among key populations. An estimated 350 000 people were newly infected in 2012.[1,5] Impressive progress was made towards achieving universal access to antiretroviral treatment (ART). The number of people receiving ART in Asia and the Pacific increased by 28% from 900 000 in 2010 to 1.25 million in 2012, covering 51% of those in need.[1,5] Nearly all (99.5%) are found in 10 of 47 countries and areas in the Western Pacific and the South-East Asia administrative regions of the World Health Organization (WHO; Table 1). Late diagnosis continues to drive the steady increase of annual AIDS-related deaths in this region (260 000 in 2012).[5]

Firm evidence has emerged over the past years on the effectiveness of antiretroviral-based prevention technologies. Antiretroviral drugs prevent: (i) HIV transmission while decreasing morbidity and mortality in HIV-infected persons (treatment as prevention (TasP));[6] (ii) HIV transmission from mother to child;[7] and (iii) HIV acquisition in HIV-uninfected individuals through post- and pre-exposure prophylaxis (PrEP).[8,9,10]

This paper discusses and describes the new evidence and current implementation challenges of ART-based prevention methods, focusing on TasP and PrEP in several Asian countries and their potential impact.

New evidence

Prevention benefit of ART, testing and treating

The study of the HIV Prevention Trials Network (HPTN) 052 was conducted at 13 sites in nine countries. It enrolled 1763 couples in which one partner was HIV-infected and the other was HIV-uninfected. The HIV-infected individuals with CD4 counts between 350 and 550 cells μL^{-1} were randomly assigned to earlier or delayed ART. The study showed that earlier ART reduced the risk of heterosexual HIV transmission by 96%.[6] Analysis of two transmission events in the ART arm (delayed and immediate) concluded that they were related to transmission shortly before or after initiation of ART before viral replication was adequately suppressed.[11] The journal *Science* chose HPTN 052 as the breakthrough of 2011.[6,12] Immediate ART was associated with a 41% reduction in HIV-related clinical events.[13] Population-based trials, such as the Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART), HPTN 071,[14] the Botswana Combination Prevention Project (ClinicalTrials.gov ID NCT01965470) and the Agence Nationale de Recherche sur le Sida et les Hepatites Virales (ANRS) 12249 TasP study,[15] are underway in sub-Saharan Africa to assess the feasibility and effectiveness of TasP as part of combination prevention. There are relatively few such studies focussing on Asia.[16,17] The HPTN 074 vanguard study for a network-based randomised HIV prevention trial comparing an integrated intervention including supported ART compared with the standard of care for IDUs may consider sites in Asia.

HPTN 052 confirmed the results of observational and epidemiological[18–21] and modelling studies[22–24] that earlier ART reduces the sexual transmission of HIV.[6] The findings created hope that elimination of new HIV infections was possible and had a galvanising effect on health authorities, such as the US President's Emergency Plan for AIDS Relief (PEPFAR) and WHO.[25] In 2012, United States guidelines recommended initiation of ART for all people living with HIV/AIDS (PLHIV), irrespective of immunological staging.[26] WHO released new guidance on HIV testing and counselling (HTC) for couples, recommending initiation of ART irrespective of CD4 count as a strategy for preventing transmission among serodiscordant couples.[27] In Asia, the results of HPTN 052 prompted Cambodia, China and Thailand to recommend earlier initiation of ART for HIV-infected individuals in serodiscordant couples.[28,29] In Indonesia, the feasibility of TasP focusing on key populations is still under consideration.

