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Chapter 12

Building capacity for the assessment of HIV drug resistance: Experiences from the PharmAccess African Studies to Evaluate Resistance Network

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ABSTRACT

The PharmAccess African Studies to Evaluate Resistance (PASER) network was established as a collaborative partnership of clinical sites, laboratories, and research groups in 6 African countries; its purpose is to build research and laboratory capacity in support of a coordinated effort to assess population-level acquired and transmitted human immunodeficiency virus type-1 drug resistance (HIVDR), thus contributing to the goals of the World Health Organization Global HIV Drug Resistance Network. PASER disseminates information to medical professionals and policy makers and conducts observational research related to HIVDR. The sustainability of the network is challenged by funding limitations, constraints in human resources, a vulnerable general health infrastructure, and high cost and complexity of molecular diagnostic testing. This report highlights experiences and challenges in the PASER network from 2006 to 2010.

INTRODUCTION

Despite enormous progress, major challenges remain to scaling up access to antiretroviral treatment (ART) for human immunodeficiency virus (HIV)–1-infected individuals in sub-Saharan Africa [1]. Under-resourced health systems result in important programmatic deficiencies, such as lack of virological monitoring, to detect treatment failure and inconsistent supply of antiretroviral drugs [2]. These deficiencies may contribute to the development of HIV drug resistance (HIVDR) during ART [3] and the subsequent transmission of drug-resistant strains to newly infected individuals [4], which has severe public health consequences in settings where treatment options are limited. Current conditions therefore advocate for the development of a global public health framework to assess and minimize the emergence of HIVDR [5].

The PharmAccess African Studies to Evaluate Resistance (PASER) network was established as a collaborative partnership of clinical sites, laboratories, and research groups in South Africa, Zambia, Zimbabwe, Uganda, Kenya, and Nigeria in 2006. PASER, jointly with its counterpart program TREAT Asia Studies to Evaluate Resistance (TASER) in Asia, constitutes a collaborative bi-regional capacity development program, which receives major financial support from the Ministry of Foreign Affairs of the Netherlands (http://www.laaser-hivaids.org). The PASER network strives to develop regional capacity for the coordinated population-level assessment of acquired and transmitted HIVDR, thereby advancing the epidemiological, clinical, and laboratory knowledge necessary for management of HIVDR in the sub-Saharan African region. PASER contributes to fulfilling the goals of the Global HIV Drug Resistance Network (HIVResNet), developed by the World Health Organization (WHO) [5]. The PASER study protocols focus on the assessment of acquired HIVDR in patients receiving first- or second-line ART (PASER Monitoring [PASER-M]) [6, 7, 8] and transmitted HIVDR in recently infected populations (PASER-Surveillance, PASER-S) [9, 10], and have been harmonized with the corresponding WHO generic protocols assessing acquired and transmitted HIVDR [11, 12], with the exception that PASER-M studies include longer patient follow-up and larger sample sizes and follow patients during both first- and second-line ART. PASER-M studies [6] have been implemented in 13 clinical sites in 6 African countries, and PASER-S studies have been conducted in Kampala [10] and Mombasa [9] (table 1). Subsequently, PASER has developed a number of projects and studies related to HIVDR. To make these studies possible, PASER enhanced the research capacity at participating sites and the HIVDR testing capacity at reference laboratories. This report highlights the experiences and challenges in the PASER network from 2006 to 2010.

Table 1. Summary of PASER achievements 2006-2010

	Target	Achieved
Capacity building		
HIVDR genotyping reference laboratories participating in TAQAS	3	3
Annual network meetings	5	5
Clinicians trained on HIVDR protocols and basic research skills	75	100
Laboratory staff trained on HIVDR protocols, GCLP, molecular diagnostics	75	86
Patient data		
HIVDR Monitoring studies		
Clinical sites / countries	15 / 7	13 / 6
Persons enrolled	3120	3007
Patient retention at 12 months of follow-up	2433	2360
HIVDR Surveillance studies		
Studies / countries	6 / 3	2 / 2
Persons enrolled	255	163

HIVDR, HIV-1 drug resistance; GCLP, Good Clinical Laboratory Practice; TAQAS, TREAT Asia Quality Assessment Scheme

NETWORK DEVELOPMENT

The PASER network is coordinated by PharmAccess Foundation, a nongovernment organization dedicated to the strengthening of health systems and improving access to quality basic healthcare in sub-Saharan Africa (http://www.pharmaccess.org), in collaboration with the Amsterdam Institute for Global Health and Development and the Department of Virology at the University Medical Center Utrecht. The creation of the network involved the selection of dedicated HIV treatment clinics, reference laboratories, and research groups in each of the African subregions. A total of 13 ART clinics and 3 laboratories in 6 countries were selected after careful assessments (figure 1). Participating clinical sites represent a variety of clinic types in terms of geography, available resources, administration (public, nongovernmental, private, and faith based), and level of experience with HIV treatment and research [6]. PASER is represented on the HIVResNet steering committee and collaborates with WHO HIVDR working groups at the national level.

