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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

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**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**

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3 **Title: Cohort Profile: the PharmAccess African (PASER-M) and the TREAT Asia**
4
5 **(TASER-M) Monitoring Studies to Evaluate Resistance – HIV Drug**
6
7 **Resistance in sub-Saharan Africa and the Asia-Pacific**
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10
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15 PharmAccess African (PASER) and TREAT Asia (TASER) Studies to Evaluate
16 Resistance
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24
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43 **Key words** HIV drug resistance; antiretroviral therapy; sub-Saharan Africa; Asia; mutations;
44 genotype; monitoring;
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How did the study come about?

According to World Health Organization (WHO) estimates, 33.4 million people were infected with the human immunodeficiency virus (HIV) type 1 globally at the end of 2008 (1). Sub-Saharan Africa and Asia are the two regions having the highest HIV prevalence with 22.4 million and 4.7 million people infected, respectively (1). Over the 5 years prior, access to combination antiretroviral therapy (ART) in low and middle-income countries increased 10-fold to 4 million people, providing coverage to 42% of those in need (2). Several studies have reported significant reductions in HIV-related morbidity and mortality for individuals with access to treatment in these regions (3-5). In resource-limited settings, to facilitate the rapid expansion of access to ART, WHO recommends a standardized, public health approach (6). This is in contrast to the individualized patient management strategies in developed countries, based on routinely available diagnostic monitoring (7). Standardized first-line ART regimens consist of a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, available in some countries as generic fixed-dose combinations (6). Recommended second-line regimens combine a ritonavir-boosted protease inhibitor (PI) with two previously unused and/or recycled NRTIs (6).

Routine HIV viral load monitoring is not generally available in resource-limited countries and treatment failure is frequently identified based on immunological definitions and/or the occurrence of clinical events (6). Virological breakthrough may be detected late while the failing regimen is continued, thus facilitating the acquisition and accumulation of drug resistance-associated mutations (8). Drug-resistant HIV variants may compromise the effectiveness of subsequent lines of treatment and their transmission to newly infected individuals has severe public health consequences (9, 10). To date, ART programs have been implemented without accompanying HIV drug resistance (HIVDR) monitoring. Monitoring studies are hampered by the lack of a molecular laboratory infrastructure required for genotypic resistance testing, logistical challenges related to maintaining specimen integrity in remote settings and the high costs of testing (11). Challenges to scaling up ART in

1
2
3 resource-limited countries, such as absence of routine virological monitoring and limited
4
5 choices of drug regimen, advocate for the development of a global public health framework to
6
7 monitor and prevent the emergence of HIVDR and thus maximize long-term ART
8
9 effectiveness (12).

10
11 HIV-1 subtype B is the predominant viral subtype in North America, Western
12
13 Europe and Australia, and antiretroviral (ARV) drugs have been developed on this subtype.
14
15 However, in sub-Saharan Africa and Asia, the genetic diversity in HIV subtypes and
16
17 circulating recombinant forms (CRFs), resulting from recombination between subtypes within
18
19 a dually infected person, is extensive (13). Although current evidence is limited, some reports
20
21 have suggested that the propensity to develop HIVDR and the spectrum of mutations that
22
23 emerge during drug selective pressure, may differ across subtypes and CRFs (14-17). Viral
24
25 heterogeneity may, therefore, have implications for rates of disease progression and patient
26
27 response to ART, warranting further study of inter-subtype differences in mutational
28
29 pathways to resistance.
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34 To help assess the extent of HIVDR in sub-Saharan Africa and Asia, LAASER
35
36 (Linking African and Asian Societies for an Enhanced Response to HIV/AIDS;
37
38 <http://www.laaser-hivaids.org>) has established a collaborative bi-regional program with the
39
40 primary aim of increasing regional capacities for the monitoring of HIVDR. PharmAccess
41
42 Foundation, a non-profit organization dedicated to the strengthening of health systems and
43
44 improving access to quality basic health care in sub-Saharan Africa, has developed the
45
46 PharmAccess African Studies to Evaluate Resistance (PASER). TREAT Asia (Therapeutics,
47
48 Research, Education and AIDS Training in Asia) is a network of clinics, hospitals and
49
50 research institutions working to ensure safe and effective delivery of HIV/AIDS treatment
51
52 throughout the Asia-Pacific and has developed the TREAT Asia Studies to Evaluate
53
54 Resistance (TASER). Both PASER and TASER programs incorporate a monitoring and
55
56 evaluation (M) and a surveillance (S) protocol. Laboratories providing genotyping results for
57
58 PASER and TASER are required to participate in the TREAT Asia Quality Assurance
59
60 Scheme (TAQAS) which is an ongoing assessment program to build genotyping laboratory

1
2
3 capacity, described elsewhere (18). The focus of this cohort profile is the monitoring and
4
5 evaluation protocols, PASER-M and TASER-M.
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9 10 **How are PASER and TASER set up and how is it funded?**