Mathematical modelling in China, where the HIV epidemic is concentrated among IDU and MSM, suggests that HIV testing and treatment are important public health strategies for prevention, similar to the effects modelled from generalised

Table 1. Estimated number of people living with HIV/AIDS (PLHIV) and the reported number of people on antiretroviral therapy (ART) in 10 countries in Asia and the Pacific, 2012

PNG, Papua New Guinea; N/A, not available

	Total population (2012)	Estimated number PLHIV (all ages, 2012)	Reported number of adults receiving ART (2012)	Coverage (range of uncertainty[A])
Cambodia	14 864 646	76 000	44 318	82% (60%–>95%)
China	1 350 695 000	780 000[113]	151 519	N/A
India	1 236 686 732	2 100 000	570 620	51% (44%–57%)
Indonesia	246 864 191	610 000	29 960	18% (12%–25%)
Malaysia	29 239 927	82 000	14 594	41% (32%–52%)
Myanmar	52 797 319	200 000	49 676	46% (41%–51%)
Nepal	27 474 377	49 000	7168	33% (28%–40%)
PNG	7 167 010	25 000	11 042	84% (73%–>95%)
Thailand	66 785 001	440 000	232 816	76% (71%–80%)
Vietnam	88 772 900	260 000	68 883	58% (19%–>95%)

[A]The range of uncertainty reflects the degree of uncertainty associated with estimates and defines the boundaries within which the actual numbers lie (see http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/20131118_Methodology.pdf, accessed 1 June 2014).

epidemics.[22,30,31] The results suggest that the ability of programs to identify people with HIV will determine the impact on reducing new HIV infections. Similarly, in Vietnam, it was found that an intervention consisting of an annual offer of voluntary HTC among IDUs and immediate ART, adding to combination prevention, could potentially reduce HIV incidence from 61 per 100 000 person-years in 2010 to 6.2 per 100 000 person-years (a 90% reduction) in 10 years.[23] The study also found that prioritising IDUs would have the greatest impact and would be a highly cost-effective approach. Preliminary modelling in Thailand suggests that the most effective strategy to achieve a reduction of new HIV cases by 2016 is to increase the uptake of HIV testing among key affected populations to 90% and to treat all HIV-infected people regardless of CD4 count as part of combination prevention.[32]

Antiretroviral PrEP for HIV-uninfected individuals

There is now conclusive evidence that daily PrEP is effective for preventing HIV acquisition during sexual intercourse and injecting drug use if the drug is taken consistently. The iPrEx clinical trial (MSM in six countries) using daily tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC) observed an overall 44% reduction in HIV acquisition compared with placebo recipients.[33] Efficacy was higher (73%) for those with good adherence, defined as pill use on 90% or more days. The subsequent iPrEx open-label extension is a continuation of the study for an additional 72 weeks.[34] It will help determine how PrEP uptake and sexual behaviour may be modulated when people know that FTC–TDF can reduce HIV infection when taken consistently along with other HIV prevention modalities. So far, of 1170 HIV-uninfected participants, 63.8% chose to take and 26.7% not take FTC–TDF in 11 sites. The results are expected later in 2014. The Partners PrEP tested once-daily oral TDF or combination FTC–TDF compared with a placebo in Kenya and Uganda. It demonstrated that both TDF alone and FTC–TDF protected HIV-uninfected men and women against HIV acquisition by 67% and 75%, respectively, although the difference was not significant. The TDF2 study in Botswana tested FTC–TDF compared with a placebo, showing a reduction of HIV acquisition by 62.2%.[35,36] Two other studies focussed on African women. VOICE[37] evaluated the safety and effectiveness of FTC–TDF, TDF and tenofovir gel compared with a placebo in Uganda, South Africa and Zimbabwe. Fem-PrEP compared FTC–TDF to a placebo in Kenya, South Africa and Tanzania.[38] Both studies did not show positive results, most probably because participants did not use the product as specified in the study protocol.[39] Other factors such as pharmacology of antiretrovirals in the female versus male genital tract and differences in genital tract inflammation among study populations are also being investigated.[40,41]

A Phase III study of daily oral TDF among IDUs in Thailand demonstrated an overall 49% effectiveness in the modified intention-to-treat analysis.[42,43] Efficacy was also highly dependent on adherence. It increased from 46% to 74% when the analysis was limited to participants with detectable TDF concentrations. PrEP may be a useful intervention for some IDUs and their sex partners, and is most likelyto be a part of a menu of preventive options where effective services are available. There is a clear need for implementation science agenda in this area.[44,45]

Operational considerations for ART-based prevention strategies

There is an unprecedented opportunity in Asia to successfully implement ART-based interventions for prevention, as impressive ART scale-up has occurred during the past years.[46,47] However, operational issues need to be carefully addressed (Box 1).

