Global Tenofovir Resistance Following 1st-Line Regimens for Adult HIV-1 Infection

Background:

WHO recommends the nucleoside reverse transcriptase (RT) inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) for first-line ART, in combination with lamivudine (3TC) or emtricitabine (FTC) and the non-nucleoside RT inhibitor (NNRTI) efavirenz (EFV). HIV-1 develops phenotypically and clinically significant tenofovir resistance usually as a result of a single mutation at position 65 (lysine to arginine; K65R) in the RT gene. Tenofovir is used as pre exposure prophylaxis and therefore it is important to understand the potential for tenofovir resistance to circulate globally. We therefore conducted a global assessment of tenofovir resistance following virological failure with TDF containing 1st line.

Methods:

A multi-centre retrospective study of cART with tenofovir plus either 3TC or FTC plus either EFV or NVP: inclusion criteria: (i) virologic failure on first line TDF containing therapy as defined by local VL thresholds or surveillance protocols and a valid resistance test; (ii) were on TDF continuously for at least 4 months prior to virologic failure; (iii) used 3TC or FTC as the second NRTI; (iv) used EFV or NVP as the NNRTI backbone; (iv) were at least 15 years of age at first line cART initiation. Resistance tests were only considered where associated with virologic failure of cART.

We estimated the odds ratios for tenofovir resistance within each study for the following covariates: baseline CD4 count (< vs ≥100); baseline viral load (< vs ≥100,000); NVP vs EFV; and 3TC vs FTC. Within-study associations were subsequently pooled between studies using a random-effects meta-analysis with DerSimonian-Laird weighting and estimates of heterogeneity taken from the Mantel-Haenszel model.

Results:

1,926 individuals from 36 countries eligible for analysis.

- Pooled odds ratio for tenofovir resistance amongst those with CD4 count <100 cells/mm³ versus ≥100 cells/mm³ was 1.49 (1.26–1.77)

- OR for VL <100,000 copies/ml versus <10,000 copies/ml was 1.16 (0.94–1.44), see Figure 2.

- Use of 3TC rather than FTC (NRTIs) was associated with a higher prevalence of tenofovir resistance [OR 1.49 (1.20 – 1.84)].

- Use of the NVP rather than EFV was associated with a higher prevalence of tenofovir resistance [OR 1.46 (1.28–1.67)].

- In Western Europe, tenofovir resistance was higher in subtype C compared with non-C, non-B infections with a pooled odds ratio of 2.44 (1.66-3.59).

- Viral load at failure is not impacted by TDF resistance (Figure 3)

Conclusions:

- Tenofovir resistance is present in nearly 60% of patients with viral failure in sub Saharan Africa, double that in high income regions.

- Associated risk factors are: low CD4 count, use of 3TC vs FTC and use of NVP vs EFV.

- TDF resistance could be mitigated by minimizing viral failure, early detection of viral failure and counselling / therapy switch.

Figure 1: Proportions of patients with viral failure harbouring drug resistance.

Figure 2: Impact of pre therapy CD4 count/viral load an resistance to tenofovir following virologic failure. Derived from random effect meta-analysis showing weighted estimates within each region. Odds ratios are reported for A baseline CD4 <100 vs. ≥100 cells/mm³ and B: viral load ≤100,000 vs. <100,000 copies HIV-1 RNA/ml. Box size is proportional to the number of individuals.

Figure 3: Box plot of log viral load by presence (TDF+) or absence (TDF-) of tenofovir resistance at viral failure in studies with at least 10 patients’ with TDF resistance and a viral load measurement at failure. Whiskers restricted to studies with at least 10 TDF resistant mutations to maintain clarity, although the pattern of similar distributions of failure viral load in the presence or absence of TDF resistance is true for all studies.