Human immunodeficiency virus and acquired immune deficiency syndrome in Asia: an update

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Prevalence estimates of human immunodeficiency virus (HIV) infection in Asia are diverse, ranging from <0.1% to 1.1%. In Asia, approximately 4.7 million people are living with HIV and 310,000 are newly infected each year. The fastest growth of the epidemic throughout Asia is among men who have sex with men (MSM). Drug resistance varies from 4%-5% in an Asian cohort to 10% in an acutely infected MSM cohort in Bangkok. A rise (4%-14%) in the prevalence of syphilis is associated with the HIV epidemic in Asia. Tuberculosis is among the most common coinfections; however, HIV testing of tuberculosis patients is not routine. Coinfection with HBV, HCV, and triple coinfection varies from 8.7%-11%, 5%-18%, and 0.4%-3% respectively. Although the World Health Organization 2013 guidelines to start antiretroviral therapy (ART) early are implemented, most patients present late, with low CD4 counts, resulting in a high mortality during the first year of ART. While integrase inhibitor-based treatments are preferred first-line treatments in high income countries, efavirenz-based treatments remain preferred treatments in resource-limited countries. HIV-1 viral load testing is not available in most of these countries, making low-cost point-of-care testing accessibility an urgent priority. Effective ART coverage to prevent new HIV infections among children in Asia remains low. To provide life-long ART for children, better use of current first-line regimens and access to pediatric second-line formulations are important. To end AIDS in Asia by 2030, committed policy with innovative strategies to enhance “reach, recruit, treat and retain” combined with effective prevention strategies are required.

Keywords: AIDS, Asia, HIV

Epidemiology

There has been wide variation in the scope of the human immunodeficiency virus (HIV) epidemic throughout Asia countries, a factor reflecting the diverse nature of the geographies and cultures of the countries in the region. The earliest cases of HIV in Asia were reported in Thailand in 1985 [1]. HIV spread among people who inject drugs (PWID) and female sex workers (FSW) and their clients. The male clients of FSW spread HIV to their spouses or casual partners and in turn, to their children by mother to child transmission [2]. This pattern still continues, but more recently, new patterns of HIV spread have emerged.

In 2012, the highest prevalence amongst those aged 15–49 years was in Thailand (1.1%) and Cambodia (0.8%), followed by Myanmar (0.6%). Prevalence rates in Indonesia, Malaysia, and Vietnam were 0.4%, and 0.3% in India*, Lao People’s Democratic Republic, and Nepal, and 0.2% in Bhutan. In other countries in the region*, the prevalence was < 0.1%. Although these rates as a proportion of the total population are low, the large numbers of people living in the region translates to high absolute numbers of people living with HIV: an estimated 4.7 million in 2012 (Table 1) [3].
With effective National responses and Community leadership, most Asian countries have had dramatic reductions in new HIV infections since 2001; however, there were approximately over 310,000 new infections in Asia in 2012* [3, 4]. PWID, FSW, and male sex workers remain high-risk groups for HIV infection. Although injecting drug use is an important factor in the spread of HIV and risk reduction strategies such as methadone substitution and clean injecting equipment are known to significantly reduce HIV transmission amongst PWID, legal and social barriers have inhibited an effective prevention response amongst this key affected population (KAP) [3, 5].

Throughout Asia, the fastest spread of the epidemic is among men who have sex with men (MSM) [6, 7]. These epidemics are predominantly concentrated in cities, and the majority of new infections occur in young MSM (Figure 1). Among MSM in Bangkok HIV prevalence is >25%. In Jakarta and Chengdu, HIV prevalence amongst MSM is approximately 15%. Behavioral surveys demonstrate inconsistent condom use and multiple sexual partners amongst MSM, and many have never been tested for HIV. The same problems are evident amongst transgender women, who feel stigmatized and discriminated against by traditional healthcare systems [8]. Projects at the Thai Red Cross AIDS Research Centre in Bangkok are using social networking tools, community-based organizations, and point-of-care testing to promote HIV testing among MSM and transgender women who have never had an HIV test, to refer and retain them in care. Such community-based voluntary counseling and testing have been shown to achieve high uptake, and are more likely to diagnose people with higher CD4 counts and successfully link them to care, than clinics and hospitals [9].