LABORATORY CAPACITY

Given that very few laboratories in the region have the required organization and expertise to develop HIVDR testing capacity and the high cost of capital equipment

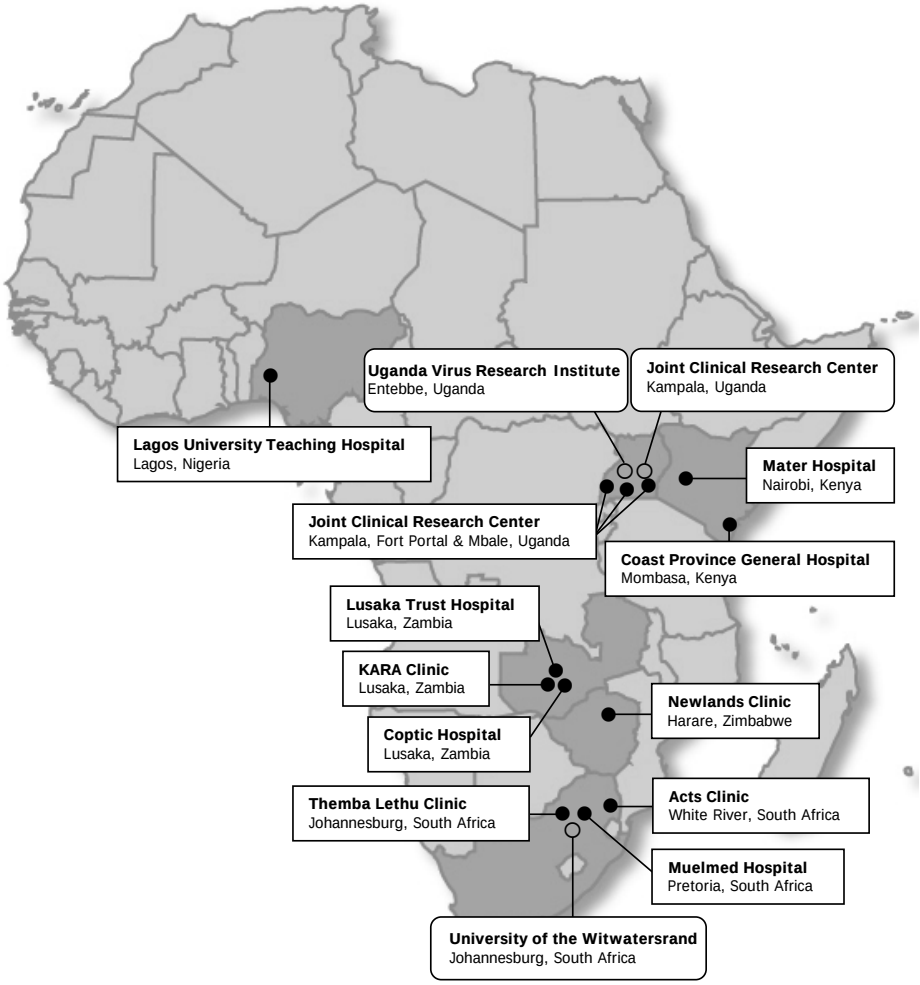

Figure 1. Geographical map of PASER sites. Closed circles represent clinical sites; open circles, reference laboratories.

for sequencing, it was decided to select and support a limited number of central reference laboratories situated in Johannesburg, Entebbe, and Kampala. Centralized laboratory testing also ensured standardization and quality assurance of the laboratory procedures. PASER provided laboratory equipment, database technology, and technical assistance, as required. Laboratory staff from all clinical sites and reference laboratories received additional training in Good Clinical Laboratory Practice and Good Molecular Diagnostics Practice, which included principles of unidirectional workflow, prevention of carryover contamination, and the principles of amplification and sequencing. Annual network meetings created a platform for laboratory staff to exchange experiences with international colleagues and interact with clinicians and study support staff. To ensure

data quality, each reference laboratory was enrolled in ≥2 external quality assurance programs for HIVDR testing. One of them is the TREAT Asia Quality Assurance Scheme (TAQAS) [13], which was set up in collaboration with a WHO-accredited regional HIVDR reference laboratory in Sydney, Australia. Before laboratories were allowed to start genotyping for PASER studies, proficiency testing was performed through TAQAS. Two reference laboratories (Johannesburg and Entebbe) have acquired WHO HIVResNet accreditation for HIVDR genotyping for public health surveillance [14], which has helped facilitate PASER studies.