11 Through the LAASER program, PASER and TASER receive financial support from the Dutch
12 Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds, PharmAccess
13 Foundation, TREAT Asia (a program of amfAR, The Foundation for AIDS research) and
14 International Civil Society Support. PASER-M is coordinated by PharmAccess Foundation, in
15 collaboration with the Amsterdam Institute for Global Health and Development (AIGHD) and
16 the Virology Department at the University Medical Center Utrecht, The Netherlands. TASER-
17 M is coordinated by TREAT Asia and its statistical and data management centre is the
18 National Centre in HIV Epidemiology and Clinical Research (NCHECR), The University of
19 New South Wales in Sydney, Australia.
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31 PASER constitutes a newly established collaboration between HIV treatment
32 clinics, laboratories with the capacity to perform genotypic sequencing and research centers.
33 Thirteen clinical sites and 2 reference laboratories in 6 African countries (Kenya, Nigeria,
34 South Africa, Uganda, Zambia and Zimbabwe) are collaborating on PASER-M (Figure 1a).
35 Details of the PASER-M collaborating clinical sites are summarized in Table 1 (web
36 appendix). Ethics approvals were obtained from the Academic Medical Center Institutional
37 Review Board (IRB) and local IRBs. Sites are government, non-government, faith-based or
38 private clinics and hospitals, situated in major cities or rural areas. ART was introduced at the
39 sites at varying time points between 1992 and 2006 (median: 2004). Eleven of 13 sites
40 provide drugs, consultations and routine lab testing free of charge. HIV viral load testing is
41 available at 8 of 13 sites.
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54 TASER collaborating sites are selected from within the existing TREAT Asia
55 network based on their laboratory capacity to perform genotypic sequencing, described
56 elsewhere (18, 19). Sites which do not have internal laboratory genotyping capacity can
57 participate through collaboration with a TAQAS-certified laboratory. Eleven clinical and
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1
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3 laboratory sites in 6 Asian countries (China, Indonesia, Malaysia, Philippines, South Korea,
4
5 Thailand) are collaborating on TASER-M (**Figure 1b**). Ethics approvals were obtained from
6
7 local IRBs having Federalwide Assurances (FWAs) in place from the United States Office for
8
9 Human Research Protections. FWAs are required for TASER sites as they participate in the
10
11 International Epidemiologic Databases to Evaluate AIDS (IeDEA) initiative, described
12
13 elsewhere (**20**). Sites are generally government or university-based clinics and hospitals or
14
15 private clinics, situated in major cities and other urban areas. Those with ethics approvals
16
17 prior to June 2010 are shown in **Figure 1b**. ART has been available in Asia for more than 10
18
19 years, even in less resourced countries in the region and all TASER-M clinical sites have on-
20
21 site virologic testing.
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23

24
25 Clinical sites follow their national guidelines to assess eligibility for ART initiation in
26
27 accordance with WHO recommendations (**6**). Genotypic resistance testing on PASER and
28
29 TASER clinical specimens are performed in TAQAS-certified genotyping laboratories (**18**).
30
31 Laboratories are encouraged to become accredited members of the WHO/HIVResNet HIV
32
33 Drug Resistance Laboratory network (**21**). Population-based nucleotide sequencing of the
34
35 HIV protease (PR) and partial reverse transcriptase (RT) gene regions is performed on
36
37 plasma specimens which have HIV RNA >1 000 copies/ml. Plasma is obtained from blood
38
39 collected in EDTA-tubes which is locally stored at -80°C and, if required, batch-shipped on
40
41 dry ice to a genotyping laboratory.
42
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44
45 PASER-M genotypic testing is concentrated in two central reference laboratories,
46
47 and thus depends on a robust cold-chain and web-based specimen tracking system for
48
49 managing specimen shipments. Approximately half of TASER-M clinical sites have an on-site
50
51 or local genotyping laboratory. Most genotyping laboratories amplify viral sequences using in-
52
53 house methods, based on assembled commercially available assay components and
54
55 laboratory-specific sequencing and amplification primers. One TASER laboratory uses the
56
57 commercial kit TruGene (Bayer HealthCare, Tarrytown, NY, USA). The online Stanford
58
59 interpretation system is used by most laboratories to identify drug resistance-associated
60
mutations (**22**). Resistance genotyping is generally performed retrospectively (i.e. not real-

1
2
3 time) for all participants. Details of the genotyping laboratories are summarized in **Table 2**
4
5 (web appendix). PASER and TASER sequences are submitted to the ViroScore database
6
7 (Advanced Biological Laboratories SA, France) for data storage.
8
9

11 **What do PASER-M and TASER-M cover and who is included in the sample?**

12
13
14 The monitoring studies are multi-center prospective cohort designs with sequential patient
15
16 enrolment. Patient eligibility criteria are listed in **Table 3**. The main study objectives are to
17
18 assess prevalence and incidence of HIVDR, mutational patterns and factors associated with
19
20 HIVDR in persons initiating first-line ART or switching to a second-line regimen due to
21
22 treatment failure under routine circumstances. Participants are required to sign informed
23
24 consent prior to study enrolment and must initiate or switch ART within 30 days (PASER-M)
25
26 or 181 days (TASER-M) following baseline specimen collection. Regimen switch due to
27
28 treatment failure may be determined clinically, as assessed by disease progression,
29
30 immunologically, by CD4 cell count, or virologically, by HIV viral load. A single drug
31
32 substitution, due to toxicity or intolerance, is not considered a regimen switch. Each site aims
33
34 to recruit a total of 240 participants. Second-line participants are recruited among first-line
35
36 participants failing therapy and the clinical site patient population. The recommended
37
38 maximum site-specific enrolment period is 18 months.
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44 **How often are participants followed-up? What data are being collected?**

