Scale-up of national antiretroviral therapy programs: progress and challenges in the Asia Pacific region

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Background: There has been tremendous scale-up of antiretroviral therapy (ART) services in the Asia Pacific region, which is home to an estimated 4.7 million persons living with HIV/AIDS. We examined treatment scale-up, ART program practices, and clinical outcome data in the nine low-and-middle-income countries that share over 95% of the HIV burden in the region.

Methods: Standardized indicators for ART scale-up and treatment outcomes were examined for Cambodia, China, India, Indonesia, Myanmar, Nepal, Papua New Guinea, Thailand, and Vietnam using data submitted by each country to the WHO/The Joint United Nations Programme on HIV/AIDS (UNAIDS)/UNICEF joint framework tool for monitoring the health sector response to HIV/AIDS. Data on ART program practices were abstracted from National HIV Treatment Guidelines for each country.

Results: At the end of 2009, over 700 000 HIV-infected persons were receiving ART in the nine focus countries. Treatment coverage varies widely in the region, ranging from 16 to 93%. All nine countries employ a public health approach to ART services and provide a standardized first-line nonnucleoside reverse transcriptase inhibitor-based regimen. Among patients initiated on first-line ART in these countries, 65–88% remain alive and on treatment 12 months later. Over 50% of mortality occurs in the first 6 months of therapy, and losses to follow-up range from 8 to 16% at 2 years.

Conclusion: Impressive ART scale-up efforts in the region have resulted in significant improvements in survival among persons receiving therapy. Continued funding support and political commitment will be essential for further expansion of public sector ART services to those in need. To improve treatment outcomes, national programs should focus on earlier identification of persons requiring ART, decentralization of ART services, and the development of stronger healthcare systems to support the provision of a continuum of HIV care. © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

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Introduction

The Asia Pacific region has the second highest HIV burden in the world, with an estimated 4.7 million persons living with HIV/AIDS [1]. In this diverse and populous region, HIV is considered a concentrated epidemic, where the prevalence of HIV is highest among key high-risk populations, including sex workers and their clients, injection drug users, and increasingly, MSM [2]. Over 95% of the HIV burden in the Asia Pacific region is borne by nine countries: Cambodia, China, India, Indonesia, Myanmar, Nepal, Papua New Guinea, Thailand, and Vietnam.

In accordance with the 2006 United Nations' Declaration to Scale-Up toward Universal Access to HIV Treatment, Care and Support Services, countries in the Asia Pacific region have defined ambitious national targets for the scale-up of antiretroviral therapy (ART) services [3]. Indeed, the dramatic expansion of treatment services in the region in the last several years has been accompanied by significant improvements in survival among persons accessing care [4–7]. As treatment programs in the region continue to mature, we are at a critical juncture to review the progress made thus far in delivering life-saving treatment to those in need. Previously published reports on HIV in Asia have focused on treatment scale-up and outcomes in individual countries [5,8] or patient cohorts [9]. However, there are no published reviews on the expansion of public sector ART services in the region that present comparable data from multiple countries. The objectives of this study are to report key indicators related to ART scale-up and describe ART program practices and clinical outcome data in the nine focus countries that bear the greatest burden of HIV in the Asia Pacific region. Examination of these data provides a unique opportunity to understand the challenges that must be overcome to ensure the long-term success of treatment services in the region.

Methods

The present review draws on several sources of data. For ART scale-up and treatment outcomes, data submitted for the 2009 and 2010 'Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector' reports were used [10] and reflect program characteristics and outcomes as of December 2009. For the Universal Access Report, the national program from each country is requested to compile and submit verified routine program data on 49 standard indicators that reflect the scale-up of priority health sector interventions for HIV prevention, treatment, care, and support. Data are submitted to WHO using the WHO/UNAIDS/UNICEF joint framework for 'Monitoring and Reporting on the Health Sector Response to HIV/AIDS' data collection tool [11,12]. Not all data submitted in the joint framework tool by each country are published in the Universal Access Report. Our review draws on both published and unpublished HIV treatment-related data submitted to the joint framework tool by each of the nine focus countries. Additional data including recent national estimates of the number of HIV-infected persons, were also obtained from each country's 'Country Progress Report on the Follow-up to the Declaration of Commitment on HIV/AIDS' for the 2008–2009 reporting period [13–21].

