

Public health research priorities for HIV/AIDS in South-East Asia

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Introduction

The South-East Asia Region has the second-highest burden of HIV/AIDS globally, with an estimated 3.6 million persons living with HIV infection. While the regional prevalence of the disease is estimated to be 0.3%, there is significant diversity in the scale and burden of the epidemic, both within and across Member countries of the Region. In some Member countries, the epidemic had remained at a low level, with very few infections reported, while other countries are experiencing a concentrated epidemic, with HIV prevalence and transmission in high-risk groups. Despite these differences, each country requires a well-coordinated response to HIV/AIDS, with the goal of preventing new infections, and providing appropriate care and treatment services to those who are already infected.

Over the past several years, there has been an impressive scale-up of both preventive as well as care and treatment services for HIV in the Region. Countries have adopted a public health approach to addressing the epidemic. The key steps of such an approach include defining the problem and risk factors, developing effective prevention and care strategies, scaling up these interventions, and monitoring and evaluating programme impact. This approach has led to the development of certain successful strategies for both prevention and care. It has also highlighted data gaps and questions that remain unanswered in the development of an effective, coordinated response. These questions can be answered through the conduct of simple, well-designed and programme impact-oriented research. With data-driven evidence to guide policy and programme initiatives, the public health approach and the overall scale-up and response to the HIV/AIDS epidemic in the Region can be greatly strengthened.

A successful response to the HIV/AIDS epidemic requires a coordinated response across multiple issues. Similarly, public health research priorities span a spectrum of topics. These range from the need for reliable epidemiological estimates of the number of persons requiring HIV treatment, the design of evidence-based targeted interventions and harm-reduction strategies to prevent infection, to the need for data-driven methods to enhance treatment outcomes in care and treatment services, with the goal of effectively decentralizing HIV health sector services through a strengthened health system. This paper describes HIV/AIDS public health research priorities for South-East Asia across four broad areas: epidemiology, prevention, treatment and care, and health systems and communities.

Epidemiological research priorities

Relevant and reliable data are needed to plan for and scale up HIV prevention, care and treatment services. In most countries, second-generation HIV surveillance systems and mathematical models are used to obtain the required data. While progress has been made in collecting the relevant information for planning and monitoring HIV programmes, several data gaps remain. In particular, there is a critical need to understand the number of people and characteristics of the population groups most at risk for HIV, the proportion of individuals who have become newly infected with HIV, the number of prevalent HIV infections, the number of HIV-infected individuals who require antiretroviral therapy (ART) and the estimated mortality due to AIDS.

Improving mapping and size estimation of most-at-risk populations

In most countries of the South-East Asia Region, estimates of populations most at risk for HIV infection remain unreliable and imprecise. In part, this is due to the fact that individuals who are most at risk for HIV are often members of hidden and/or stigmatized groups, such as men who have sex with men (MSM), injection drug users (IDUs), and sex workers (SW) and their clients. This lack of reliable estimates makes it difficult to plan prevention, care and treatment services for these populations. Moreover, without reliable denominators, it is hard to measure and monitor trends in service coverage. Several methods have been employed with varying degrees of success for estimating the size of these hard-to-measure populations, including the capture–recapture method, the multiplier method, the population survey method, census and respondent-driven sampling. Research is needed to develop better methods and tools to map and measure the size of most-at-risk populations more precisely.

Measuring HIV incidence

HIV incidence is the most valuable information to identify programme needs and effectiveness. Unfortunately, direct measures of HIV incidence using population-based cohort studies are logistically difficult and expensive. At present, countries use alternative methods as a proxy for measuring HIV incidence, such as trends in HIV prevalence among 15–24-year-olds, mathematical modelling, or measuring HIV in repeat testers such as blood donors. The recent development of a simple serological assay that can distinguish recent from established HIV infections, known as STARHS (serological testing algorithms for recent HIV seroconversion), provides an opportunity for countries in this Region to more directly estimate HIV incidence. Because of assay variability due to various factors including HIV subtype, countries will first need to ascertain the window period between HIV seroconversion and the time at which the STARHS testing algorithm reaches a pre-set cut-off. In addition, operations research should also be conducted at the country level to ascertain the correction factor to account for false-positive test results among patients on ART.