In some countries such as Cambodia and Thailand, antenatal screening and prevention of mother to child transmission (PMCT) programmes have been very effective in reducing new HIV infections among children. However, regional PMCT program coverage is only 19%, and women may only receive single dose nevirapine, rather than WHO recommended combination antiretroviral therapy (ART) [3].

Migrant workers who move to the cities in search of work are another KAP often overlooked in National Treatment Responses. Thailand will begin to cover healthcare for migrant workers in 2015. In addition, Thailand is showing regional leadership in implementing programs in an effort to end the acquired immune deficiency syndrome (AIDS) epidemic. The 2014 Thai National Treatment Guidelines recommend ART at any CD4 count, and funding has been approved to launch these guidelines in healthcare schemes throughout the country in 2015 [10].

*Estimates for China and India are based on 2011 National Data

Table 1. Number of people living with human immunodeficiency virus (HIV), number of new infections and acquired immune deficiency syndrome (AIDS) related deaths in 2012, in Asian countries with the highest HIV burden [3, 4].

<table>
<thead>
<tr>
<th>Country</th>
<th>People living with HIV</th>
<th>Number of new infections</th>
<th>AIDS-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>2,100,000</td>
<td>130,000</td>
<td>147,000</td>
</tr>
<tr>
<td>China</td>
<td>780,000</td>
<td>48,000</td>
<td>28,000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>610,000</td>
<td>76,000</td>
<td>27,000</td>
</tr>
<tr>
<td>Thailand</td>
<td>450,000</td>
<td>9,000</td>
<td>19,000</td>
</tr>
<tr>
<td>Vietnam</td>
<td>260,000</td>
<td>13,000</td>
<td>12,500</td>
</tr>
<tr>
<td>Myanmar</td>
<td>200,000</td>
<td>7,100</td>
<td>12,000</td>
</tr>
<tr>
<td>Pakistan</td>
<td>87,000</td>
<td>19,000</td>
<td>3,500</td>
</tr>
<tr>
<td>Malaysia</td>
<td>82,000</td>
<td>7,400</td>
<td>5,200</td>
</tr>
<tr>
<td>Cambodia</td>
<td>76,000</td>
<td>1,400</td>
<td>2,700</td>
</tr>
<tr>
<td>Nepal</td>
<td>49,000</td>
<td>1200</td>
<td>4100</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>25,000</td>
<td>&lt;1000</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>Philippines</td>
<td>15,000</td>
<td>1,800</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>12,000</td>
<td>1,000</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>
HIV subtypes in Asia

The three most common HIV-1 subtypes found in Asia are subtypes B, CRF01_AE, and C [11]. Dominant HIV-1 subtype distribution varies between countries. Japan, South Korea, and Mongolia are infected mainly with subtype B, whereas subtype C is the major subtype found in India, Nepal, Bangladesh, and Papua New Guinea. Subtype A is the most common subtype found in Pakistan. All Southeast Asian countries, except the Philippines (subtype B and CRF01_AE), are predominantly infected with a recombinant subtype, CRF01_AE. More new CRF subtypes have recently been reported in this region, including CRF62_BC, CRF65_cpx (both from China) [12, 13], CRF07_BC (from Taiwan) [14], and CRF58_01B (from Malaysia) [15]. Nonetheless, different HIV-1 subtypes show no significant clinical impact either on disease progression, responses to ART or HIV drug resistance profiles [16, 17]. Some reports have suggested that subtype CRF01_AE may prefer CXCR-4 coreceptor use compared with subtype B, so that CCR-5 inhibitor prescription probability would be lower [18, 19]. However, a recent study has indicated an overestimation of CXCR4-use by genotypic prediction algorithms [20].