Estimates of the number of HIV-infected persons eligible for ART were obtained from the 2008 WHO/UNAIDS Towards Universal Access Report [22]. Updated estimates have not been published to date and are only anticipated at the end of 2010. Additional country-level scale-up and treatment outcome data were obtained from peer-reviewed published literature (using the search terms 'Asia', 'HIV', and 'antiretroviral therapy' in PubMed) and abstracts presented at international scientific conferences, including the International AIDS Conference and the Conference on Retrovirus and Opportunistic Infections. Data on ART program practices and recommended antiretroviral regimens were abstracted from the latest published version of National HIV Treatment Guidelines from each country [23–31].

Results

Public sector antiretroviral therapy scale-up

At the beginning of 2003, an estimated 67 000 HIV-infected persons were receiving ART across the nine focus countries. As of December 2009 over 700 000 persons living with HIV were receiving ART (Fig. 1) [13–21], indicating treatment coverage for approximately one-third of the estimated 1.5 million persons in need of ART in these nine countries [10]. The extent of ART coverage varies widely across countries in the region. Based on a CD4 cell count threshold of 200 cells/μl or less for ART initiation, some countries, including Cambodia, Papua New Guinea, and Thailand have either achieved or are approaching their universal access goals of providing ART to 80% of persons who require treatment [17,19,20]. In other countries, ART programs continue to expand, with treatment coverage ranging from 16 to 57% of those in need of ART [13,16,18,21] (Table 1) [22]. As estimates for those who require ART are revised to account for updated recommendations to start ART for anyone with a CD4 cell count of 350 cell/μl or less [33], national treatment coverage rates will accordingly decrease to reflect these broader eligibility criteria.

In several countries, including Vietnam and Indonesia, ART is currently provided to eligible patients at 28–30% of the hospitals and clinics where HIV treatment services

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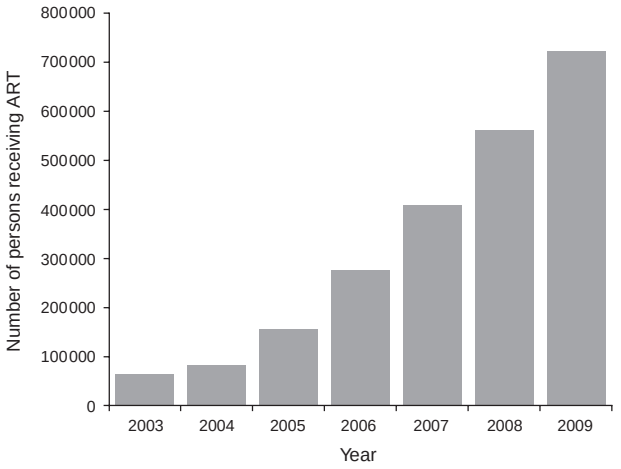

Fig. 1. Antiretroviral therapy scale-up in the Asia Pacific region, 2003–2009. The number of HIV-infected individuals receiving ART in the nine countries that share more than 95% of the HIV/AIDS burden in the Asia Pacific region has increased from 67 000 in 2003 to over 720 000 in 2009. Source: Country Reports on the Follow up to the Declaration of Commitment On HIV/AIDS (UNGASS), 2008–2009 Reporting Period [13–21].

have been planned [10,16,21]. Since 2006, HIV treatment services in Thailand were integrated into the government's universal healthcare coverage scheme, and ART is now available at 95% of the 1066 hospitals designated for the provision of ART across Thailand's 1057 districts [10,17]. Expansion of services has been rapid, as in India, where treatment started in eight facilities in 2004, and is now available at 230 primary ART centers and an additional 260 follow-up care centers across the country [15].

The involvement of nongovernmental organizations (NGOs) has also been an integral part of ART scale-up. In Myanmar and Papua New Guinea, almost 50% of the health facilities that provide ART services are supported by NGOs or faith-based organizations [18,19]. NGOs also play a crucial role in linking facility-based services with community-based care and support in several countries, including Vietnam, where civil society groups provide over 50% of home-based care services for patients receiving ART [21]. The private medical sector provides HIV treatment services to an additional several thousand HIV-infected individuals in several countries, including India [34].