Measuring HIV prevalence among the low-risk (general) population

It is important to measure HIV prevalence in low-risk populations to know the extent of HIV spread to the general population, and to plan for care and treatment services at a national level. The unlinked anonymous testing (UAT) approach has been used for sentinel surveillance among antenatal clinic (ANC) attendees as a proxy for the low-risk population. With the expansion of prevention of mother-to-child transmission (PMTCT) programmes and the call of universal coverage, it is difficult to ethically justify a UAT approach to HIV testing for pregnant women. Thus, switching to surveillance among

PMTCT centres offers many benefits over the UAT approach, including improved representativeness and coverage due to a large number of sites, a higher precision of prevalence estimates due to a larger sample size and cost savings. However, a major drawback of PMTCT data is that HIV prevalence estimates from prevention of parent-to-child transmission (PMTCT) programme data could be biased if some women refuse to take the HIV test. Therefore, research is needed to characterize the quantity and direction of bias in PMTCT data compared with UAT data as a gold standard. Also, because pregnant women are not truly representative of the standard for the general population, periodic population-based surveys will still be required in selected geographical areas to ascertain the calibration factor for adjusting HIV data obtained from ANC attendees.

Measuring HIV-associated mortality

Information on HIV-related deaths is important for monitoring HIV care and treatment programmes as well as for demonstrating the relative impact of HIV-related mortality as compared with other causes of death in a given country or region. Most deaths in South-East Asia occur at home. Given the weak vital registration systems in Member countries, verbal autopsy may be a useful approach to measure HIV-associated mortality as part of larger mortality studies. Standard tools and questionnaires for conducting verbal autopsies exist. However, operational research efforts are required to first validate and adapt the generic procedures, questionnaires and other verbal autopsy tools to the social and cultural milieu of South-East Asian countries. Measuring the impact of HIV-related care and treatment on mortality is equally important. Conducting operations research at sentinel ART centres within each Member country will permit the analysis of routine ART programme cohort data to calculate HIV/AIDS-related mortality among patients receiving treatment.

Estimation of antiretroviral treatment needs

Presently, countries rely on mathematical models for estimating ART needs among adults and children. The models use generic assumptions based on data from mainly African and a few Thai studies. There is a need to generate regional data to modify and refine these generic assumptions. The specific data needed to refine key assumptions are: (1) the cumulative proportion of adult men and women and children progressing from HIV infection to advanced infection (needing ART), and to AIDS death; (2) the proportion of adult men and women, and children surviving and remaining on first-line drugs at 12 months and 24 months after the start of treatment. The second of these goals can be readily accomplished by analysing routine ART programme cohort data.