Cascade of interventions from HIV testing to treatment

Taking full advantage of ART prevention and treatment benefits requires multiple intervention steps, including linking HIV testing to care services and adherence to ART. Only high uptake of each step of the cascade can achieve viral suppression at population level.[48,49] Together, these elements comprise what has become known as the ‘treatment cascade’. Country examples are developed below to illustrate the ‘cascade’.

Elimination of new HIV infections in Cambodia

One of the recent and most commonly cited successes in Asia took place in Cambodia.[50] Associated with scale-up of HIV testing and ART, the estimated number of new HIV infections plummeted from almost 20 978 in 1995 to around 1300 in 2012 and the estimated national HIV prevalence declined from 2% in 1998 to 0.7% in 2012.[51] Documenting the treatment cascade in the real world is complex. The number of HIV tests performed has increased considerably, with 707 667 clients tested at 253 sites (2012), up from few clients in 12 sites in 2000.[52] The current monitoring system only allows visualisation of the distribution of PLHIV in care (Fig. 1*a*). The median CD4 count at enrolment to care from 33 sites increased to 194 cells μL^{-1} (6442 samples) in 2011 from 112 cells μL^{-1} (2932 samples) in 2006, suggesting that more HIV-infected individuals are starting ART earlier (National Center for HIV/AIDS, Dermatology and STD database). However, this is still far below the new 2013 WHO guidelines of starting at CD4 <500 cells μL^{-1}. Getting an HIV test result involves delays with client or specimen referral for confirmatory HIV testing, and receiving the CD4 count result (2–4 weeks) adds further delay and risks losing individuals between HIV testing and care (Table 2).[53] The latest reported retention rates of individuals on ART at 33 ART sites at 12, 24 and 60 months were 92.6%, 84.2% and 78%, respectively (2011).[54]

The country is poised to strive towards the elimination of new HIV infections by 2020, an initiative labelled as ‘Cambodia

Box 1. Operational considerations for implementing antiretroviral-based prevention strategies

1. Cascade of interventions from HIV testing to treatment
2. Acute and early HIV infection
3. HIV drug resistance
4. Monitoring and evaluation