45
46 Participants are followed up as per local standard of care guidelines. The frequency of follow-
47
48 up visits for patients varies by site (range: every 1 to 6 months). The studies make use of
49
50 clinical data collected during routine visits and recorded in medical records. HIV viral load
51
52 measurement and, if HIV RNA value >1 000 copies/ml, genotypic resistance testing is
53
54 performed on plasma specimens taken at baseline, prior to regimen switch due to treatment
55
56 failure and at annual follow-up. For patients failing a first-line regimen, the treatment failure
57
58 data collection becomes the new baseline for the second-line regimen. Annual follow-up is
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3 then calculated from this point. For patients failing a second-line ART, the treatment failure
4 data collection is the final assessment prior to the patient going off study.
5
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7
8 PASER-M clinical data are recorded on standardized hard-copy data forms which
9 are completed at three-monthly intervals and entered in a web-based clinical data system,
10 called the HAART Monitoring System. PharmAccess performs quality assurance measures
11 which include (i) source data verification during 3 to 6-monthly site audits, (ii) checks to
12 identify data entry inconsistencies or suspect data values and (iii) specimen tracking.
13
14

15
16 TASER-M site personnel extract clinical data from site databases and medical records
17 collected as part of usual care. From March 2008 to March 2009, TASER-M data were
18 submitted electronically to NCHECR on a quarterly basis, as part of study start up, then at 6
19 monthly intervals. At each transfer, NCHECR performs quality assurance measures which
20 include (i) checks to identify data entry inconsistencies or suspect data values, (ii) specimen
21 tracking and (iii) ARV history completeness. Annually, a random 10% of TASER-M patients
22 are selected for internal site audit where submitted data is compared to patient medical
23 records.
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36 The studies capture standardized virologic and genotypic data at protocol
37 determined intervals. Genotyping data consists of HIV subtype and HIVDR mutations,
38 including insertions and deletions. TASER-M also records discordant subtypes, i.e. when the
39 PR and RT region subtypes differ. Laboratory specimen tracking information is recorded
40 during specimen processing, allowing assessment of pre-analytical and assay validity.
41
42 Genotyping laboratories complete an annual laboratory survey which includes the dynamic
43 range of the virologic assay used, the regions of PR and RT genome routinely sequenced
44 and the interpretation algorithm used. Observational patient data includes demographic
45 parameters, physical measures, Centers for Disease Control and Prevention (CDC) class
46 (TASER-M) or WHO clinical stage (PASER-M), serology of hepatitis and syphilis (TASER-M),
47 opportunistic infections, current ART regimen, ARV history, concomitant medications, routine
48 laboratory parameters (including CD4 counts) and assessment of drug adherence. Main
49 analyses will include age, sex, ethnicity, HIV exposure category, WHO clinical stage
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3 (PASER-M) or CDC class (TASER-M), viral hepatitis co-infection status, CD4 count, HIV viral
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5 load, HIV subtype, drug adherence, ARV history and ART regimen as covariates. Predictors
6
7 of drug resistance will be assessed using logistic regression models. Incidence of drug
8
9 resistance will be summarized using person-years methods and Kaplan-Meier plots. Cox
10
11 proportional hazards models will be used to assess risk factors associated with developing
12
13 drug resistance.
14
15

16 17 18 **What is the anticipated attrition?**

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20 The actual attrition in PASER-M and TASER-M cannot currently be accurately estimated
21
22 because the duration of follow-up in the databases is still limited. In sub-Saharan Africa
23
24 patient retention in routine ART programs has been estimated at 61.6% (23) to 66.8% (2) at
25
26 24 months on ART, attrition being mainly due to loss of follow-up and early death (23).
27
28

29 Therefore, in PASER-M the original site-specific sample size was calculated accounting for
30
31 20% loss to follow up and 25% mortality after 24 months. Attrition is expected to vary
32
33 between sites, as a result of differences in patient populations, care provided and provisions
34
35 for tracing lost to follow-up. TASER-M sites are generally sourced from the ongoing TREAT
36
37 Asia HIV Observational Database (TAHOD) (19). Loss to follow-up for TAHOD was 6.9/100
38
39 person-years for the 12-month period from September 2007 - September 2008. Since
40
41 TASER-M monitors specified outcomes, we speculate that TASER-M follow-up will be similar
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43 to TAHOD or better.
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49 **What has been found?**

50 51 **PASER-M**

52 Patient recruitment commenced in March 2007 and was completed in September 2009.
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54 Twelve of 13 sites reached the site-specific target of 240 participants, enrolling a total of 3
55
56 005 participants. Excluding patients with protocol violations (n=16) and key data missing
57
58 (n=4), 2 985 patients were included in the analysis. Of these, 2 736 (91.6%) were eligible for
59
60 a first-line ART regimen and 249 (8.3%) were eligible for second-line ART due to treatment