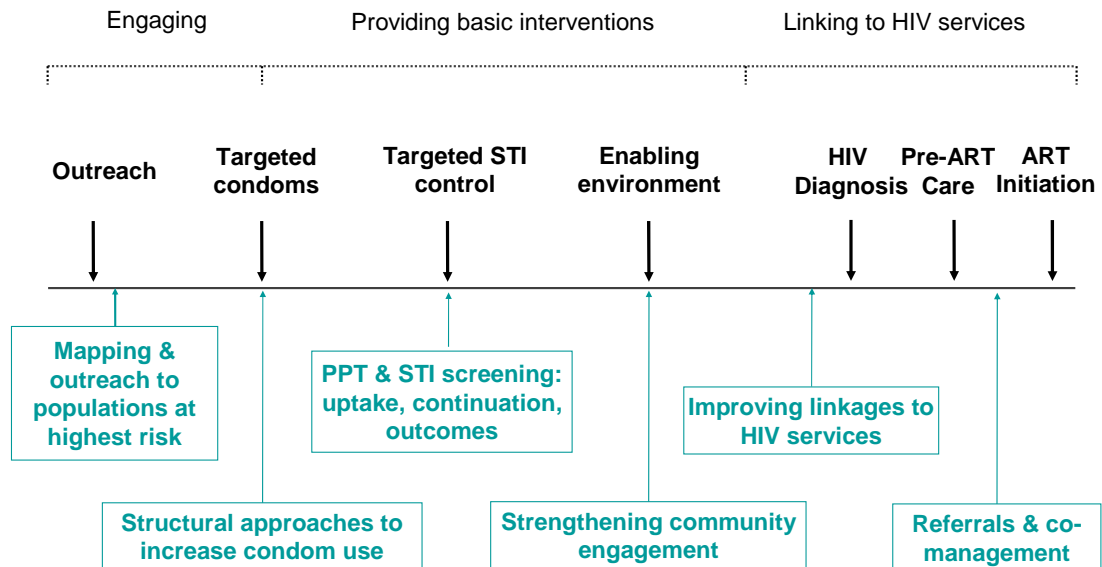
Research priorities in HIV prevention

Preventing sexual transmission of HIV/STI

The sexual transmission of HIV and other sexually transmitted infections (STIs) in the South-East Asia Region is disproportionately driven by high-incidence sex work areas and other settings where rates of partner change are high. In these settings, low rates of condom use and high rates of other STIs are key determinants of HIV transmission. Regional experience has shown that successful prevention of sexual transmission of HIV involves increased condom use, enhanced identification and treatment of STIs, and the

presence of an enabling environment supportive of prevention efforts. Targeted interventions directed at the highest-risk populations which address these key factors are further strengthened by improved linkages to HIV health and support services. For bridging populations and the general population, prevention objectives are more general and less intensive, and include raising awareness of HIV risk, and improving access to quality clinical services for STIs and HIV testing and counselling. The research priorities for improving the outcomes of and impact related to prevention of sexual transmission of HIV follow this programme logic (Figure 1).

Figure 1: Regional operations research opportunities in HIV prevention



Note: PPT=Presumptive prophylactic treatment

Targeted condom programmes: Experience from Thailand and other countries in the Region demonstrates that structural approaches to increasing condom use in sex work settings, such as 100% condom use policies (CUP), can lead to rapid increases in condom use and reduction in the incidence of STI and HIV. Peer- and community-based interventions have also been used to achieve high rates of condom use in a variety of settings, including less organized non-brothel settings. On the other hand, some countries have faced cultural resistance when attempting to establish condom policies. Research priorities include formative research in the adaptation of successful intervention models, and operations research to improve condom use rates among clients of SWs. Factors that are important in successful peer programmes should be systematically identified and subsequently used to guide targeted interventions. Additionally, research to explore the feasibility and uptake of other barrier protection for SWs, including female-controlled methods, such as the female condom and the diaphragm, should also be supported. As data accumulate on the effectiveness of microbicides, it will be important to evaluate whether these new barrier methods truly reduce the number of unprotected sex acts, rather than simply substituting for male condom use.

Targeted STI services: STI services for female, male and transgender SWs form an integral part of targeted interventions. Unlike services provided for the general population, STI screening and presumptive treatment may be justified in high-risk

populations due to the high prevalence of asymptomatic STIs. Similarly, different approaches to counselling and partner treatment may be employed among high-risk populations. Key questions that require systematic investigation focus on quantifying the coverage, uptake, quality and continued utilization of STI services among high-risk groups. Operations research should further evaluate methods for increasing the uptake of services, as well as quantify the optimal frequency of screening visits for presumptive STI treatment. In addition, innovative approaches to partner treatment, such as take-home doses for partners, should be studied and validated under field conditions to provide evidence for wider implementation of such programmes.

Access to HIV services for high-risk populations: SWs, MSM and IDUs have a disproportionately high prevalence of HIV, yet their access to health services may be limited by social marginalization, stigma and discrimination. In fact, providing care and treatment can serve to augment prevention efforts for these populations. Access to health-care can be facilitated through referrals and linkages between targeted intervention sites and HIV treatment facilities. The co-management of patients between specialized ART or PMTCT sites and providers at targeted intervention sites is a largely unexplored area of operations research that merits further attention.