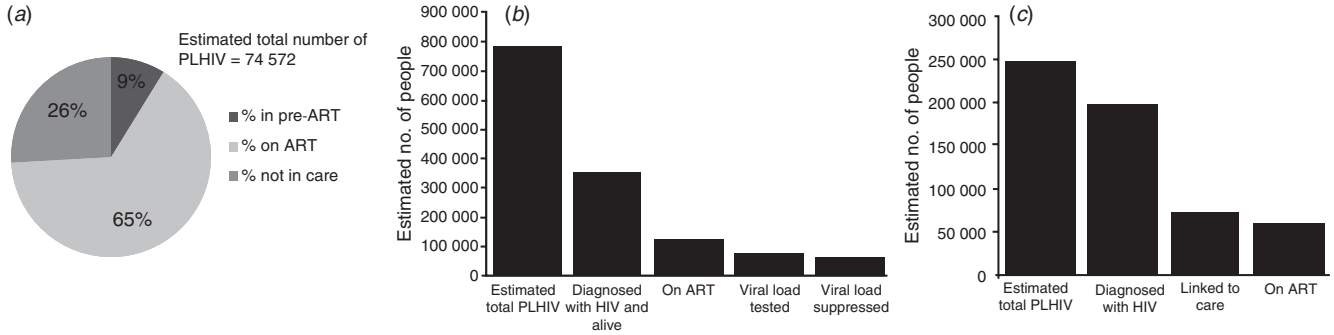

Fig. 1. (*a*) Distribution of people living with HIV/AIDS (PLHIV) in the care cascade, Cambodia (2012). Source: National Centre for HIV/AIDS, Dermatology and STD, Ministry of Health, Phnom Penh, Cambodia, 2012. (*b*) HIV treatment cascade, China (2011). Source: National Center for AIDS, STD Control and Prevention, Chinese Center for Disease Control and Prevention. (*c*) HIV treatment cascade, Vietnam (2011). Source: Vietnam Administration of HIV/AIDS Control.

3.0'.[55] This includes major efforts on identifying new HIV infections through partner testing, contact tracing, targeted community-based testing among key populations, earlier treatment, task shifting and decentralisation of services.[56]

The Chinese approach to ART-based prevention

At the end of 2011, there were an estimated 780 000 PLHIV in China. Of the 48 000 new infections, 52.2% were acquired through heterosexual transmission, 29.4% in MSM and 18.0% in IDUs. China has already incorporated new ART prevention tools into its national HIV control strategy, with a focus on serodiscordant couples and PrEP. The national targets are to reduce new infections by 25% and AIDS mortality by 30% by 2015. It has been estimated through mathematical modelling that quadrupling HIV testing and treatment rates could potentially avert 120 000 new HIV infections and 160 000 AIDS-related deaths in the next half decade.[30]

The biggest challenge for China in the cascade is how to get people diagnosed for HIV (Table 2; Fig. 1*b*). Late diagnosis is still an issue; for example, an analysis of data from China's National Free Antiretroviral Treatment Program during 2002–09 suggested a significant association between low baseline CD4 cell count (30% with CD4 <50 cells μL^{-1}) with high initial mortality following treatment initiation, emphasising the need to begin treatment sooner.[57,58] A retrospective analysis on the prevention benefit of ART in China suggests a 26% relative reduction in HIV transmission in the treated group, supporting earlier observations and supporting the feasibility of such a public health prevention strategy on a national scale.[59,60] However, the protective effect was only observed during the first year and a nonsignificant protective effect was seen thereafter. Moreover, no persistent preventive benefit was seen in couples when the partner had become HIV-infected by injecting drugs, which might suggest that they access treatment too late or are not retained on ART.[58,60] The documentation of implementation efforts will provide valuable insights into the incorporation of new biomedical tools into existing prevention strategies.[61–63] The Chinese Center for Disease Control and Prevention has initiated a community randomised control trial: the Treat ALL initiative (Guangxi NDA R01) in four counties with the goal of reducing community viral load and mortality through a 'treat ALL' initiative (Z. Wu, pers. comm.).

The Thai approach to ART-based prevention

According to the Asian Epidemic Model (a process model tailored to Asian epidemics),[64] there will be an estimated 43 040 new HIV cases in Thailand during 2012–16,[65] 41% occurring in MSM and 32% in heterosexual couples. Of the estimated 480 000 PLHIV,[5] 64% are aware of their HIV status and have registered in care. Based on data from the National Health Security Office, the largest national health insurance system which covers 77% of patients receiving ART, 81% of the 173 010 patients who registered for ART were retained on treatment after >6 months (S. Bhakeecheep, pers. comm.). Viral load suppression (<50 copies mL^{-1}) was achieved by 71% of those on ART for >6 months. The main challenge for Thailand remains for people to know their HIV status; various service delivery models are currently piloted to increase access and promote 'same hour testing' (Table 2). A demonstration project enrolling 800 participants from three provinces to evaluate the feasibility of the 'test and treat' strategy among Thai MSM and transgender women is currently ongoing (NCT01869595, Nittaya Phanuphak, pers. comm.). The main endpoints include acceptance of regular HIV testing and immediate ART once diagnosed with HIV, adherence to ART, long-term achievement of viral load suppression in blood and anogenital compartments, and changes in risk behaviour and rates of sexually transmissible infections over the study period.