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3 failure. Patient characteristics are summarized in **Table 4**. For first-line patients, the median
4
5 age was 36.8 years (IQR: 31.3-42.6) and 58% were women. HIV exposure was
6
7 predominantly reported as heterosexual contact. More than 60% had advanced disease
8
9 (classified as WHO stage III or IV) and 37% had pre-therapy CD4 counts of less than 100
10
11 cells/ μ L. Across all 13 sites, median baseline CD4 counts of first-line patients were <200
12
13 cells/ μ L (site median 135 cells/ μ L, range: 93 – 191). Median baseline HIV viral load was 4.9
14
15 \log_{10} copies/ml (IQR: 4.2-5.5). The most frequently prescribed first-line regimens were based
16
17 on NNRTIs (99.7%), i.e. efavirenz (EFV) and nevirapine (NVP) at 60% and 40%,
18
19 respectively. First-line dual NRTI backbones were predominantly lamivudine
20
21 (3TC)/zidovudine (AZT) (37%), emtricitabine (FTC)/tenofovir (TDF) (34%) and 3TC/stavudine
22
23 (d4T) (26%). Overall, 67% of patients started a 3TC-containing first-line regimen. Among
24
25 patients initiating first-line ART, 95% (n=2 598) reported to be ARV-naïve and 5% (n=138)
26
27 had previous ARV experience, which included ART (n=60), mono/dual therapy (n=6), single-
28
29 dose NVP for prevention of mother-to-child transmission of HIV (PMTCT) (n=35),
30
31 combination therapy for PMTCT (n=19), and unspecified (n=22). Compared with ARV-naïve
32
33 first-line patients, ARV-experienced first-line patients had higher median CD4 counts (177 vs.
34
35 133 cells/ μ L, $p < 0.0001$), were younger (median 34.7 vs. 37.0 years, $p < 0.0001$) and were
36
37 more likely to be female (76.1% vs. 57.5%; $p < 0.001$). Other baseline characteristics did not
38
39 differ between ARV-naïve and ARV-experienced patients.
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41
42
43

44 For the 249 (8.3%) patients switching to second-line ART, the median age was 38.6 years
45
46 (IQR: 32.9-44.2) and sex was equally distributed. HIV exposure was predominantly
47
48 heterosexual contact and 48% of patients had advanced disease (classified as WHO stage III
49
50 or IV). Median CD4 count was 125 cells/ μ L (IQR: 46-196). Median pre-switch HIV viral load
51
52 was 4.1 \log_{10} copies/ml (IQR: 3.2-5.0). Ritonavir-boosted lopinavir (LPV) was the PI used
53
54 almost exclusively (98%).
55
56

57 As shown in **Table 5**, analysis of the first available 1 795 viral sequences demonstrated that
58
59 the most common HIV subtypes in the cohort were C (1216, 68.7%), A (338, 18.7%) and D
60
(179, 10.0%). The first PASER report published in 2008 reviewed the available data on

1
2
3 HIVDR in sub-Saharan Africa (11). Baseline HIVDR data from Lusaka, Zambia has recently
4
5 been published (24). International presentations have summarized preliminary baseline
6
7 HIVDR mutations and subtype distributions (25, 26).
8
9

10 11 **TASER-M**

12 Patient recruitment commenced in March 2007 and for the March 2009 transfer, 7 sites from
13
14 Thailand, Hong Kong and Malaysia provided data. Of 773 patients, 755 (97.7%) commenced
15
16 ART within 181 days of baseline specimen collection and 728 (96.4%) participants had
17
18 genotypic data available. Of these, 693 (95.2%) ARV-naïve patients and 10 (1.4%) ARV-
19
20 experienced patients following prior PMTCT were eligible for first-line regimens. A further 25
21
22 (3.5%) patients were eligible for second-line ART following first-line treatment failure. Patient
23
24 characteristics are summarized in **Table 4**. For ARV-naïve first-line patients, the median age
25
26 was 36.5 years. Almost two thirds of patients were male and HIV exposure was
27
28 predominantly heterosexual contact. More than one third of patients were classified as CDC
29
30 class C and almost half of patients had pre-therapy CD4 counts less than 100 cells/ μ L.
31
32 Median baseline HIV viral load was 5.0 log₁₀ copies/ml (IQR: 5.4-6.8) and the most common
33
34 first-line regimens were based on NNRTIs (85.6%). Excluding 14 (2.4%) patients on a
35
36 randomized clinical trial with a blinded NNRTI component, NVP was more commonly
37
38 prescribed than EFV at 56% and 42%, respectively. First-line dual NRTI backbones were
39
40 predominantly 3TC/d4T (47%), 3TC/AZT (29%) and 3TC/TDF (10%). For first-line PI
41
42 regimens, the favored NRTI backbone was TDF/ FTC (33%) compared to 3TC/d4T (30%) or
43
44 3TC/AZT (18%). For the ritonavir-boosted PI component, atazanavir (ATZ) was only slightly
45
46 favored over LPV at 43% vs 41%, respectively. Overall, 542 (91.4%) of ARV naive patients
47
48 started a 3TC-containing first-line regimen. The 10 PMTCT patients received perinatal
49
50 prophylaxis of AZT/3TC/NVP (n=7), AZT (n=2) or AZT/NVP (n=1) for between 14 and 102
51
52 days and all were prescribed AZT/3TC/NVP as first-line regimens.
53
54 For the 25 (3.4%) second-line patients, 22 (88%) were of thai ethnicity and the median age
55
56 was 36.5 years (IQR: 32.4 - 41.9). Females were in the majority (64%), HIV exposure was
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3 predominantly heterosexual (92%) and 60% of patients had experienced at least one CDC
4 class C event. Of 21 patients with CD4 counts available within 6 months of starting a second-
5 line therapy, the median CD4 count was 197 (IQR: 109 - 299). Median pre-switch HIV viral
6 load was 4.0 log₁₀ copies per/ml (IQR: 3.6 - 4.5). All patients were on PI-based regimens,
7 following failure on first-line NNRTI-based regimens (median duration 30.3 months). The
8 most commonly prescribed PI was ritonavir-boosted LPV (88%). As shown in **Table 5**, from
9 analysis of the 728 available viral sequences, the most common subtypes were CRF01_AE
10 (584, 80.2%) and subtype B (111, 15.2%). Non-CRF01_AE recombinants were identified in 8
11 (1.1%) patient specimens. For 21 (2.9%) specimens, the subtype differed between PR and
12 RT regions suggesting dual infection or recombination. International presentations have
13 summarized 2009 baseline HIVDR mutations and subtype distributions (**27, 28**).

