

PASER poster presentation at the International HIV/AIDS Drug Resistance Workshop (IHDRW) in Florida

On behalf of PASER Raph Hamers, PhD student of the PASER program, hosted a poster presentation at the International HIV/AIDS Drug Resistance Workshop (IHDRW) in Florida. The five day workshop (9-13 June) has gained the reputation over the last 17 years as being the premier meeting on HIVDR. Leading laboratory and clinical scientists present their latest research at this Workshop, which often results in innovative approaches to antiretroviral therapy. The Workshop is renowned for the quality of the data presented and the depth of the scientific interaction and debate.

The PASER poster presented at IHDRW was titled:

“Prevalence of drug-resistant HIV-1 variants at initiation of standard first-line HAART in Africa.”

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Background: This study aimed to assess the prevalence of baseline drug-resistant HIV-1 variants in adults initiating standard first-line HAART at 7 treatment clinics in Zambia, South Africa and Kenya, in the context of the rapid HAART scale-up.

Methods: HIV-1 pol gene was sequenced in 900 chronically HIV-1 infected adults enrolled in the multi-center PASER Monitoring Cohort, during 2007-2008. Participants were categorized as “antiretroviral (ARV)-naïve” (never exposed) or “ARV-experienced” (history of ARV for prophylaxis and/or treatment more than 1 month before initiating HAART). Resistance-associated mutations were identified using the 2009 Surveillance Drug Resistance Mutation list. Subtypes were assessed using the REGA subtyping tool.

Table 1: Baseline characteristics of participants

| | Overall | With RAM | Without RAM |
|--|--------------|--------------|--------------|
| Participants - No (%) | 900 | 61 (6.8) | 839 (93.2) |
| Female sex - No (%) | 512 (56.9) | 36 (59.0) | 476 (56.7) |
| Mean age - Years (sd) | 38.1 (9.8) | 36.9 (9.2) | 38.2 (9.9) |
| WHO clinical stage III/IV - No (%) | 522 (58.0) | 33 (54.1) | 489 (58.3) |
| Route of transmission - No (%) | | | |
| - Heterosexual | 455 (50.6) | 30 (49.1) | 427 (50.9) |
| - Unknown | 440 (48.9) | 31 (50.1) | 409 (49.1) |
| Median CD4 - Cells/mm ³ (Iqr) | 124 (54-198) | 104 (34-174) | 126 (55-198) |
| HIV-1 viral load - Mean (sd) | 5.0 (0.8) | 5.0 (0.6) | 5.0 (0.8) |
| ARV history - No (%) | | 15 (24.6) | 42 (5.0) |
| - HAART | | 8 (13.1) | 28 (3.3) |
| - Mono/dual therapy | | 2 (3.3) | 1 (0.1) |
| - PMTCT single-dose NVP | | 2 (3.3) | 4 (0.5) |
| - PMTCT combination therapy | | 2 (3.3) | 6 (0.7) |
| - Other/Unknown | | 1 (1.6) | 3 (0.4) |