A recent study on attitudes towards and preferences for PrEP among Thai MSM demonstrated that PrEP uptake could be considerable, despite multiple challenges related to HIV testing requirements, prescription inconvenience and expense perceived by MSM.[66] The next steps are demonstration projects to develop delivery systems for HIV testing, PrEP prescription, monitoring and linkages to other HIV prevention and treatment services.

Challenges and opportunities for ART-based prevention in Vietnam

Vietnam has a concentrated HIV epidemic, with the highest prevalence among IDUs (11.6% in 2012).[67] Along with harm

Table 2. Key challenges for harnessing prevention benefits of antiretroviral therapy (ART)
MSM, men who have sex with men; SWs, sex workers; IDUs, injecting drug users

Challenges	Proposed interventions
HIV prevention and testing uptake is very limited among key populations: • Low access to harm reduction services and targeted intervention sites for SWs, MSM and transgender women • Prevailing stigma and discrimination towards key populations and HIV prevent individuals coming forward for HIV testing and enrol into care	Expand access to targeted interventions for key populations and promote equal access to health services including HIV testing and treatment; for example: • Methadone clinics for IDUs, sexual health clinics, drop-in centres, mobile clinics and peer outreach as entry points for key populations • Initiate social change communication and awareness about HIV
HIV is diagnosed late: • High cost for HIV testing and retesting in low-level and concentrated epidemics • HIV testing facilities are not decentralised to lower levels of health care and to the community resulting in delays due to specimen and client referral • Confirmatory HIV testing in national-level public health laboratories results in delays in receiving test results • Annual HIV retesting of HIV-uninfected key populations, partner testing of HIV-infected individuals and couple testing are not systematically implemented	Implement and expand active finding of HIV cases: • Integrate HIV testing with other routine diagnostic tests to normalise HIV testing and save operational costs • Various service delivery models such as offering HIV testing in mobile clinics at daytime and night-time venues, drop-in centres and private hospitals promoting 'same hour' testing • Decentralise HIV testing to lower-level health facilities and community-based settings, including conducting the first screening test through trained peer-counsellors • Validate the HIV testing algorithm, allow confirmatory HIV testing in lower-level facilities and strengthen quality management systems to include community-based testing strategies • Annual HIV retesting of key populations, partner testing of HIV-infected individuals and couple testing in antenatal care, family planning, pre-ART and ART services
Substantial numbers of people diagnosed with HIV infection are lost to follow-up and not effectively linked to care, and hence are starting ART late • High loss to follow-up of individuals in pre-ART care • Lack of communication among peer-outreach workers, PLHIV groups and health care workers across prevention, care and treatment services resulting in major leakage within the treatment cascade	Active communication across services of the treatment cascade • Pilot initiation of immediate ART in the few newly diagnosed HIV infections and the few individuals in pre-ART • Introduce the concept of shared confidentiality among trained peer outreach workers in prevention and other care providers with the clients' consent
Attrition is high and adherence suboptimal in many countries • Discontinuation of ART due to loss to follow-up (e.g. cross-border and in-country migration) • Discontinuation of ART due to deaths attributable to HIV not reported • Discontinuation of ART while remaining in care	Approaches to ensure retention and adherence • Ensure continued financing for HIV care, ART and referral mechanisms for internal and external migrants • Strengthen civil registration systems and reporting of deaths attributable to HIV • While remaining in care: - offer couple or partner family counselling and care of HIV-infected individuals - introduce health care worker- and peer supporter-guided voluntary disclosure of HIV status to partners, and mentor treatment supporter or buddy systems
Monitoring and evaluation systems do not allow communication across the treatment cascade	Linking HIV testing to care and ART records • Implement unique health identifiers to allow communication across the cascade • Include indicators that allow analysis of individuals who retest for HIV, partner testing of HIV-infected individuals and couple counselling.