Prevention among drug users

Injecting drug use is a major mode of transmission of HIV in South-East Asia and the prevalence of HIV among IDUs continues to be high. Harm reduction programmes have demonstrated effectiveness in preventing and reducing the transmission of bloodborne viruses. Interventions are focused on preventing unsafe injecting and sexual risk, and reducing the frequency of injecting itself by providing sterile injecting equipment, condoms and opioid substitution therapy (OST). However, the coverage and reach of these interventions in the Region remains largely suboptimal. Operations research at the local level to understand the determinants of ongoing access and uptake of services is crucial to increasing the coverage of harm reduction programmes for IDUs. Systematic evaluation of these factors can also provide data to guide which model of service delivery is appropriate to a specific context or locality.

A major challenge to effective HIV prevention for substance users in South-East Asia is posed by the widespread and increasing use of both injected and non-injected amphetamine-type stimulants (ATS). During the past decade, there has been a major transition from opioid drugs to ATS use in both Thailand and Myanmar. Use of ATS has been also reported among MSM and SWs. The increased frequency of unprotected sexual encounters among those using ART poses significant challenges for preventing HIV spread. Furthermore, the lack of therapeutic options such as OST for ATS users complicates treatment and reduces options for the prevention of unsafe injections. Research to identify effective treatment options for ATS users is an urgent necessity. In addition, operations research on interventions and strategies to reduce sexual risk-taking and unsafe sex among ATS users is also essential.

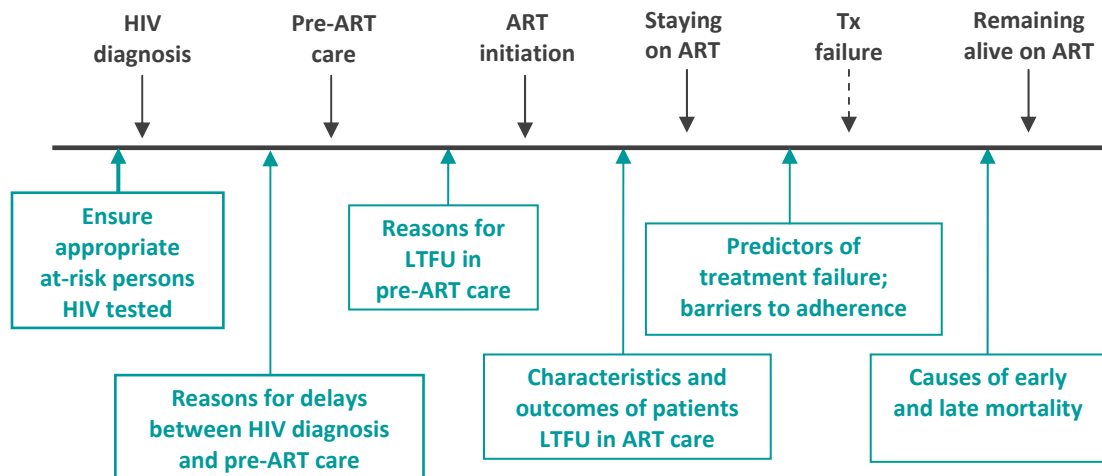
Key factors impacting on treatment outcomes for IDUs in relation to OST and ART are retention and adherence. In terms of drug treatment, good outcomes are associated with retention in treatment for a duration of two years or more. Some common proximate factors that may affect treatment retention include adequacy of withdrawal management, satisfaction with the programme, efficacy of trigger management and relapse prevention strategies, optimal and individualized treatment planning, and adequate treatment of depression and co-morbidities. Socioeconomic factors such as access to stable housing and support for transport costs are also likely to have a bearing. However, actual

research on the determinants of retention and adherence to OST in this Region is lacking. In order to design effective OST and ART, understanding the key factors that determine adherence and retention is a priority.

Research priorities for HIV care, support and treatment services

Over the past two decades, HIV clinical research efforts have focused on the development of potent ART regimens, effective treatment of opportunistic infections (OIs), and appropriate ART monitoring, among many other important issues. The results of these research efforts have greatly benefited thousands of HIV-infected people by extending survival and reducing morbidity. The scale-up of HIV treatment programmes in the South-East Asia Region over the past several years has also raised several important challenges and questions for which evidence-based answers are needed (Figure 2). Key issues that require further investigation include effectively expanding HIV diagnostic services, enhancing ART treatment outcomes, determining the best approaches to manage persons coinfecting with HIV and tuberculosis (TB), preventing and evaluating the emergence of HIV drug resistance (HIV DR), and determining effective methods to decentralize HIV treatment services.