14
15 Complete baseline and prospective outcome data for PASER-M and TASER-M are
16 anticipated to become available in 2010-2013.

17 18 19 **What are the main strengths and weaknesses?**

20 Programs that monitor national and regional levels of primary and secondary HIVDR
21 contribute to evidence-based recommendations to inform treatment guidelines and provide
22 feedback on the success of HIV treatment and prevention programs. PASER and TASER,
23 with TAQAS, are developing capacity in sub-Saharan Africa and the Asia-Pacific for
24 coordinated HIVDR monitoring and genotypic laboratory testing. The study protocols are
25 harmonized with the WHO HIV Drug Resistance Prevention Survey protocol (**29**). An
26 important strength is the large number of patients and sites participating, representing a
27 diverse spectrum of patient populations, clinic types, ART regimens and HIV subtypes.
28 Opportunities exist to investigate the impact of drug resistance on HIV natural history, rates
29 of disease progression and response to treatment in non-B subtypes. Data from genotypic
30 resistance testing will also provide insight into the population genetics and dynamics of
31 transmitted HIVDR in the region.

1
2
3 PASER-M and TASER-M have several limitations. First, patient samples at each
4 site are not necessarily representative of the site, country or region. Second, data quality
5 depends on the completeness of clinical information captured through routine patient care. In
6
7
8
9
10 PASER-M, data may have been collected under varying conditions, since some sites had no
11
12 or limited research experience at study initiation. Third, at some sites, study initiation was
13
14 delayed by several months due to the time required for contract negotiation, IRB study
15
16 approval and, in TASER-M, procurement of FWAs. After study initiation, recruiting the
17
18 required number of patients within the recommended 18 month period proved difficult for
19
20 some sites, due to asymptomatic patients not seeking care or treatment, cost of medication
21
22 or low-prevalence in their setting. Fourth, HIVDR monitoring activities in resource-limited
23
24 countries in sub-Saharan Africa are limited by high costs of laboratory testing. To address
25
26 this challenge, PASER has initiated a public-private consortium, called Affordable Resistance
27
28 Test for Africa (ART-A), which aims to evaluate affordable test algorithms for the detection
29
30 and interpretation of HIVDR for use in laboratories and clinics (<http://www.arta-africa.org>).
31
32
33

34 35 **How can I collaborate? Where can I find out more?**

36
37 Ownership of individual site data remains with the contributing site. Sites are represented by
38
39 their principal investigators on the respective PASER and TASER Steering Committees.
40
41 Research is to be the subject of peer-reviewed publications and analysis priorities are driven
42
43 by a concept sheet process. Both studies accept concept proposals from external
44
45 researchers for review, if submitted in collaboration with one or more of the site principal
46
47 investigators. The PASER and TASER protocols contribute data under the LAASER
48
49 partnership (<http://www.laaser-hivaid.org>) and TASER also contributes data to leDEA (20).
50
51 Collaborating sites are also encouraged to make an appropriate subset of their data available
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53 to Ministry of Health in their respective country in order to contribute to local efforts in
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55 monitoring HIVDR. Questions regarding participation, research concepts or requests for data
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Conflict of interest None declared

Appendix

The PharmAccess African Studies to Evaluate Resistance

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3 **Figures & Tables**
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7 **Figure 1a.** Geographical location of PASER-M collaborating sites