The expansion of ART services for children in the region has been slower, in part because of the limited availability of pediatric antiretroviral drug formulations, as was the case in China [35]. Successful scale-up of pediatric ART has also required additional focused efforts to diagnose and link children to treatment services [36]. In Cambodia, ART services for children have been available since 2001, but were given further priority in 2004 when the government issued a policy package of guidelines, training, and drug supply provisions for the management of pediatric HIV [37]. Similarly in India, the implementation of an intensive pediatric HIV initiative designed to increase access to care for HIV-infected children resulted in the successful expansion of pediatric ART services from 1800 children in 2006 to over 17 000 children in 2009 [15,38].

Table 1. Scale-up of antiretroviral therapy services in the Asia Pacific region.

Country	Number of HIV-infected (% adult prevalence)[a]	Year ART program started	Estimated number eligible for ART[b]	Currently receiving ART (% of eligible)[c]	Children receiving ART[d]
Cambodia	57 900 (0.70%)	2001	40 000	37 315 (93%)	3638
China[e]	740 000 (0.06%)	2002	—	65 481 (–)	1594
India[f]	2 270 000 (0.29%)	2004	—	320 074 (–)	17 952
Indonesia	330 000 (0.22%)	2005	43 000	15 442 (36%)	356
Myanmar	238 000 (0.61%)	2005	75 000	21 138 (28%)	1535
Nepal	70 000 (0.49%)	2004	20 000	3226 (16%)	178
Papua New Guinea	34 000 (0.9%)	2004	9065	6751 (75%)	427
Thailand	530 000 (1.3%)	2000	275 000	216 118 (78%)	8076
Vietnam	254 000 (0.44%)	2005	67 000	37 995 (57%)	1987

[a]Data reflect national estimates of number and prevalence of HIV/AIDS in 2009 (Cambodia, China, Myanmar, Papua New Guinea, Thailand, Vietnam), 2008 (India, Indonesia) or 2007 (Nepal) as reported in Country Reports on the Follow-up to the Declaration of Commitment on HIV/AIDS (UNGASS), 2008–2009 reporting period [13–21], and for Papua New Guinea, the results of a national consensus meeting [32].
[b]The number of HIV-infected persons eligible for antiretroviral therapy (ART) is based on estimates published in the 2008 UNAIDS/WHO Towards Universal Access Report, which reported the estimated number in need of first-line ART in 2007. This estimate reflects the number of HIV-infected persons who require ART based on CD4 cell eligibility criteria of $\leq$200 cells/μl [22]. UNAIDS/WHO estimates for number eligible for ART are currently under revision. As countries revise their National HIV Treatment Guidelines and increase CD4 cell count thresholds for ART initiation, the number of persons estimated to be eligible for ART is expected to increase.
[c]Source: Country reports on the follow-up to the Declaration of Commitment on HIV/AIDS (UNGASS), 2008–2009 reporting period [13–21]. The ''percent of eligible receiving ART'' listed should be interpreted with caution as estimates for ''currently receiving ART'' are from 2009/2010, while estimates for ''numbers eligible for ART'' are from 2007/2008.
[d]Individuals <15 years of age are considered children.
[e]There is no published estimate of the number of persons requiring ART in China in the UNIADS/WHO 2008 Towards Universal Access Report. However, the Chinese Ministry of Health reports a 2009 estimate of the number of people with AIDS as 105 000 [14].
[f]There is no published estimate of the number of persons requiring ART in India in the UNAIDS/WHO 2008 Universal Access Report.

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Table 2. Antiretroviral therapy program characteristics in the Asia Pacific region.