Figure 2: Regional operational research opportunities in HIV care and treatment



Note: LTFU=lost to follow-up

Effectively expanding HIV diagnostic services

In concentrated epidemic settings, which characterize most of the countries in the South-East Asia Region, HIV testing is often done through provider-initiated testing and counselling (PITC). Determining methods to ensure that the appropriate at-risk persons are referred and tested for HIV is the first step toward linking at-risk and infected persons to necessary care and treatment. The next programmatic challenge is to evaluate methods to improve the linkage between HIV testing services and clinical care. Advanced disease at the time of treatment initiation has been repeatedly shown to be associated with poorer treatment outcomes and early mortality. Therefore, understanding the factors that contribute to successful and prompt linkage to care, as

well as the barriers that prevent such linkage, will be important to inform programme policy as both HIV testing and care services continue to expand in the Region.

These challenges and questions apply equally to testing and counselling of pregnant women for HIV infection. In the South-East Asia Region, Thailand has made impressive progress toward providing universal access to HIV testing, counselling and appropriate prophylaxis for pregnant women with HIV infection. However, many challenges remain in the other countries to effectively expanding the implementation and uptake of PMTCT services. In order to increase the effectiveness of PMTCT programmes across the Region, it is critical to systematically determine the barriers and facilitators to the uptake of PMTCT services in Member countries. These barriers may also include structural issues such as overall low uptake of ANC services and/or low rates of birth/delivery inside the medical system. As such, collaboration with appropriate partners in reproductive and child health would be both useful and recommended. Such systematic investigation can provide data and guidance for the further development and refining of PMTCT services in Member countries. Such services should appropriately support testing and counselling pregnant women for HIV, and subsequently successfully link women diagnosed with HIV infection to necessary and timely prevention and treatment interventions.

Enhancing ART outcomes

In the past several years, there has been an impressive scale-up of HIV treatment services in the South-East Asia Region. This massive scale-up of ART services has extended the lives of thousands of persons living with HIV/AIDS. As HIV-infected persons receiving ART in the Region enter their second, third, and fourth years of therapy, the attention of national programmes has appropriately begun to focus on the issue of successfully retaining patients on lifelong treatment. Analysis of routine ART programme data in India and other countries in the Region indicate that loss to follow up among patients receiving ART is a significant issue requiring attention. The systematic evaluation of factors related to treatment failure and loss to follow up, as well as the outcomes of patients who are classified as lost to follow up is thus a priority for Member countries. Understanding the causes and consequences of these issues is a critical step to further strengthening ART and HIV treatment services for people living with HIV in the Region.

Treatment adherence remains one of the key elements in ensuring sustained ART benefits. Multiple studies have demonstrated the association between adherence and treatment outcomes as well as survival. However, inconsistent or suboptimal treatment adherence remains a significant issue for many patients receiving ART in the Region, and systematic examination of this issue is urgently required. Assessment of clinical and field-based strategies to maximize ART adherence in the Region include validation of feasible and accurate objective measures of adherence, and evaluation of factors that prevent and facilitate high-level treatment adherence. These factors may be related to individual patient behaviour or linked to structural factors such as transportation or cost barriers. The systematic identification of these factors can serve to guide programmes to develop effective interventions that can enhance adherence and subsequently improve overall treatment outcomes.

Improving the management of HIV and TB coinfection

TB remains the most common OI and a leading cause of death among HIV-infected persons in the Region. Thus, efforts to improve the diagnosis, treatment and prevention of TB among HIV-infected persons are a high priority. From an operational perspective, three areas can be highlighted as priorities for programmatic research. First, the development and evaluation of simple screening tools that are both sensitive and specific for the identification or exclusion of active TB among HIV-infected persons is an urgent priority. Validation of such a screening tool in field conditions will be necessary to ensure that patients seen even outside major medical centres can be referred early for the appropriate management of HIV/TB coinfection. Second, because TB is so prevalent among HIV-infected persons in the South-East Asia Region, and because such persons remain at risk for TB even after initiating ART, appropriate field methods to implement isonicotinic acid hydrazide (INH) prophylaxis therapy warrant prompt evaluation. While INH prophylaxis has been demonstrated to clearly reduce the risk of active TB, programmatic questions related to effectiveness in the field, and appropriate duration of prophylaxis remain, and should be systematically evaluated at the country level. Finally, due to the expansion of ART services, HIV-infected persons with varying levels of immunosuppression are often congregated in the same facility. Because of the high prevalence of TB among HIV-infected patients, these facilities can inadvertently serve as a platform for nosocomial transmission of TB. Therefore, the evaluation and identification of low-cost measures to reduce the spread of nosocomial TB transmission urgently needs investigation.