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9 **Figure 1b.** Geographical location of TASER-M collaborating sites
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14 **Table 1.** Patient eligibility criteria for PASER-M and TASER-M
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16 **Table 2.** Baseline patient characteristics, by network and line of ART
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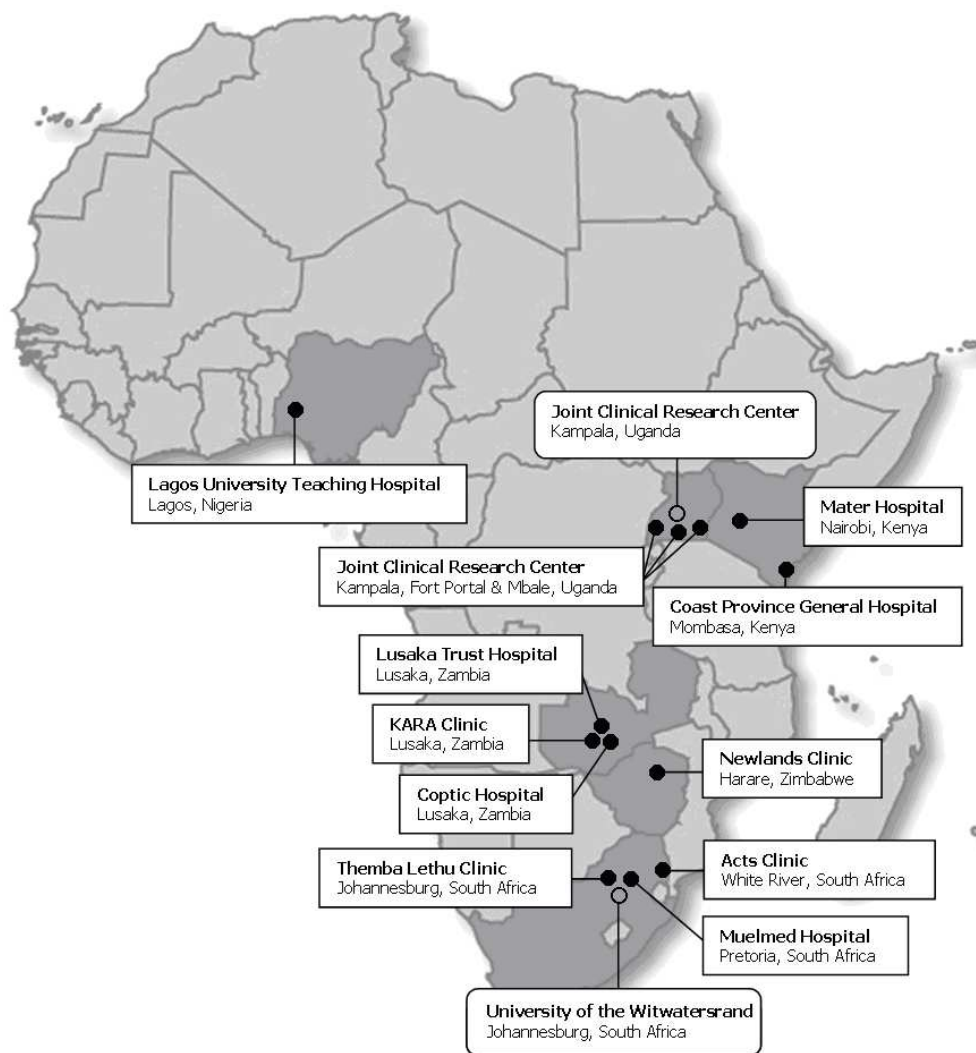
18 **Table 3.** HIV subtypes and circulating recombinant forms by region and country
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22 **Web Appendix**
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24 **Table 1.** Characteristics of the PASER-M collaborating clinical sites (web appendix)
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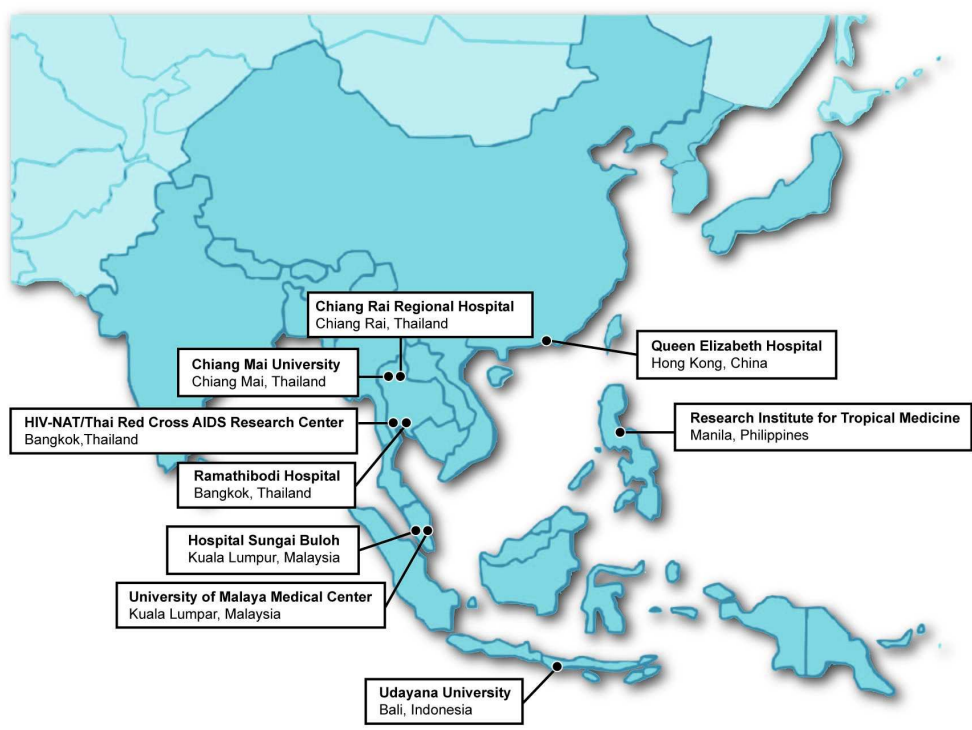
27 **Table 2.** PASER and TASER genotyping laboratories (web appendix)
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Geographical location of PASER-M (a) and TASER-M (b) collaborating sites
233x247mm (96 x 96 DPI)

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Geographical location of PASER-M (a) and TASER-M (b) collaborating sites
619x464mm (72 x 72 DPI)

Only

Table 3. Patient eligibility criteria for PASER-M and TASER-M

Inclusion criteria

- Confirmed HIV-1 infection;
- ≥18 years of age;
- Eligible ^a for initiation of a first-line ART regimen, or switch from a first-line ART regimen (containing at least 3 antiretroviral drugs and taken for at least 6 months) to a second-line ART regimen due to virologic, immunologic and/or clinical failure
- Signed informed consent for study participation prior to enrolment

Exclusion criteria

- Currently taking ART (minimum of 3 drug regimen), if initiating a first-line ART regimen ^b
- Pregnancy at enrolment ^c
- HIV-1/2 dual-infection (in endemic countries only) ^c

ART, combination antiretroviral therapy

^a Eligibility for ART initiation defined in accordance with national ART guidelines (i.e. advanced immunodeficiency as defined by CD4 cell count <200 or <350 cells/ μ l, or advanced clinical disease according to WHO clinical stage/CDC classification).

