



Karolinska Institutet

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Virologic failure and HIV-1 drug resistance among antiretroviral therapy recipients in an urban resource- limited setting - the South African Virologic Evaluation (SAVE) study

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av

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Abstract

In sub-Saharan Africa, more than four million HIV-infected people have been initiated on antiretroviral therapy (ART); most only have access to first line-treatment, and few ART clinics can provide second-line regimens to everyone in need due to the cost of equipment to detect virologic failure and the cost of alternative drugs. Hence, sustaining the usage of first-line regimens is crucial. More than 25% of ART recipients are residents of South Africa. The overall aim of this thesis was to study determinants of virologic failure and the development of drug resistance among ART recipients in South Africa.

Article I: We assessed, longitudinally, risk factors for incomplete adherence in a cohort of HIV-infected women (n=154) initiating ART and examined the association between adherence to ART and virologic response. Seven per cent had a viral load (VL) >400 copies/ml at month 6 on ART. Incomplete adherence was associated with lower education (p=0.01) and lack of financial support from a partner (p=0.02) after adjustment for confounders. Only when adherence levels dropped below 80% was there a significant association with viremia in the group overall, although adherence <95% was associated with viremia among those exposed to single-dose nevirapine (sdNVP).

Article II: Risk factors for virologic failure were assessed among long-term ART recipients in a cross-sectional study in Soweto, among 998 patients receiving ART for >12 months. Fourteen per cent (n=139) of line-one ART recipients (n=883) had VL >400 copies/ml; 12% (102/882) on first-line vs 33% (37/115) on the second-line regimen were viremic. Two-thirds vs one-third on line-one vs line-two ART had drug-resistance mutations (DRM). A history of poor adherence, concurrent HIV/TB treatment, being at a public clinic and not having a refrigerator at home were risk factors for virologic failure on treatment

Article III: In a retrospective cohort study among 456 non-nucleoside reverse transcriptase inhibitor (NNRTI) recipients in Soweto, we assessed the association between coming late for drug refill visits, as one of the World Health Organization Early Warning Indicators (WHO-EWIs), and treatment failure. After a median of 15 months on ART, 19% (n=88) and 19% (n=87) had failed virologically (here defined as two repeated VL>50 copies/ml) and immunologically (as defined by WHO) respectively, and both types of failure were associated with coming late to drug refill. In the final multivariable model risk factors for virologic failure were incomplete adherence and previous exposure to sdNVP or any other antiretrovirals (ARVs). In Kaplan-Meier analysis the virologic failure rate by month 48 was 19% (adherent) vs 37% (non-adherent).

Article IV: Risk factors for HIV-1 DRM development and persistence of viremia were assessed among 43 NNRTI-recipients with a VL >400 copies/ml after a minimum of 12 months on ART. Sequences were obtained from 38/43. Of those, 82% had 1-7 DRM. In bivariate analysis remote exposure to sdNVP or prior ARVs; higher CD4 cell counts; lower VL; and >6 months of virologic failure were significantly associated with number of DRM. Among 25 viremic patients that were continued on an NNRTI-containing regimen despite viremia, 12 (48%) re-suppressed after a median of 8 months, 6 with K103N and 3 with M184V. Thirteen (52%) had continued virologic failure, which was significantly associated with detectable VL >6 months prior to study enrollment and number of DRM.

Conclusion: Overall, about 1 in 10 failed virologically in these urban township settings in Johannesburg, South Africa. Most patients failing virologically after long-term ART had at least one DRM. Intensive adherence support appears particularly important among women with pre-exposure to ARVs and patients showing virologic failure. Adherence to drug refills works as an early warning indicator for both virologic and immunologic failure, and can be used in settings where measurement of viremia is unavailable.

Keywords: HIV-1, South Africa, Soweto, antiretroviral therapy, subtype C, adherence, virologic failure, drug resistance, World Health Organization, early warning indicators.

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