Transmission of HIV-1 drug resistance in Asia

An approximate 4%–5% HIV-1 drug resistance (HDR) transmission rate was reported from an Asian cohort [21, 22, 23]. This was associated with a more than 3 times increased risk of antiretroviral treatment failure [22]. Among recently infected patients, the most common resistance mutations include M184I/V and T215D/E/F/I/S/Y (1.1%, to nucleoside analog reverse transcriptase inhibitors or NRTIs), Y181C (1.3%, to non-nucleoside analog reverse transcriptase inhibitors or NNRTIs), and M46I (1.5%, to protease inhibitors or PIs) [23]. Although the current HDR transmission rate in Asia is still considered as low to moderate according to the WHO definition, expanding the ART coverage program in this region will eventually further increase the rate of drug resistance transmission so that a baseline HIV-drug resistance test will be required in the near future. The transmission rate is higher in MSM than in other risk groups, and according to the most recent report in MSM with acute HIV infection in Bangkok, the HDR transmission rate was close to 10% [24]. It is therefore justified to consider HIV drug resistance testing in MSM, in settings where affordability is not an issue.

Acute HIV Infection and HIV cure research

Asia, and Thailand in particular, is one of the global leaders on acute HIV infection (AHI) and cure research [25, 26]. Using the approach of pooled nucleic acid testing (NAT) of fourth-generation enzyme immunoassay (EIA)-negative samples, and subsequent less sensitive EIA testing of fourth-generation EIA-positive samples at the Thai Red Cross Anonymous Clinic in Bangkok, which serves approximately 20,000–25,000 HIV tested clients each year, the HIV incidence rate was approximately 2.7 per 100 person-years. The majority were MSM. Such a large scale prospective screening program has made diagnosis of the very early stage of acute
HIV infection (known as Fiebig stage I) feasible. The investigators were recently able to further stratify Fiebig stage I by the use of a fourth generation EIA, and found that patients with AHI who are NAT positive, but fourth and third generation EIA negative, have much lower HIV-1 RNA and DNA than the other strata. This prospective cohort has created an opportunity to investigate HIV cure research [27, 28].

**Coinfections in Asia**

**TB-HIV coinfection**

The Asia–Pacific region contributes more than a half of all tuberculosis (TB) cases worldwide; TB is one of the most common coinfections found among HIV patients in this region. However, routine testing of TB patients for HIV infection is not universally implemented [29]. The HIV prevalence in TB patients varies from 0.1% in the Philippines to 3%–9% in Indonesia, Cambodia, Vietnam, India and Myanmar, and to 14%–15% in Papua New Guinea and Thailand. From a large Asian pediatric HIV cohort “TApHOD”, 17% reported pulmonary TB in a period of 13 years of follow-up [30]. Median CD4 count was only 100 cells/mm³ among TB-HIV coinfected patients in an Asian adult HIV cohort, with a mortality rate up to 4 per 100 person-years [31]. Because most patients in these 2 cohorts had advanced HIV infection, one-third also had extrapulmonary TB.

**Viral hepatitis coinfection in Asia**

Studies from Cambodia, China, Myanmar, and Thailand have reported hepatitis B virus (HBV) coinfection rates varying from 8.7%–11%, hepatitis C virus (HCV) coinfection from 5%–18%, and triple infection from 0.4%–3% [32-35]. HCV coinfection is much more common among PWID, i.e., 98% in Vietnam, 82% in China, and 50% in Thailand are anti-HCV seropositive [32, 36, 37]. HBV and HCV coinfection is associated with higher mortality and more antiretroviral (ARV) drug-related hepatotoxicity compared with HIV monoinfection [38]. The majority of hepatitis B coinfection in Southeast Asia is genotype C. In Thailand, most HCV are genotype 3 is significantly related to intravenous drug use, whereas; in Vietnam, genotype 6 is most common [39]. Immunopathogenesis studies of HBV or HCV coinfection, or triple infection, in this region have demonstrated a link between microbial translocation and immune activation, and the risk of death or HBV-hepatitis flare in patients who are initiating ART [40, 41]. Two randomized-controlled studies of HBV-HIV coinfection in Thailand have shown superior efficacy on HBV viral suppression with tenofovir disoproxil fumarate combined with emtricitabine or lamivudine, than either of the latter two agents used alone [42, 43]. Twenty-two percent of patients developed early hepatitic flare (EHF, defined as alanine transaminase >5 × the upper limit of normal in the first 12 weeks). This was associated with a higher rate of hepatitis B surface antigen (HBsAg) and the extracellular form of hepatitis B core antigen (HBeAg) loss compared to those without EHF [44].