Figure 1: RAM frequencies by site in ARV naïve participants

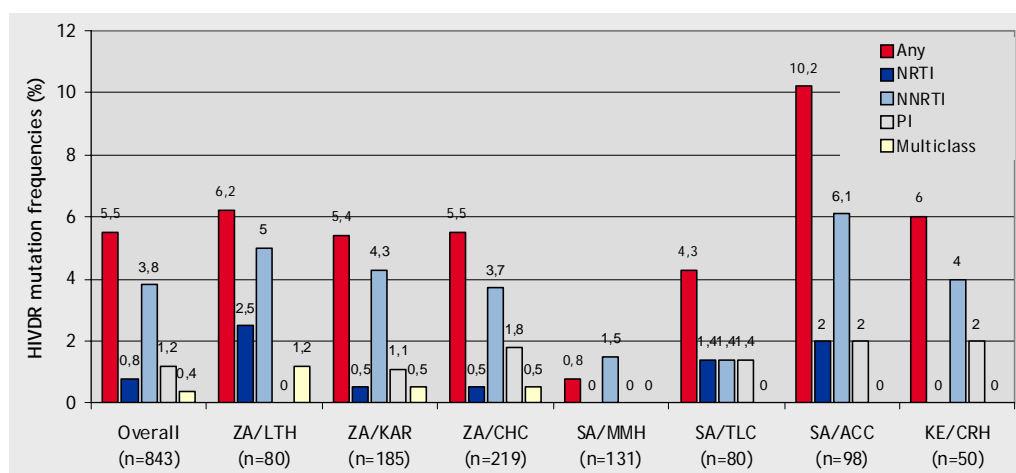


Table 2: Frequencies of resistance-associate mutations

Results: In ARV-naïve individuals (n=843), 5.5% carried any resistance mutation, 0.8%, 3.8% and 1.2% to NRTIs, NNRTIs and PIs, respectively. Across sites, the overall prevalence was 1.5% (Pretoria), 4.3% (Johannesburg), 5.4% (Lusaka1), 5.5% (Lusaka2), 6.0% (Mombasa), 6.2% (Lusaka3) and 10.2% (White River-WR). At all sites, NNRTI-resistance was most prevalent. Among 10 WR individuals with resistant HIV-1, 2 had M46I in protease and 5 females ≥ 1 NNRTI-mutations. Among ARV-experienced individuals (n=57), 40% had previously used HAART, 5% mono/dual therapy, 11% single-dose nevirapine for PMTCT, 14% combination therapy for PMTCT, and 30% other therapy; of these, 26.3% carried any mutation, 8.8%, 19.3% and 0% to NRTIs, NNRTIs and PIs, respectively. Dual-class resistance was found in 4 participants, 3 of whom were ARV-naïve. Most frequently observed mutations were: K103N, Y181C, G190A, K103S, L90M, K101E, and M184V. Subtype C was predominant (90%), followed by A, D, G, CRF_AG, and B. Baseline characteristics such as sex, age, disease stage, CD4+, HIV-RNA and subtypes did not differ between participants with or without resistance mutations.

| | Overall | ARV naive | ARV experienced |
|---------------------------|-------------------|-------------------|----------------------|
| Participants - No (%) | 900 | 843 (94) | 57 (6) |
| Any RAM - No (% , CI 95%) | 61 (6.8, 5.2-8.6) | 46 (5.5, 4.0-7.2) | 15 (26.3, 15.5-39.7) |
| NRTI - No (% , CI 95%) | 12 (1.3, 0.7-2.3) | 7 (0.8, 0.3-1.7) | 5 (8.8, 2.9-19.3) |
| M184V | 4 (0.44) | 2 (0.24) | 2 (3.51) |
| K65R | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| D67N | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| D67E | 2 (0.22) | 2 (0.24) | 0 (0.0) |
| K70R | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| V75T | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| K219E | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| M41L | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| T69D | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| L74I | 1 (0.11) | 0 (0.0) | 1 (1.75) |
| V75S | 1 (0.11) | 0 (0.0) | 1 (1.75) |
| T215I | 1 (0.11) | 0 (0.0) | 1 (1.75) |
| T215D | 1 (0.11) | 0 (0.0) | 1 (1.75) |
| NNRTI - No (% , CI 95%) | 43 (4.8, 3.5-6.4) | 32 (3.8, 2.6-5.3) | 11 (19.3, 10.0-31.9) |
| K103N | 21 (2.34) | 15 (1.81) | 5 (8.77) |
| Y181C | 12 (1.33) | 10 (1.20) | 2 (3.51) |
| G190A | 7 (0.78) | 5 (0.60) | 2 (3.51) |
| K103S | 5 (0.56) | 5 (0.60) | 0 (0.0) |
| K101E | 4 (0.44) | 2 (0.24) | 2 (3.51) |
| L100I | 3 (0.34) | 3 (0.36) | 0 (0.0) |
| V106M | 2 (0.22) | 1 (0.12) | 1 (1.75) |
| Y188C | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| G190S | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| P225H | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| PI - No (% , CI 95%) | 10 (1.1, 0.5-2.0) | 10 (1.2, 0.6-2.0) | 0 (0.0, 0.0-6.3) |
| L90M | 5 (0.56) | 5 (0.60) | 0 (0.0) |
| M46I | 2 (0.22) | 2 (0.24) | 0 (0.0) |
| I85V | 2 (0.22) | 2 (0.24) | 0 (0.0) |
| I50L | 1 (0.11) | 1 (0.12) | 0 (0.0) |
| Dualclass - No (% ,) | 4 (0.4) | 3 (0.36) | 1 (1.8) |
| Tripleclass - No (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Conclusion: Among individuals in the cohort with earlier ARV exposure, 26% harbored resistance at initiation of standard first-line HAART. Among ARV-naïve individuals >5% carried resistance. NNRTI-resistance was most prevalent, in contrast to countries with a long treatment history where baseline resistance is dominated by NRTI-mutations. We cannot exclude that undisclosed PMTCT may have contributed to the high rates observed. Longitudinal monitoring studies are needed to

determine the consequences for treatment outcome and to ensure adequate selection of first-line regimens.