reduction programs and other HIV prevention interventions targeting key populations,[68,69] ART has rapidly expanded in Vietnam, with 72 711 people receiving ART at the end of 2012, representing 60% coverage among those in need.[69] The Vietnam Ministry of Health now aims to assess the acceptability and feasibility of earlier diagnosis and ART among key populations. However, several operational and structural challenges and gaps remain across the care cascade to achieve the modelled impact (Fig. 1*c*).[23] First, HTC uptake is very limited among key populations, with only 31% of IDU, 40% of female SWs and 39% of MSM reported that they had received HTC in the past 12 months and knew their test results in 2012 (Table 2).[69] An analysis of the new HIV diagnosis and the clinic enrolment data at national[70] and provincial levels[70] suggests that a substantial number of people diagnosed with HIV infection are lost to follow-up and are not effectively linked to care. People are also starting ART late,[70,71] with a median CD4 count of 93 cells mm^{-3} in 2010, associated with a higher attrition rate.[72] Attrition was defined as discontinuation of ART due to death or loss to follow-up, or discontinuation of ART medications while remaining in care. Furthermore, nearly 25% reported suboptimal adherence to

ART,[73] compromising viral suppression. Importantly, stigma, discrimination and punitive policies on drug use and sex work have posed significant structural barriers to timely and safe access to the HIV testing and treatment services for key populations.[72]

The large number of peer educators (6300) and partners (11 800) involved in HIV prevention outreach[70] could facilitate earlier uptake of HIV diagnosis and treatment, and support retention across the cascade in these populations. The government of Vietnam plans to expand methadone maintenance therapy to 80 000 IDUs by 2015,[70] which could serve as an effective platform to offer periodic HTC and ART among IDUs. Studies suggest that once IDU start ART, they have equally good responses to ART in achieving CD4 increase[74] and viral suppression[75] compared with non-IDUs. Decentralisation of HTC and ART, and enhanced community engagement are now being piloted to promote earlier diagnosis and treatment initiation.[76]

Other countries in Asia

With the exception of Indonesia and India, ART-based prevention interventions have not yet been considered by other Asian countries. However, as a concern, treatment coverage in Indonesia is particularly low (Table 1). The majority among people on ART were IDUs and only 55% were still on treatment at the end of 2012 (F. Widjayanti, WHO Indonesia, pers. comm.).

Treatment of acute and early HIV infection

Understanding early viral and immune events during acute HIV infection is critical to inform prevention and treatment efforts, particularly in high HIV incidence populations such as MSM and IDUs. Individuals with acute HIV infection have an eight- to 26-fold greater risk for transmitting HIV compared with those with chronic infections due to their high viral load.[77–79] People are highly infectious during the window period when HIV testing strategies using routine screening tests do not allow detection. The relative contribution of the early phase (the phase of HIV infection during the first 3–6 months after infection, which includes acute HIV infection) to HIV transmission in the context of TasP has been extensively modelled and reviewed, with differing results.[80] Interventions that rely on identifying and treating HIV-infected persons will have little to no effect on transmission, particularly among MSM with multiple partnerships of various durations and sexual behaviours during early infection.[81,82] Cohen *et al.* argue that 38% of incident HIV infections arise from contact with early HIV infection index cases during the first 4.8 months. Others argue that this is too high, proposing instead that only 2–4% of incident infections occur during acute HIV infection, and that annual testing and immediate treatment would still be sufficient to eliminate transmission.[82] However, little is known about acute and early HIV infection in Asia, with the exception of China and Thailand. Adding strategies for earlier detection of HIV-1 infection using pooled HIV nucleic acid amplification testing in antibody-negative blood samples from high-incidence populations of MSM was considered effective for intervening early with behavioural interventions and earlier treatment during a period with such a high transmission risk in Bangkok, Thailand,[83,84] and Lianing province, China.[85]