Interestingly, a Thai study found a high proportion (>70%) of HBV-HIV coinfected patients had low levels of vitamin D both before and after long-term ART [45]. Thus, patients in whom long-term tenofovir-based treatment is needed, assessment of vitamin D levels and proper supplementation may be important to minimize the risk of osteoporosis. In some high income Asian countries such as Japan, HCV-infected patients can get access to highly effective and well-tolerated oral direct-acting antiviral treatments. However, because of their high cost, these treatments are not available for patients in low-middle income countries in the region.

**Syphilis and other sexually-transmitted infections (STIs) are on the rise in Asia**

Recent studies have shown a rise (4%–14%) and association between syphilis and HIV epidemics in various populations, including MSM [46-49], PWID, and sex workers [50]. Recent findings from Thailand’s ‘Test-and-Treat’ pilot program have shown a high prevalence of STIs among MSM and transgender women, particular among those with HIV infection (syphilis 27% vs 5.8%, gonorrhea 24.8% vs 8.5%, Chlamydia infection 37.5% vs 18% in HIV+ vs HIV–, respectively) [51]. STI screening should therefore be included in HIV prevention and care programs.

**Recent HIV treatment guidelines and their implementation**

The recent World Health Organization (WHO) Treatment Guidelines 2013 has increased the CD4 count eligibility criteria for commencing ART for treating and preventing HIV infection from <350, to <500 cells/mm³ [52]. This recommendation will bring together clinical, service delivery, and programmatic guidance for low- and middle-income countries
across all age ranges. These new, consolidated WHO guidelines, are also more practical because they recommend a single pill regimen including tenofovir, lamivudine, or emtricitabine, and efavirenz, as preferred first-line therapy for all settings, including pregnant women and individuals with active tuberculosis. By contrast, the most recent U.S. Department of Health and Human Services (DHHS) guidelines issued in 2015 include only integrase inhibitor- and darunavir-based (only one from the protease inhibitor class), but not NNRTI-based, as their preferred first antiretroviral treatment regimen [53]. Most resource-limited countries have implemented the WHO 2013 consolidated guidelines. In 2014, Thailand has however announced new HIV treatment and Prevention Guidelines 2014 to initiate ART for all HIV-infected individuals, regardless of CD4 count [54]. This is in line with the committed national policy for ending AIDS by 2030. Of note, the most recent findings a major international randomized trial named “START” showed that starting ART earlier with a CD4 cell count >500 compared to when CD4 cell count <350 cells/mm³, reduces the risk of developing serious AIDS-related and non-AIDS related events by up to 50% [55]. This important result strongly supports the Thai guideline recommendation of offering ART to all patients, regardless of their CD4 cell count.

**Late presentation of patients is a major challenge**

Although over the past few years most countries have implemented earlier ART for HIV patients, recruiting patients with a high CD4 cell count has not been successful. Published data from several countries have found median CD4 cell counts at diagnosis to be lower than 100–150 cells/mm³ [56-59]. Such advanced stage presentation has led to a high mortality rate [60]. New strategies for earlier recruitment of patients for HIV diagnosis and treatment is therefore warranted.

**Viral load and CD4 count monitoring in Asia**

Only a few low-middle income countries in Asia, such as Thailand and Cambodia, have provided HIV-1 plasma viral load as a component of their national HIV treatment programs. Nonetheless all countries include CD4 counts in their programs. Although routine versus clinical-driven laboratory monitoring in the first 3 years of ART has shown no significant difference on clinical progression and death rates [61, 62], late switching to second-line ART after failure may compromise future ARV options [63]. Point-of-care (POC) tests for CD4 count have been evaluated in some Asian countries [64-66] and by the WHO [67] and the results support its relevance for wide implementation, while expanding HIV treatment in this region. Some HIV-1 viral load point-of-care tests have been evaluated in Sub Saharan Africa with convincing reports [68, 69]. The challenges and strategies for the use of these POC tests in Asian settings should be considered for integration into their national programs [70]. In terms of how often to follow-up CD4 counts, among patients with viral suppression, an annual CD4 count test is sufficient [71]. The recent Thai guidelines recommend to monitor CD4 count and viral load twice yearly until the CD4 is >350, and/or viral load falls to <50 copies/mL, then once yearly thereafter [54].