HIV viral load and HIVDR genotyping was conducted on stored plasma. A consequence of centralized testing was the need for cold chain logistics across country borders. In preparation for the start of the studies, dedicated laboratory staff members received training on specimen handling and documentation according to protocol requirements, including the use of a Web-based specimen track and trace system. Sites received freezers for adequate specimen storage, if required. Funding for installing power back-up systems was not available, and, unfortunately, 1 site experienced interruptions in power supply for some time, which may have affected the quality of stored specimens. Specimen tracking data for PASER-M demonstrated 99% timely plasma separation (<12 hours), 98% timely storage at -80°C (<36 hours), and 99% receipt in adequate condition at the reference laboratory.

All generated sequences were submitted to the Web-based ViroScore Suite database (Advanced Biological Laboratories) for data storage and quality control. Due to logistic constraints, HIVDR testing was performed retrospectively and did not directly influence patient care. To address the high cost (USD 200 per test) and complexity of plasma-based genotyping [15], PASER has initiated a public-private consortium, called Affordable Resistance Test for Africa (ART-A), funded through the Netherlands-African Partnership for Capacity Development and Clinical Interventions Against Poverty-Related Diseases, which aims to develop and implement novel affordable and simple diagnostic technology for HIV viral load testing as well as the detection and interpretation of HIVDR in African clinics and laboratories (http://www.arta-africa.org).

CAPACITY FOR STUDIES TO ASSESS HIVDR

Many medical professionals in the PASER network did not have any prior research experience. Regular monitoring visits to the participating sites were conducted and were partly dedicated to teaching and training of basic research skills to site investigators, clinicians, nurses, and laboratory technicians. Annual network meetings were used to

provide skills building workshops on research methods, good clinical practice, and HIV disease management, including clinical and laboratory aspects of HIVDR: a total of 100 clinicians and 86 laboratorians received training at 5 network meetings (table 1). PASER-M has achieved 96% (n=3007) of the anticipated patient recruitment, with 82% retained in follow-up after 12 months (table 1). PASER-S studies have been successfully conducted in Kampala (78 participants) [10] and Mombasa (85 participants) (table 1). Several site investigators are actively involved in the analysis and reporting of study findings to local health policy makers and the public health community. Central clinical data collection for PASER-M was performed through the Web-based clincal database developed by PharmAccess. Despite the program's efforts to upgrade on-site information and communication technology capacity, many clinics did not have in-office personal computer workstations and reliable internet connections. Therefore, PASER-M used hard-copy data collection forms, which were subsequently transferred to the web-based database. PASER-M was initially monitored by a clinical research associate (CRA) from the Netherlands through regular site monitoring visits. As of 2008, the local study nurses at the sites in Nigeria, Kenya, and Uganda received training and mentoring in CRA monitoring. By 2010, the locally trained CRAs were capable of conducting study monitoring independently.

DISCUSSION

The PASER program has established a regional collaborative network to strengthen research and laboratory capacity for the population-level assessment of HIVDR, with effective linkages between clinical sites and reference laboratories. Key achievements of the PASER program are summarized in table 1. Building sustainable relationships and networks is important for the clinical and scientific communities within countries and regions, to facilitate the exchange of information and experience. PASER (with TASER) has brought together multidisciplinary stakeholders from academia, governments, nongovernment organizations, private sector, and civil society in Africa and Asia to draw attention to the imminent threat of HIVDR. Through the assessment of HIVDR at national and regional levels, PASER will contribute to evidence-based recommendations to inform ART guidelines and to provide feedback on the success of HIV treatment and prevention programs. The ART-A project is expected to produce simplified and affordable alternative HIVDR assessment tools, which will facilitate future HIVDR studies.