The need for HIV drug resistance surveillance

If people did not use ART or if ART suppressed the virus completely, there would be no drug resistance. A recent systematic review of HIV drug resistance studies in Asia showed that there were variable rates of pretreatment and acquired HIV drug resistance in populations receiving ART. Transmitted HIV drug resistance appears to be low (<5%) in the region, indicating that the first-line ART regimens are likely to be effective.[86] In high-income settings such as Taiwan (China) and Hong Kong (China), transmitted HIV drug-resistance rates have stabilised or are decreasing over time. This differs from Japan, where the prevalence of transmitted resistance in newly diagnosed patients has increased from 5.9% to 11.9% between 2003 and 2010.[87,88] The TREAT Asia/amfAR study evaluating transmitted HIV drug resistance and acquired HIV drug resistance showed that in ART-naïve patients from eight sites in Hong Kong (China), Malaysia and Thailand, 13.8% had more than one resistance-associated mutation, mostly to nucleoside analogue reverse transcriptase inhibitors and non-nucleoside analogue reserve transcriptase inhibitors. Protease inhibitor resistance was minimal (0.4%).[89,90] In a recent study, individuals with recent HIV-1 infection had a higher prevalence of pretreatment drug resistance compared with those with chronic infection (6.1% *v.* 4.0%) and had a higher frequency of resistance to protease inhibitors. Individuals who reported nonheterosexual contact as a risk factor were more likely to have drug resistance.[91]

Drug resistance peaks at some intermediate level of compliance or effectiveness.[92] One modelling study predicts that even with a very high usage of ART (a median of 70% of HIV-infected men receiving therapy), transmitted resistance would initially increase but would then fairly quickly stabilise at a relatively low level (between 6% and 21%). On the other hand, a high prevalence of drug resistance emerges because the majority of cases arise as a result of acquired resistance.[93] An increased level of acquired resistance would result in a greater need for second-line regimens and would drive up the costs.[94] Other models have predicted that drug resistance could be widespread in sub-Saharan Africa, due to losses to follow-up, inadequate adherence or the evolution of resistance,[95] although actual data from programs and population-based threshold studies suggest that these claims may not reflect the actual situation.[88,96] Taken together, these findings call for the surveillance of HIV drug resistance in programs that evaluate 'test and treat' strategies.

Monitoring and evaluation: from effectiveness to impact

Conceptually and programmatically, monitoring and evaluating of TasP and ART programs are almost identical. Just adding a denominator and few indicators would help TasP monitoring. However, the generation of data for population size estimations or even disaggregation of such data by subpopulation or geographical area is complex. Moreover, linking data from HIV testing to individuals ultimately diagnosed and enrolled

in care and treatment is virtually not possible in most Asian countries, except in settings where unique health identifiers have been in place such as China and Thailand. In fact, most countries still count the number of HIV tests performed; hardly any monitoring system allows HIV-uninfected or HIV-infected individuals who are retested to be differentiated. Patient records do not include an option to identify partners tested, or couples counselled and tested. Current monitoring systems do not allow the tracking of referral processes.

At the impact level, TasP is expected to reduce the number of new HIV infections. It requires the measurement of HIV incidence or seroconversion. Prospective cohort studies with longitudinal follow-up of HIV-uninfected individuals are the gold standard methodology to estimate HIV incidence rates but are long and expensive to carry out. Monitoring HIV prevalence trends is currently used as a rough proxy for HIV incidence, in combination with the use of modelling to project and test the plausibility of attribution of measured changes in incidence to TasP.[49] This requires measurement of the viral load in PLHIV. However, in many resource-constrained countries in Asia, viral load measurement is not routinely offered except in China and Thailand. Obtaining representative samples of viral load measurements among patients on ART could only be an interim measure, provided that a high proportion of people with HIV are identified and treated.

A concern impacting effectiveness is whether increased ART use in a given population will lead to treatment optimism and behavioural disinhibition among various sectors of the population, not only among those who initiate ART, but also among uninfected persons and undiagnosed HIV-infected individuals.