**Antiretroviral therapy options in Asia**

In resource-rich Asian countries such as Japan, the preferred first-line ART is an integrase inhibitor-based regimen (dolutegravir in particular), which is similar to the most recent recommendations in the U.S. DHHS guidelines (April 2015) [53]. By contrast, because of cost constraints, most Asian countries still recommend non-nucleoside analog reverse transcriptase-based antiretrovirals, efavirenz in particular, as their preferred regimens [52]. Efavirenz causes central neurological side-effects and rash in 5%–10% of treated patients which limits the tolerability of the drug, and this may prove a challenge for Asia, while implementing recommendations to commence ART at a 500 cell/mm³ CD4 count or higher threshold.

**Table 2. Comparison of guideline recommendations for initiating antiretroviral therapy**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>CD4</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. DHHS 2015 [53]</td>
<td>All</td>
<td>When the patient is ready and committed to treatment</td>
</tr>
<tr>
<td>WHO 2013 [52] and most Asian countries</td>
<td>&lt;500</td>
<td>Regardless of CD4 for specific settings and the patient is ready and committed to treatment</td>
</tr>
<tr>
<td>Thailand 2014 [54]</td>
<td>All</td>
<td>When the patient is ready and committed to treatment</td>
</tr>
</tbody>
</table>
Optimizing antiretroviral therapy in Asia

In general, ARV drug development for licensing has been based on pharmacokinetic results among Western volunteers. Furthermore, the final dose selected for phase III trials and approval is decided by the principle of selecting the highest tolerated dose to provide an adequate drug resistance barrier. The trade-off is however, more toxicity and higher costs. Optimizing antiretroviral dosage to improve tolerability and as a cost-saving measure is therefore relevant [72]. Several pharmacokinetic studies have been performed in our center with a similar observation that Thai patients, when taking a standard dose of nevirapine, efavirenz, lopinavir, and atazanavir according to the approved instructions, had approximately 30% higher drug exposure than has been observed in patients in the West [73-75]. However, to implement dose optimization at the national level, well-designed randomized-controlled trials (RCT) are warranted. The ENCORE study, a large scale non-inferiority RCT, supports the use of 400 mg of efavirenz for routine care regardless of ethnicity or body weight [76].

A Thai study found that lowering the dose of the integrase inhibitor “raltegravir” from 800 to 400 mg once daily resulted in suboptimal levels [77]. An approximately 30% reduction in lopinavir dose when boosted with ritonavir found noninferiority to the standard dose for maintaining HIV viral suppression in well-virologically controlled Thai children. Lower rates of dyslipidemia were also observed [78]. Another low dose versus standard dose atazanavir (200 vs 300 mg daily) noninferiority randomized-study known as “LASA” has recently been completed and the results will be presented at the next IAS conference in Vancouver 2015 [79]. It is estimated that integrating these antiretroviral dose optimization studies into policy and practice will save hundreds of millions of U.S. dollars worldwide [72].

Children with HIV infection in Asia

Like adults, HIV-infected children in Asia commence ART in more advanced stages, indicated by low CD4 percentages and a high proportion with World Health Organization (WHO) stage 3 or 4 disease [80]. Of note, while the majority of the ART-treated children from Thai and Vietnamese cohorts achieve virologic control and good CD4 count responses [81, 82], a high loss to follow-up rate in a pre-ART cohort was reported from India [83]. Thus, proper strategies to improve early diagnosis and treatment for children infected with HIV are urgently needed for resource-limited Asian countries. From a large Asian Pediatric cohort “TapHOD”, 10% of HIV-infected children are taking second-line ART [84]. To provide life-long ART for children, better use of current first-line regimens and broader access to heat-stable, pediatric second-line formulations are important.