^b Specified PASER-M definition: re-initiation of a first-line ART regimen less than 30 days after stopping previous first-line ART (previous use of antiretroviral prophylaxis or mono/dual therapy is not an exclusion criterion).

^c Exclusion criteria applicable to PASER-M only

Table 4. Baseline patient characteristics, by network and line of ART

	PASER-M (Africa)				TASER-M (Asia)		
	Total	Initiation of first-line ART ^a		Switch to second-line ART ^b	Initiation of first-line ART ^a		Switch to second-line ART ^b
		ARV-naive	ARV-experienced ^c		ARV-naive	ARV-experienced ^c	
Patients – no. (%)	3713	2598 (87.0)	138 (4.6)	249 (8.3)	693 (95.2)	10 (1.4)	25 (3.4)
Sex							
Female – no. (%)	1988 (53.5)	1494 (57.5)	105 (76.1)	124 (49.8)	239 (34.5)	10 (100.0)	16 (64.0)
Male – no. (%)	1725 (46.5)	1104 (42.5)	33 (23.9)	125 (50.2)	454 (65.5)	0 (0.0)	9 (36.0)
Age (years) – median (IQR)	36.9 (31.7-43.3)	37.0 (31.2-42.8)	34.7 (29.2-40.2)	38.6 (32.9-44.2)	36.5 (31.1-43.2)	33.1 (27.4-38.4)	36.5 (32.4-41.9)
18-29	707 (19.0)	490 (18.9)	39 (28.3)	28 (11.2)	143 (20.6)	3 (30.0)	4 (16.0)
30-39	1668 (44.9)	1176 (45.3)	65 (47.1)	112 (45.0)	298 (43.0)	5 (50.0)	12 (48.0)
≥40	1338 (36.0)	932 (35.9)	34 (24.6)	109 (43.8)	252 (36.4)	2 (20.0)	9 (36.0)
HIV exposure – no. (%)							
Heterosexual contact	2583 (69.6)	1731 (66.6)	108 (78.3)	191 (76.7)	520 (75.0)	10 (100.0)	23 (92.0)
Homosexual contact	134 (3.6)	4 (0.2)	0 (0.0)	0 (0.0)	128 (18.5)	0 (0.0)	2 (8.0)
Other ^d	996 (26.8)	863 (33.2)	30 (21.7)	58 (23.3)	45 (6.5)	0 (0.0)	0 (0.0)
WHO clinical stage – no. (%)							
I	493 (16.5)	393 (15.1)	25 (18.1)	75 (30.1)	na	na	na
II	711 (23.8)	623 (24.0)	33 (23.9)	55 (22.1)	na	na	na
III	1281 (42.9)	1145 (44.1)	59 (42.8)	77 (30.9)	na	na	na
IV	500 (16.7)	437 (16.8)	21 (15.2)	42 (16.9)	na	na	na
CDC classification – no. (%)							
A	302 (41.5)	na	na	na	296 (42.7)	0 (0.0)	6 (24.0)
B	166 (22.8)	na	na	na	152 (21.9)	10 (100.0)	4 (16.0)
C	260 (35.7)	na	na	na	245 (35.4)	0 (0.0)	15 (60.0)
Ever pulmonary TB – no. (%)	741 (20.0)	569 (21.9)	25 (18.1)	74 (29.7)	69 (10.0)	na	4 (16.0)
Hepatitis B ^f – no. (%)	36 (4.9)	na	na	na	35 (5.1)	0 (0.0)	1 (4.0)
Hepatitis C ^g – no. (%)	56 (7.7)	na	na	na	55 (7.9)	0 (0.0)	1 (4.0)
History of ARV drug use – no. (%)							
ART	422 (11.4)	na	138 (100.0)	249 (100.0)	na	10 (100.0)	25 (100.0)
	334 (9.0)	na	60 (43.5)	249 (100.0)	na	0 (0.0)	25 (100.0)