PrEP challenges and barriers

In Asia, implementing PrEP is even more challenging than TasP, as services and systems to retest HIV-uninfected individuals, monitor the retesting frequency and provide ART to HIV-uninfected individuals do not exist.[10] The success of PrEP introduction depends heavily on the willingness of individuals to take the drug, to be able to pay for antiretroviral drugs, access to HIV testing at least every 3–6 months and to adhere to PrEP.

In a setting with a very high HIV incidence among young MSM in Bangkok,[97] a survey on willingness to take PrEP revealed that despite the multiple challenges, MSM would be willing to take PrEP (39.2% definitely and 49.2% probably).[66] Similar results were reported from Chiang Mai in Thailand.[98] Studies conducted in China among MSM and serodiscordant heterosexual couples have revealed high rates of potential acceptance of PrEP in 85.9% of 405 female SWs interviewed in Guangxi, 67.8% of 153 MSM in Beijing and 84.6% of 351 HIV-uninfected partners in serodiscordant heterosexual couples in three cities in Xinjiang.[68] Whether PrEP uptake will be that high in the real world remains to be shown.

Discussion

TasP may be more feasible and effective in concentrated than in generalised epidemics, as resources for HIV testing and linkage to ART services could focus on confined and much smaller populations than those in generalised epidemics in sub-Saharan Africa.[99] However, transmission probability varies by route of infection. It remains unclear whether TasP will be as efficacious in preventing HIV transmission through penile–anal intercourse[100–102] and through sharing of contaminated injecting equipment as among heterosexual couples.

A limitation of this review is that many studies rely on observational and retrospective data analysis. For example, the beneficial effect of ART among IDUs from an outpatient clinic in Hanoi supports publications from other countries.[103] In a meta-analysis of studies of HIV-infected IDUs, adherence to ART has been shown to be comparable to people who do not inject.[104] Additional analysis is required to understand the contrasting results from China. The authors discussed that poor treatment adherence in China and nonlinked HIV transmission in this retrospective analysis of the national database were contributing factors.[58]

Evaluating both the prevention and treatment benefits and risks of TasP will be of critical importance, as Asian countries are expanding access to ART. The maximum population-level impact will only be achieved if countries are able to rachet up the HIV case detection rates and monitor individuals through the testing, care and treatment cascade. Although HIV testing and treatment are expanding, innovative strategies are needed to ensure effective linkages between HIV testing, enrolment and retention in HIV care for PLHIV.

PrEP and TasP should be delivered as part of combination prevention.[10,105,106] Implementing PrEP remains challenging, as services and systems catering to HIV-uninfected individuals are not well developed. New antiretroviral-based prevention tools do not justify forgoing condom use and harm reduction interventions for IDUs. Effective harm reduction interventions to prevent transmission among IDUs do exist. There is no reason to believe that IDUs are less likely to access available prevention services.[107,108] However, IDUs, MSM and SWs are the most underserved populations for HIV prevention and care services, and remain at a very high risk of HIV acquisition. All possible means to prevent HIV transmission and acquisition should be used. Significant overlapping transmission risks exist between these populations and PrEP and TasP may be a promising addition to the existing prevention interventions. Increasing awareness about benefits of TasP and PrEP in the community[109,110] and among health care workers[111] are of critical importance. Monitoring such programs will be complex. A phased approach for both TasP and PrEP is required, taking science, health system realities and ethical considerations into account.

Conclusions

There is an unprecedented opportunity in Asia to implement antiretroviral-based interventions for prevention successfully, as impressive ART scale-up has occurred during the past years in the region. Several countries are now paving the way to success. TasP and PrEP studies in key populations in Asia are, however, much needed to address challenges and provide insights into the applicability of these interventions to groups where firm evidence about feasibility and real-world effectiveness are still lacking.

Conflicts of interest

None declared.

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