Country	CD4 cell thresholds for ART initiation according to WHO disease stage	Routine first-line ART monitoring
Cambodia	Any WHO stage: CD4 ≤350 WHO stage 3 or 4: any CD4	Clinical: monthly CD4: Baseline and every 6 months
China	WHO stage 1, 2: suggest CD4 200–350 WHO stage 3: suggest any CD4 WHO stage 4: any CD4	Clinical: Monthly for first 3 months and then every 3 months CD4: Baseline, every 3 months x 1 year, and then 6 months Viral load: 6 months after ART initiation, and then yearly
India	WHO stage 1, 2: CD4 <250 WHO stage 3: CD4 <350 WHO stage 4: any CD4	Clinical: monthly CD4: baseline and every 6 months
Indonesia	WHO stage 1, 2: CD4 <250 WHO stage 3, 4: any CD4	Clinical: monthly CD4: baseline and every 6 months
Myanmar	WHO stage 1, 2: CD4 <200 WHO stage 3: 200–350 WHO stage 4: any CD4	Clinical: monthly for first 3 months, and then every 3–6 months CD4: baseline and every 6 months
Nepal	WHO stage 1, 2: CD4 <200 WHO stage 3: consider CD4 <350 WHO stage 4: any CD4	Clinical: monthly for first 3 months, and then every 3 months CD4: baseline and every 6 months
Papua New Guinea	WHO stage 1, 2: CD4 <350 WHO stage 3 + symptoms: any CD4 WHO stage 4: any CD4	Clinical: monthly for 6 months, and then every 2–3 months CD4: baseline and every 6 months
Thailand	Asymptomatic: CD4 <350 Symptomatic or AIDS: any CD4	Clinical: Monthly x 6 months, and then every 3–6 months, if stable CD4: baseline and every 6 months Viral load: every 6–12 months
Vietnam	WHO stage 1, 2: CD4<200 WHO stage 3: CD4 <350 WHO stage 4: any CD4	Clinical: monthly CD4: baseline and every 6 months

ART, antiretroviral therapy. CD4 cell counts in cells/μl. Source: Country National Treatment Guidelines [23–31,39].

National program characteristics

National HIV Treatment Guidelines are in place in all nine focus countries (Table 2) [23–31,39]. In accordance with newly updated 2010 WHO guidelines for ART in adults and adolescents [33], the treatment programs of Papua New Guinea, Thailand and Cambodia have recently revised national treatment policies and now recommend initiation of ART for all HIV-infected individuals with CD4 cell count of 350 cells/μl or less, irrespective of clinical stage [24,30,39]. Similar changes to the CD4 cell threshold for ART initiation are presently under review in Indonesia and Nepal and are expected to be published later this year (*personal communication, Ministries of Health of Indonesia and Nepal*). Revision of National Treatment Guidelines is planned in 2010 and 2011 in India, Myanmar, China, and Papua New Guinea. Current published treatment guidelines in India and Vietnam recommend the initiation of ART for anyone with WHO stage 3 disease and a CD4 cell count below 350 cells/μl [26,31]. Guidelines in China and Indonesia recommend consideration of ART for all individuals with WHO stage 3 disease [23,25]. In all countries, ART initiation criterion for pregnant women is the same as for nonpregnant HIV-infected adults. This year, the national program in Thailand will pilot a program of ART for all HIV-infected pregnant women irrespective of CD4 cell count to assess the feasibility of this approach on a national level [17].

Standard nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, most frequently zidovudine (AZT) or stavudine (D4T) in combination with lamivudine (3TC) and nevirapine (NVP), remain the most commonly used first-line therapy in the region. Given concerns for long-term toxicity associated with D4T, national programs in China, India, Indonesia, Myanmar, Nepal, Papua New Guinea, and Thailand now recommend the use of AZT with 3TC as the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for first-line ART [23–28,30]. The use of efavirenz (EFV) in first-line ART is generally reserved for cases of TB-HIV coinfection or in instances of intolerance to NVP. At present, tenofovir is not routinely prescribed as a component of routine first-line ART in any country, though newly released treatment guidelines in Thailand list tenofovir as a preferred first-line NRTI [24]. Other countries may similarly opt to phase out D4T use and

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transition toward greater use of less toxic first-line ART regimens in the coming few years [33,40].

Recommended routine patient monitoring for ART response in all nine focus countries includes periodic clinical assessments and evaluation of CD4 cell counts every 6 months. Since 2006, routine HIV RNA testing for all patients receiving first-line ART has been implemented in Thailand [24]. The China Free ART program supports HIV RNA testing 6 months after treatment initiation with subsequent annual viral load testing [23]. In other countries, HIV RNA testing for patients receiving ART in the national program is reserved for special studies or to evaluate eligibility for second-line ART.

Antiretroviral therapy clinical outcomes

Analyses of cohorts initiated on first-line ART through government programs in the region indicate that 65–88% of patients remain alive and on treatment 12 months later (Table 3) [13–21]. For example, among 5184 patients initiated on ART at 31 treatment facilities in Vietnam between January and December 2008, 84% remained alive and on treatment 12 months later [21]. In Thailand, analysis conducted in 2008 using patient data entered in the public sector National Health Security Office (NHSO) database, indicated that 85% of 27 103 patients with at least 12 months of follow-up clinical data remained alive and on therapy 1 year after initiation of first-line [17].