Mono or dual therapy	10 (0.3)	na	6 (4.3)	4 (1.6)	na	0 (0.0)	0 (0.0)
Single-dose NVP for PMTCT	36 (1.0)	na	35 (25.4)	1 (0.4)	na	0 (0.0)	0 (0.0)
Combination therapy for PMTCT	31 (0.8)	na	19 (13.8)	2 (0.8)	na	10 (100.0)	0 (0.0)
Unspecified	22 (0.6)	na	22 (15.9)	0 (0.0)	na	0 (0.0)	0 (0.0)
CD4 cell count (cells/μL) - median (IQR)	129 (56-205)	133 (62-204)	177 (92-262)	125 (46-196)	99 (33.5-201)	169 (151-222)	197 (109-299)
<100	1456 (39.2)	975 (37.5)	38 (27.5)	102 (41.0)	337 (48.6)	1 (10.0)	3 (12.0)
100-199	1215 (32.7)	914 (35.2)	42 (30.4)	81 (32.5)	164 (23.7)	6 (60.0)	8 (32.0)
\geq 200	1007 (27.1)	702 (27.0)	57 (41.3)	64 (25.7)	171 (24.7)	3 (30.0)	10 (40.0)
Unknown	25 (0.7)	7 (0.3)	1 (0.7)	2 (0.8)	21 (3.0)	0 (0.0)	4 (16.0)
HIV-1 RNA (log₁₀ copies/ml) – median (IQR)	4.9 (4.3-5.5)	4.9 (4.3-5.6)	4.8 (4.2-5.5)	4.1 (3.2-5.0)	5.0 (5.4-6.8)	4.8 (4.5-5.0)	4.0 (3.6-4.5)
ART regimen							
NNRTI-based triple regimen	3330 (89.7)	2590 (99.7)	135 (97.8)	2 (0.8)	593 (85.6)	10 (100.0)	0 (0.0)
AZT-containing	1302 (35.1)	964 (37.2)	51 (37.8)	1 (0.4)	170 (28.7)	10 (100.0)	0 (0.0)
TDF-containing	1088 (29.3)	868 (33.5)	49 (36.3)	1 (0.4)	110 (18.5)	0 (0.0)	0 (0.0)
d4T-containing	833 (22.4)	690 (26.6)	33 (24.4)	0 (0.0)	276 (46.5)	0 (0.0)	0 (0.0)
ABC-containing	106 (2.9)	68 (2.6)	2 (1.5)	0 (0.0)	37 (6.2)	0 (0.0)	0 (0.0)
3TC-containing	2387 (71.7)	1746 (67.4)	89 (65.9)	0 (0.0)	542 (91.4)	10 (100.0)	0 (0.0)
FTC-containing	942 (28.3)	843 (32.5)	48 (35.6)	0 (0.0)	49 (8.3)	0 (0.0)	0 (0.0)
PI-based triple regimen	351 (9.5)	6 (0.2)	0 (0.0)	247 (99.2)	73 (10.5)	0 (0.0)	25 (100.0)
Triple NRTI regimen	29 (0.8)	2 (0.1)	3 (2.2)	0 (0.0)	24 (3.5)	0 (0.0)	0 (0.0)
NNRTI+PI-based regimen	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)

Data are n (%) of patients, unless otherwise indicated.

ART, combination antiretroviral therapy; ARV, antiretroviral; CDC, US Center for Disease Control and Prevention; WHO, World Health Organization; PMTCT, prevention of mother-to-child transmission of HIV-1; TB, tuberculosis; IQR, interquartile range; NVP, nevirapine; d4T, stavudine; AZT, zidovudine; TDF, tenofovir; ABC, abacavir; 3TC, lamivudine; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

^a Eligibility for ART initiation in accordance with national ART guidelines (i.e. advanced immunodeficiency as defined by CD4 cell count <200 or <350 cells/ μ L, or advanced clinical disease according to WHO clinical stages or CDC classification).

^b Regimen switch due to treatment failure, defined by local standard of care guidelines as determined clinically, immunologically or virologically.

^c ARV-experienced is defined as any previous use of ARVs, i.e. (first-line) ART, mono/dual therapy, and/or PMTCT

^d Includes recipients of blood products, injecting drug users, perinatal transmission and unknown exposures

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^f Hepatitis B positive status was defined as being HBsAg positive

^g Hepatitis C positive status was defined as being HCV antibody positive

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Table 5. HIV subtypes and circulating recombinant forms ^a by region and country

	PASER-M (Africa)					TASER-M (Asia) ^b				
	Total	South Africa	Zambia	Uganda	Kenya	Nigeria	Zimbabwe	Thailand	Hong Kong	Malaysia
n (%)	2523 (100.0)	624 (24.7)	583 (23.1)	410 (16.3)	140 (5.5)	21(0.8)	17 (0.7)	542 (21.5)	111 (4.4)	75 (3.0)
A	340 (13.6)	2 (0.3)	4 (0.7)	235 (57.3)	97 (69.1)	1 (4.8)		1 (0.2)		
B	114 (4.5)	3 (0.5)						37 (7.0)	55 (49.5)	19 (25.3)
C	1236 (49.2)	617 (98.9)	571 (97.9)	9 (2.2)	19 (13.6)		17 (100.0)		2 (1.8)	1 (1.3)
D	179 (7.1)	1 (0.2)	1 (0.2)	160 (39.0)	17 (12.1)					
G	11 (0.4)		2 (0.3)	1 (0.2)	2 (1.4)	6 (28.6)				
CRF01_AE	585 (23.2)							485 (89.5)	52 (46.8)	48 (64.0)
CRF02_AG	20 (0.8)	1 (0.2)	3 (0.5)	1 (0.2)		14 (66.7)		1 (0.2)		
Other recombinants or discordant subtypes	32 (1.3)		2 (0.3)	1 (0.2)	2 (1.4)			18 (3.3)	2 (1.8)	7 (9.3)
Unclassified	6 (0.2)			3 (0.7)	3 (2.1)					

Data are n (%) of subtypes/CRFs, unless otherwise indicated.

CRF, circulating recombinant form;

^a HIV subtypes were determined from the *pol* sequences, using the REGA HIV-1 subtyping algorithm version 2.0 (<http://dbpartners.stanford.edu/RegaSubtyping>) and/or Stanford HIV drug resistance database (<http://hivdb.stanford.edu>).

^b The collaborating sites in Philippines, South Korea and Indonesia had not yet provided sequence data at time of the current analysis.