Several local challenges were faced during the development of the PASER network, such as political instability, competing interests, complexity of specimen logistics, failure to negotiate contracts, or inability to obtain ethical clearance. The study lead time was

substantially prolonged at some sites due to lengthy bureaucratic procedures in obtaining ethics approvals and permission to ship specimens abroad to the regional reference laboratories (e.g., in Ethiopia, Kenya, and Zimbabwe). The implementation of PASER-S proved challenging because of difficulties in identifying recently HIV-infected individuals even at antenatal clinics and voluntary counseling and testing sites. The sustainability of a research and surveillance network primarily depends on funding, and the current core funding for PASER will end in December 2011. Site investigators are committed to continuing the network, and efforts are ongoing to secure funding and ensure sustainability of the network. Other challenges include constraints in human resources, the need for continued training and education, the vulnerable general health infrastructure in many settings, and the urgent need for simplified and affordable diagnostic technology. The enhanced commitment of global health donors and technical agencies, including WHO, to establish and maintain surveillance networks to track the emergence and spread of HIVDR is crucial in this respect.

In conclusion, this report provides practice-based lessons from the PASER network. We believe that PASER has considerably improved the clinical research and laboratory capacity for the assessment of HIVDR in the African region. The network provides opportunities for further knowledge exchange, public health research, and health system development. For PASER to become sustainable, extended funding needs to be urgently secured, the cost and complexity of molecular laboratory testing need to be addressed, and the capacities of and collaborations between local, regional, and global institutions need to be further strengthened.

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Contributors

All authors have contributed extensively to the development and implementation of PASER. RLH wrote the first draft of the manuscript. RLH, ES, and KCES aggregated operational data. CK, CLW, WS, KCES, and TFRW critically reviewed the paper. All authors reviewed and approved the final manuscript. TFRW is the guarantor.

REFERENCES

1. World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010. Available at: http://www.who.int/hiv/pub/tuapr_2010_en.pdf. Accessed 1 June 2011.
2. Hamers RL, Derdelinckx I, Van Vugt M, Stevens W, Rinke de Wit TF, Schuurman R. The status of HIV-1 resistance to antiretroviral drugs in sub-Saharan Africa. Antivir Ther 2008; 13:625–39.
3. Gupta RK, Hill A, Sawyer AW, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. Lancet Infect Dis 2009; 9:409–17.
4. Hamers RL, Wallis CL, Kityo C, Siwale M, Mandaliya K, Conradie F, et al. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicenter observational study. The Lancet Infectious Diseases 2011; 11:750–9.
5. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antivir Ther 2008; 13(Suppl 2):1–13.
6. Hamers RL, Oyomopito R, Kityo C, et al. Cohort Profile: the PharmAccess African (PASER-M) and the TREAT Asia (TASER-M) monitoring Studies to Evaluate Resistance–HIV drug resistance in sub-Saharan Africa and the Asia-Pacific. Int J Epidemiol. 2011;[Epub ahead of print].
7. Hamers RL, Schuurman R, Sigaloff KCE, et al. Effect of pretreatment HIV-1 drug-resistance on immunological, virological and drug-resistance outcomes of first-line antiretroviral treatment: multicenter cohort in six African countries. The Lancet Infectious Diseases 2011.
8. Sigaloff KCE, Hamers RL, Wallis CL, et al. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. J Acquir Immune Defic Syndr 2011; 58:23–31.
9. Sigaloff KCE, Mandaliya K, Hamers RL, et al. High prevalence of transmitted antiretroviral drug resistance among newly HIV-1 diagnosed adults in Mombasa, Kenya. Aids Research and Human Retroviruses 2011 [Epub ahead of print].
10. Ndembi N, Hamers R, Sigaloff K, et al. Transmitted antiretroviral drug resistance spreading in Kampala? AIDS 2011; 25:905–10.
11. Jordan MR, Bennett DE, Bertagnolio S, Gilks CF, Sutherland D. World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites. Antivir Ther 2008; 13(Suppl 2):15–23.
12. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther 2008;13(Suppl 2):25–36.
13. Land S, Cunningham P, Zhou J, et al. TREAT Asia Quality Assessment Scheme (TAQAS) to standardize the outcome of HIV genotypic resistance testing in a group of Asian laboratories. J Virol Methods 2009; 159:185–93.
14. Bertagnolio S, Derdelinckx I, Parker M, et al.World Health Organization/HIVResNet drug resistance laboratory strategy. Antivir Ther 2008;13(Suppl 2):49–57.
15. Hamers RL, Smit PW, Stevens W, Schuurman R, Rinke de Wit TF. Dried fluid spots for HIV type-1 viral load and resistance genotyping: a systematic review. Antivir Ther 2009; 14:619–29.