Longer-term outcomes are available from several national programs and indicate that in Cambodia, China, India, Myanmar, and Vietnam, 71–78% of patients initiated on first-line therapy remain alive and on ART at 24 months [12,41]. Recently published analyses of over 58 000 patients initiated on ART in Thailand's national program between 2000 and 2006 indicate the overall probability of survival after 5 years was 78% [5].

Published national program data from Thailand and India indicate an 11% mortality rate in the first 12 months of ART [5,41]. The majority of deaths among patients in China, India, and Thailand occurred in the first 6 months of ART and was greatest among patients with baseline CD4 cell count below 50 cells/μl [5,7,41]. Published data indicate that the median CD4 cell count at which patients initiate ART in the region remains low, ranging from 41 cells/μl among patients in Thailand's NHSO program to 119 cells/μl in a three-center 2004 patient cohort in India [5,41]. Changes and substitutions in first-line regimens were required in almost 20% of patients in the Indian and Thai cohorts, primarily due to the development of medication-related adverse events.

Rates of loss to follow-up (LFU) in the region range from 8.8% (median 1.6 years of follow-up) to 16% (median 2 years of follow-up) in the Thai and Indian cohorts, respectively. Almost 35% of patients in the Indian cohort reported missing at least one monthly drug pick-up in a 24-month period [41]. Suboptimal adherence and losses to follow-up are two factors that have raised concern for the potential development of HIV drug resistance and treatment failure.

Analyses of pediatric treatment outcomes are available from a few national programs. An evaluation of 85 ART-naive and treatment-experienced children initiated on first-line ART in 2005 in one county program in China revealed that two (2%) died at 12 months, and the median CD4 cell count increased from 116 to 340 cells/μl [35]. In southern India, analysis of treatment outcomes in 216 children initiated on ART indicated 89% survival on therapy at 30 months [42]. Similarly, evaluation of outcomes among 3409 children initiated on ART at provincial and district level treatment facilities in Thailand revealed 93% survival at 12 months and 88% probability of survival after 5 years [43].

Management of tuberculosis coinfection

Several national programs in the region have initiated collaborative efforts with tuberculosis (TB) program counterparts to integrate HIV and TB diagnosis and treatment. Nevertheless, the proportion of HIV-infected persons in the region with incident TB who are estimated to have received concurrent ART and antituberculous therapy remains relatively low, ranging from 3 and 11% in

Table 3. Antiretroviral therapy program 12-month treatment outcomes, Asia Pacific.

Country	No. of patients alive and on ART at 12 months	Percentage (95% CI)	Cohort definition
Cambodia	2858/3296	87% (86–88%)	Patients started on ART in 2008 with 12-month outcomes
China	14004/17007	82% (81–83%)	Patients started on ART in 2008 with 12-month outcomes
India	2732/3414	80% (79–81%)	Patients started on ART in 2006 at 11 centers
Indonesia	520/801	65% (62–68%)	Patients started on ART in 2006 at 12 centers
Myanmar	1990/2274	88% (86–89%)	Patients started on ART in 2008 with 12-month outcomes
Nepal	225/274	82% (77–86%)	Patients started on ART in 2008 at 18 centers
PNG	1455/1772	82% (80–84%)	Patients with 12-month outcomes in December 2009
Thailand	23076/27103	85% (84–86%)	Patients started on ART in 2008 with 12-month outcomes
Vietnam	4363/5184	84% (83–85%)	Patients started on ART in 2008 across 31 sites

ART, antiretroviral therapy; PNG, Papua New Guinea. Source: Country Reports on the Follow up to the Declaration of Commitment on HIV/AIDS (UNGASS), 2008–2009 Reporting Period [13–21].

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Table 4. First-line antiretroviral therapy treatment failure criteria and preferred second-line antiretroviral therapy regimens, Asia Pacific 2009.