Eliminating new infection in children in Asia

Effective antiretroviral regimen coverage for preventing new HIV infections among children remains low in Asia. In 2012, coverage was estimated at only 18% in South and Southeast Asia, 26% in East Asia and 49% in Oceania. This is well below the 62% average for low- and middle-income countries worldwide [85]. Across Asia, countries have different degrees of challenges in eliminating new infections in children: these include stigma, adequate donor funding, health care infrastructure and capacity.

HIV and aging in Asia

Up to 20% of patients in a large Asian cohort were older than 50 years [86]. A study from China found an increase of older patients (>50) from 0% in 2000 to 22% in 2012 [87]. Another Chinese study also showed the proportion of older patients increased to 42.7% in 2011, from 16.5% in 2007 [88]. Nevertheless, “age effects” are similar across the resource-rich and resource-limited divide, thus future ageing-related findings will likely also be applicable to Asia. The challenges in managing older patients include more atherosclerotic-associated comorbidities, higher risk of treatment-related toxicity, polypharmacy, and drug–drug interactions, and neurocognitive disorders [89].

High impact research in Asia and the Pacific

Region specific scientific and clinical evidence to guide country policies, treatment and prevention clinical practice are warranted. In the past decades, several countries in this region have initiated or collaborated in clinical and/or epidemiological research studies that are relevant and have significant impact on HIV treatment and prevention. Setting up and maintaining research centers or institutes in this region is therefore essential. For instance, TREAT Asia (Therapeutics Research, Education, and AIDS Training in Asia), originally set-up by the American AIDS foundation, has played a major role in cohort-based clinical
research, education, and advocacy of evidence-based HIV-related policies. This has been achieved through a collaborative network of clinics, hospitals, research institutions, and civil society in this region to ensure the safe and effective delivery of HIV treatments to adults and children across the Asia-Pacific [90, 91]. The Thai Red Cross AIDS Research Center, either through HIV-NAT or SEARCH or its prevention department, have contributed relevant evidence through treatment strategic research, acute HIV infection and cure research, and treatment-as-prevention, respectively [92-94]. RIHES (the Research Institute for Health Sciences) of Chiang mai University, Thailand has contributed significantly on various major HIV prevention research strategies, especially pre-exposure prophylaxis and treatment-as-prevention [95]. The Kirby Institute, Sydney, Australia is another key player in initiating high impact research, not only relevant to this region, but also globally through multinational clinical trials addressing various strategic HIV treatments [76, 96].

Ending AIDS policy in Asia

Asia–Pacific countries, during the Asia–Pacific Intergovernmental Meeting on HIV and AIDS in Bangkok, Thailand, have shown their commitment to ending AIDS by 2030 [97]. To implement the policy, a number of countries such as Thailand, China Cambodia, and Indonesia, have started their own pilot programs focusing on most-at-risk populations i.e., MSM, commercial sex workers, and PWID, respectively. The Adam’s Love website, run by the Thai Red Cross AIDS Research Center, has recently published the usefulness of using social networking technologies to engage MSM for early HIV testing and treatment. However, in reality, most reports have shown median CD4 cell counts of the patients at diagnosis and prior to commencing ART was lower than 150 cells/mm³, and the loss to follow-up rate increased while expanding the coverage [98].

To end AIDS, each country must therefore to develop a strategy to diagnose HIV-infected patients early, link them to ART services and retain them on treatment with a high rate of virological control [99]. Cassell and his colleagues have recently proposed ‘4 priorities for “getting to zero” in this region: (1) innovative strategies to reach, test, treat, and retain in services the individuals most likely to acquire or transmit HIV; (2) task shifting and enhanced partnerships between the public sector and civil society; (3) improved “cascade” data systems to assess and promote service uptake and retention; and (4) policy and financing reform to enhance HIV testing and treatment access among key populations [100].

Conclusion

Asian countries show a wide variation in HIV epidemics that reflects the diversity of the individual countries in the region. The capability of each country in fighting HIV/AIDS is also vastly diverse with different outcomes. Unless policy and financial reform with innovative strategies are executed, it is uncertain whether Asia can succeed in its aim to end AIDS by 2030.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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