Evaluation and prevention of HIV drug resistance (HIV DR)

The development of some degree of HIV DR is inevitable in populations taking ART because of the occurrence of mutations during HIV replication, the chronic nature of HIV infection and the need for lifelong treatment. The development of HIV DR can result in reduced effectiveness of ART, and has also been associated with poorer survival. In order to systematically address the issue of HIV DR, it is essential for each Member country to establish a countrywide strategy for the prevention and monitoring of HIV DR as part of the national AIDS control programme. The main components of such a system include the collection of early warning indicators, ART site factors that are associated with treatment success/failure and the preventable emergence of HIV DR, and conducting periodic surveys at sentinel ART sites to evaluate the emergence and patterns of transmitted drug resistance among recently infected HIV-positive individuals, and acquired HIV DR among patients receiving ART through the national programme. The collection and analyses of these data will ultimately serve to strengthen the provision and success of first-line ART services in Member countries.

Research priorities for health systems and community awareness

The successful scale-up of HIV prevention, care and treatment services depends heavily on the existence of sound health systems in a country. Several health systems issues that will play a key role in the success of scaling up require evaluation and attention, including methods for decentralization of care, mobilization of a well-trained and adequate health workforce, and the development of effective health information systems.

Strategies to decentralize HIV treatment services

HIV care services in several Member countries have initially been introduced at tertiary-level institutions, often in large metropolitan centres. However, for successful provision of lifelong HIV treatment, these services will need to be expanded to more peripheral levels in the coming years. Such expansion and decentralization are key factors in

ensuring improved access to HIV health-care services. Identifying successful methods of providing primary-level care and treatment for HIV-infected persons at the peripheral level is thus a priority. Certain strategies, including the Integrated Management of Adult Infections (IMAI), which involve engaging and training primary-level health-care workers to effectively triage and refer HIV-infected patients for additional medical care, and to community care centres, that provide routine follow-up care for HIV patients close to their residence, have been successfully piloted at the district and regional levels in some South-East Asian countries. Such strategies need to be further adapted to the local health-care and sociocultural structure and subsequently evaluated in order to strengthen decentralization efforts.

Health workforce mobilization

The sustained success of HIV prevention, care and treatment services relies equally heavily on the presence of a stable and trained health workforce. In part, this will require innovative approaches to ensure that medical and paramedical workers are offered appropriate and ongoing training to ensure that quality care and treatment services can be delivered. At the same time, the expansion of HIV services to more peripheral locations highlights the need to explore and evaluate the increasing role of community health workers and community volunteers to deliver and support prevention and care services.

Revitalizing health information systems

The scale-up of HIV treatment services in many South-East Asian countries has underscored the need for reliable, flexible and simple health information systems that can be used in a variety of health-care settings. Because programme monitoring and evaluation relies at its core on reliable patient data, the health information system should ideally provide a useful platform for clinical management as well as readily analysable data for programme management at a national level. Operationally, these systems will need to be piloted, evaluated and validated in a variety of field conditions in order to ensure that such an information system will truly be effective for a diverse population.

Enhancing community involvement

Community building is a key component for the success of prevention, care and support initiatives throughout the Region. The involvement of peers and community leaders has been demonstrated to help improve the uptake and outcomes of targeted interventions as well as treatment services in several countries. Furthermore, peer and community involvement plays a key role in reducing HIV-related stigma, which in itself continues to act as a barrier to successful treatment outcomes in many settings. Strategies to develop and sustain community and peer involvement in prevention services have been employed in several key settings in the Region, and warrant systematic evaluation and potential further implementation. Similarly, the appropriate roles of community leaders and peer supporters in enhancing treatment outcomes and providing psychosocial support need to be explored further. Evaluating and quantifying the benefits of such community involvement will provide necessary evidence for the future financial and governmental support of such community-based initiatives.