Country	Criteria for diagnosis of first-line ART failure	Additional tests to determine eligibility for second-line ART	Preferred second-line ART regimen
Cambodia[a,b]	Clinical or immunologic failure detected after ≥6 m ART	Confirmatory HIV RNA testing for patients with first-line failure If HIV RNA > 1000 copies/ml → adherence counseling Repeat HIV RNA test → > 1000 copies/ml referred for second-line ART	TDF + 3TC + LPV/r
China[a,c]	Clinical failure detected after ≥3 m ART Immunologic failure after ≥12 m ART	Confirmatory HIV RNA testing for patients with first-line failure If HIV RNA > 10000 copies/ml → referred for second-line ART in WHO stage 3 or 4 disease	TDF + 3TC + LPV/r
India[a,d]	Clinical or immunologic failure detected after ≥6 m ART	Confirmatory HIV RNA testing for patients with first-line failure If HIV RNA > 10000 copies/ml → referred for second-line ART	TDF + 3TC + LPV/r +/- AZT
Indonesia[a,d]	Clinical or immunologic failure detected after ≥6 m ART	Confirmatory HIV RNA testing for patients with first-line failure If HIV RNA > 10000 copies/ml → referred for second-line ART	TDF + 3TC + LPV/r +/- AZT or DDI + ABC + LPV/r
Myanmar[a,d]	Clinical or immunologic failure detected after ≥12 m ART	No additional testing	TDF + ABC + LPV/r
Nepal[a,d]	Clinical or Immunologic failure detected after ≥12 m ART	No additional testing	TDF + ABC + LPV/r or SQV/r DDI + ABC + LPV/r or SQV/r
Papua New Guinea[a,d]	Clinical or immunologic failure detected after ≥6m ART	No additional testing	TDF + ABC + LPV/r or SQV/r DDI + ABC + LPV/r or SQV/r
Thailand[a,d]	Clinical or immunologic failure detected after ≥6m ART HIV RNA of >1000 copies/ml detected in routine viral load testing	No additional testing for patients with first-line failure detected by routine HIV RNA testing Confirmatory HIV RNA testing for patients with immunologic or clinical first-line failure If HIV RNA > 1000 copies/ml → referred for second-line ART after genotypic resistance testing	2NRTI + boosted PI selected based on results of genotypic resistance test results
Vietnam[a,d]	Clinical or immunologic failure detected after ≥6m ART	Confirmatory HIV RNA testing for patients with immunologic or clinical first-line failure If HIV RNA > 10000 copies/ml → referred for second-line ART	TDF + DDI + LPV/r or SQV/r ABC + DDI + LPV/r or SQV/r

ART, antiretroviral therapy; AZT, zidovudine; NRTI, nucleoside reverse transcriptase inhibitor.
[a]Clinical failure: development of new or recurrent OI.
[b]Immunologic failure in Cambodia is defined as development of any one of the following: failure to gain >50 CD4 cells in 12 months, fall of CD4 cell count to pre-ART baseline, fall of CD4 cell count by >50% peak on treatment value, CD4 cell count <200 after 18 months.
[c]Immunologic failure in China is defined as development of any one of the following: failure to gain >25–50 CD4 cells in 12 months, failure to achieve CD4 cell count >100 at 12 months, fall of CD4 cell count to pre-ART baseline, fall of CD4 cell count by >50% peak on treatment value.
[d]Immunologic failure in all other countries is defined as development of any one of the following: fall of CD4 cell count to pre-ART baseline, fall of CD4 cell count to less than 50% of peak on treatment value, failure to achieve CD4 cell count >100 cells/μl.
Source: Country National Treatment Guidelines [23–31,39].

Indonesia and Myanmar [16,18], respectively, to 26–27% in Thailand, Papua New Guinea, and Vietnam [17,19,21]. Although the provision of isoniazid prophylaxis therapy (IPT) to HIV-infected patients is not currently in place in most countries, pilot programs to evaluate such preventive therapy have recently started in Papua New Guinea and Myanmar.

Treatment failure and second-line antiretroviral therapy

As treatment services mature, some proportion of ART patients are expected to develop first-line treatment failure. The diagnosis of treatment failure and the decision to switch to second-line ART is based on immunologic and clinical criteria alone in some countries, including Nepal, Myanmar, and Papua New Guinea [27,28,30] (Table 4) [23–31,39]. The use of confirmatory viral load testing is employed in other countries, including Cambodia, China, and India, where adherent first-line patients who meet immunologic or clinical failure criteria are re-evaluated with HIV RNA testing. Second-line ART is recommended for those in whom the viral load is above a prespecified threshold [23,26,29].