Taking the research agenda forward

The research priorities for HIV/AIDS in the South-East Asia Region range from those focused on prevention to those related to enhancing treatment outcomes and further strengthening the health systems on which all these programme activities rely. While

some of these research priorities can be applied equally to different Member countries, others will have more relevance in countries with a higher burden of HIV/AIDS. The national HIV/AIDS programmes in each country will have to prioritize specific research needs in light of the local context of the epidemic. Furthermore, the implementation of quality research requires national-level commitment to ensure trained practitioners and experts of varied backgrounds, who can effectively design, conduct, supervise and analyse research studies.

Ultimately, the goals of such research activities are to advance, improve and enhance a given country's national response to HIV/AIDS. For research results to truly impact programme activities and policy, mechanisms will be required to ensure that research findings can be broadly communicated to local stakeholders as well as national decision-makers. The success of research ultimately relies on effective partnerships between local, nongovernmental, state, national and international partners, who can together effectively translate research findings into policy and practice to better control the HIV epidemic in this Region.

Bibliography

1. *HIV/AIDS in South East Asia Region*. New Delhi, WHO Regional Office for South-East Asia, March 2007.
2. *Expanding access to HIV/AIDS treatments: operational research to scale up antiretroviral treatment in the South-East Asia Region*. New Delhi, WHO Regional Office for South East Asia, 2004
3. UNAIDS Inter-agency Task Team on Young People. In Ross D, Dick B, Ferguson J, eds. *Preventing HIV/AIDS in young people: evidence from developing countries on what works*. [?Place], World Health Organization, 2006 (WHO Technical Report Series 938).
4. Centers for Disease Control and Prevention. *Compendium of HIV prevention interventions with evidence of effectiveness*. August 2001.
5. Madon T, Hofman KJ, Kupfer L, Glass RI. Public health: implementation science. *Science*, 2007, 318:[1728-9].
6. Lyles CM et al. Best evidence intervention: finding from a systemic review of behavioral intervention for US populations at high risk 2000–2004. *American Journal of Public Health*, 2007, 97: 133-43.
7. Whitescarver J, Wetheimer WJ, Eisinger RW. *National Health Institutes of Health: AIDS research and funding*. USA, National Institutes of Health, 2002.
8. Zulu I et al. Priorities in antiretroviral therapy research in sub-Saharan Africa: a 2002 consensus conference in Zambia. *Acquired Immune Deficiency Syndromes*, 2004, 36: 831-4.
9. Jaffar S et al. Antiretroviral treatment in resource poor settings: public health research priorities. *Tropical Medicine and International Health*, 2005, 10:293–299.
10. Hanenberg RS, Rojanapithayakorn W, Kunasol P, Sokal DC. Impact of Thailand's HIV-control programme as indicated by the decline of sexually transmitted diseases. *Lancet*. 1994 Jul 23;344(8917):243-5.
11. UNAIDS. *Initiating second-generation HIV surveillance systems: practical guidelines*. Geneva, WHO & UNAIDS, 2002.
12. Ghys PD et al. The UNAIDS estimation and projection package: a software package to estimate and project national HIV epidemics. *Sexually Transmitted Infections*, 2004, 80 Suppl 1:i5–9.
13. UNAIDS/WHO. *Estimating the size of populations at risk for HIV*. Geneva, WHO and UNAIDS, 2003.
14. Rutherford GW, Schwarcz SK, McFarland W. Surveillance for incident HIV infection: new technology and new opportunities. *Journal of Acquired Immune Deficiency Syndromes*, 2000,25 Suppl 2:S115–119.
15. Anker M et al. A standard verbal autopsy method for investigating cause of death in infants and children. Geneva, World Health Organization, 1999. (WHO/CDS/CSR/ISR/99.4).
16. INDEPTH Network. INDEPTH Standardized verbal autopsy questionnaire. Revised August 2003. http://www.indepth-network.org/core_documents/indepthtools.htm (20 June 2008?).