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The HIV RNA threshold used to trigger switches to second line-ART in some countries, including China and Cambodia [23,29], is 1000 copies/ml. Presently, India, Indonesia, and Vietnam employ a threshold of 10 000 copies/ml for eligibility to switch to second-line ART [25,26,31], though these thresholds may soon be modified to concur with the 2010 WHO HIV treatment recommendations [33]. In Thailand, first-line treatment failure is detected by routine viral load monitoring, and national guidelines also support the use of HIV genotypic resistance testing to guide the selection of a second-line regimen [24]. Most other countries have adopted a public health approach to the provision of second-line ART, where the regimen is standardized and consists of a boosted protease inhibitor in combination with two to three NRTIs (Table 4). A recent Medicin sans Frontieres evaluation of 113 patients receiving lopinavir/ritonavir-based second-line ART in Cambodia indicates median CD4 cell count gains of 180 cells/μl at 12 months, with 89% demonstrating virologic suppression [44]. Large-scale analyses of clinical outcomes among public sector patients receiving second-line ART are awaited.

Injection drug users

In several Asian countries, including China, Indonesia, Myanmar, and Vietnam, injecting drug users (IDUs) comprise a sizable proportion (up to 50%) of the HIV-infected population. In all of these countries, ART initiation criteria among IDUs are the same as for the general HIV-infected population, and some treatment guidelines explicitly state that active use of illicit drugs should not preclude access to ART [23,27,31]. Despite this, ART coverage rates among IDUs remain low, in part because clients in this population are often fearful of arrest or discrimination [45]. However, recent data from Vietnam underscore that treatment success can be achieved with IDUs. In a Hanoi-based cohort of 100 IDUs receiving ART demonstrated 73% virologic suppression at 12 months, in spite of self-reported active drug use in 48% of patients [46].

Discussion

In the past 5 years, there has been unprecedented expansion of HIV treatment services in the Asia Pacific region. The growth of these programs has been a result of combined efforts by community advocacy groups, the medical and public health community, donor agencies, and strong political commitment on the part of national health ministries [10,22,47–49]. Treatment activities in some countries, including those in Thailand and China, receive a substantial proportion of financial support from government sources [5,45,50]. Other national treatment programs in the region continue to rely heavily on external donor funding from several agencies, especially the Global Fund to fight AIDS, TB, and Malaria. As a result of these collaborative efforts, over 700 000 HIV-infected individuals currently receive ART in the region. Nevertheless, the majority of persons in Asia Pacific countries who are estimated to require treatment still do not receive ART, highlighting the need for increased momentum to expand treatment access in the coming years.

In order to successfully scale-up treatment services to meet universal access goals, national programs face several key technical and operational challenges. First, there is an urgent need to efficiently identify HIV-infected individuals in earlier stages of disease and link them with treatment services. This is essential not only to increase overall ART coverage rates, but it also can contribute to improved ART outcomes [51]. Short-term survival of patients in high-burden Asia-Pacific countries is comparable to reported outcomes from other resource-limited settings [52,53]. However, as in other regions, early mortality remains a significant concern and is highest in patients who initiate ART at low CD4 cell counts [54]. Although several countries have revised treatment guidelines to recommend ART initiation at higher CD4 cell counts, the vast majority of patients in the region still initiate treatment at CD4 counts below 200 cells/μl. Determining the factors that can facilitate the timely linkage of HIV patients to both care (pre-ART) and treatment (ART) services will be an essential step in improving program outcomes. Individuals diagnosed with HIV who are not yet eligible for ART should be linked to pre-ART care services, which will allow them to receive the benefits of cotrimoxazole prophylaxis [55], regular monitoring of disease progression, and early identification of the need for ART initiation.

In the concentrated epidemic settings that characterize HIV in Asia Pacific countries, it will be important to coordinate HIV diagnosis efforts with community organizations that work with MSM, sex workers, and IDUs in order to ensure equitable access to treatment services for these frequently marginalized populations. Linking harm reduction services, including opioid substitution therapy and needle exchange programs, with ART services will be essential to ensure that IDUs sustain the long-term benefits of therapy [45,56]. Strengthening collaborative activities between TB and HIV/AIDS programs is similarly critical to ensure TB-HIV-coinfected patients receive timely ART, as global and regional data have repeatedly shown that initiation of ART is associated with dramatic reductions in mortality for this population [54,57,58].

As ART services in the Asia Pacific mature, national programs also need to develop strategies to retain patients on lifelong treatment. A recently published analysis of observational data from multiple resource-limited countries indicates that rates of LFU are higher where the pace of ART scale-up is fastest [59]. Minimizing losses to follow-up and enhancing adherence will be essential to

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prevent the development of HIV drug resistance, and can contribute to maintaining the durability of affordable first-line regimens [60,61]. Employing a combination of methods, including working with community-based organizations and people living with HIV/AIDS (PLHA) networks, utilizing outreach workers, and tracing death registries has been shown to improve adherence and reduce LFU among patients [62,63].

National programs in the region have started to roll out second-line treatment and several countries are beginning to utilize viral load testing for the diagnosis and management of treatment failure. Determining the best methods for the diagnosis and management of treatment failure is presently a central challenge for many ART programs. Relying solely on clinical or immunologic criteria to diagnose treatment failure may permit the accumulation of HIV drug resistance mutations that can limit the efficacy of future drug options [64,65]. The ongoing evaluation of ART-monitoring strategies, the immunologic and HIV RNA thresholds used to switch therapy, and the specific second-line regimens that are utilized by countries in the region will be important to inform programs as they expand both first-line and second-line treatment services.

HIV treatment services in many Asia Pacific countries were initially introduced at tertiary-level institutions in urban centers. As ART services continue to expand, it will be critical to identify methods to decentralize HIV treatment services for the provision of lifelong therapy. The experiences of Thailand have demonstrated the importance of a strong healthcare system and stable health workforce to successfully decentralize HIV treatment services [5,66,67]. Indeed, the goal of decentralizing ART services provides an opportunity to strengthen underlying healthcare and laboratory infrastructures throughout the region. Strategies that involve training primary healthcare workers to effectively provide follow-up ART services have been successfully piloted in the region [68]. These and other models demonstrate how utilizing outreach workers, peer educators, and volunteers to deliver services in a continuum of care model can improve treatment uptake and outcomes [59,63]. With the support of national HIV programs, the participation of PLHA networks in service delivery in Thailand and Cambodia has enhanced treatment linkages and played a key role in reducing HIV-related stigma, thus serving to improve adherence and other treatment outcomes [69,70].

Increased external funding has been a major driver in the rapid scale-up of ART services both globally and in the Asia Pacific region. As a result, the long-term sustainability of free ART in many countries currently depends heavily on sustained support from donor agencies. In order to expand treatment and improve outcomes, increasing levels of financial commitment for ART programs on the part of national ministries of health will also be essential. Advocacy for reduced pricing of drugs, the expanded availability of affordable and better tolerated medications with fewer long-term side effects, and the development of low-cost point-of-care monitoring strategies are essential to ensure that patients in the Asia Pacific receive the highest standard of HIV treatment [71].

There are several limitations to our review. We have focused on ART scale-up and outcomes in public sector programs throughout the Asia Pacific region, where the majority of infected persons receive treatment in the nine focus countries. However, our review does not capture data from the private healthcare sector, which continues to play an important role in ART delivery in several countries. Because prescription practices in the private sector are often unregulated and patients frequently have limited resources to consistently pay for drugs, these individuals may be at heightened risk to develop treatment failure and drug resistance. It will be important to gather systematic and accurate data on treatment delivery in the private sector to inform measures to standardize and improve clinical practices and outcomes in private facilities.

Our review also highlights the limited availability of medium-term and long-term outcome data from many countries in the region. As patients enter their fourth and fifth years on ART, there may be differing patterns of treatment adherence, LFU, and the development of both infectious and noninfectious complications. It will be critical to build appropriate data systems and national-level analytic capacity to evaluate longer-term data to guide programmatic interventions to sustain improved survival and quality of life [45,62].

The successes of ART scale-up in the Asia Pacific have demonstrated the ability of health programs in low-income and middle-income countries in the region to rapidly implement and expand life-extending treatment services to thousands of HIV-infected persons. In this vast and complex region, many challenges remain and well coordinated efforts will be needed for continued progress. Increased efforts to expand and integrate HIV testing and ART services, the development of stronger healthcare systems to support the provision of a continuum of HIV care, and sustained funding will help country programs achieve goals of universal access to ART.

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