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MRC/UVRI PUBLICATIONS DIGEST – APRIL 2017

Mutational Correlates of Virological Failure in Individuals Receiving a WHO-RecommendedTenofovir-Containing First-Line Regimen: An International Collaboration.

Rhee SY, Varghese V, Holmes SP, Van Zyl GU, Steegen K, Boyd MA, Cooper DA, Nsanzimana S, Saravanan S, Charpentier C, de Oliveira T, Etiebet MA, Garcia F, Goedhals D, Gomes P, Günthard HF, Hamers RL, Hoffmann CJ, Hunt G, Jiamsakul A, Kaleebu P, Kanki P, Kantor R, Kerschberger B, Marconi VC, D'amour Ndahimana J, Ndembi N, Ngo-Giang-Huong N, Rokx C, Santoro MM, Schapiro JM, Schmidt D, Seu L, Sigaloff KCE, Sirivichayakul S, Skhosana L, Sunpath H, Tang M, Yang C, Carmona S, Gupta RK, Shafer RW.
EBioMedicine. 2017 Apr;18:225-235. doi: 10.1016/j.ebiom.2017.03.024. Epub 2017 Mar 19.

Tenofovir disoproxil fumarate (TDF) genotypic resistance defined by K65R/N and/or K70E/Q/G occurs in 20% to 60% of individuals with virological failure (VF) on a WHO-ecommended TDF-containing first-line regimen. However, the full spectrum of reverse transcriptase (RT) mutations selected in individuals with VF on such a regimen is not known. To identify TDF regimen-associated mutations (TRAMs), we compared the proportion of each RT mutation in 2873 individuals with VF on a WHO-recommended first-line TDF-containing regimen to its proportion in a cohort of 50,803 antiretroviral-naïve individuals. To identify TRAMs specifically associated with TDF-selection pressure, we compared the proportion of each TRAM to its proportion in a cohort of 5805 individuals with VF on a first-line thymidine analog-containing regimen. We identified 83 TRAMs including 33 NRTI-associated, 40 NNRTI-associated, and 10 uncommon mutations of uncertain provenance. Of the 33 NRTI-associated TRAMs, 12 - A62V, K65R/N, S68G/N/D, K70E/Q/T, L74I, V75L, and Y115F - were more common among individuals receiving a first-line TDF-containing compared to a first-line thymidine analog-containing regimen. These 12 TDF-selected TRAMs will be important for monitoring TDF-associated transmitted drug-resistance and for determining the extent of reduced TDF susceptibility in individuals with VF on a TDF-containing regimen.

Hepatitis B serological markers and plasma DNA concentrations: baseline results from the DART trial.

Price H, Dunn D, Zachary T, Vudriko T, Chirara M, Kityo C, Munderi P, Spyer M, Hakim J, Gilks C, Kaleebu P, Pillay D, Gilson R; DART Virology Group. ***AIDS. 2017 May 15;31(8):1109-1117. doi: 10.1097/QAD.0000000000001454.***

OBJECTIVES:

To examine hepatitis B (HBV) serological markers and plasma DNA concentrations in a large group of untreated HBV/HIV-coinfected individuals in two sub-Saharan settings.

DESIGN:

Baseline analysis of a randomized controlled trial.

METHODS:
DART was a large trial of treatment monitoring practices in HIV-infected adults with advanced disease starting antiretroviral therapy at centres in Kampala or Entebbe, Uganda (n=2317) and Harare, Zimbabwe (n=999). HBV serological markers [antibody to HBV core antigen, HBV surface antigen (HBsAg), antibody to HBV surface antigen, HBV 'e' antigen (HBeAg), and antibody to hepatitis B 'e' antigen] and plasma HBV DNA viral load were measured retrospectively on stored baseline samples. Logistic regression was used to examine associations with baseline demographic and clinical factors.

RESULTS:
The rate of HBsAg positivity was significantly higher in Zimbabwe than Uganda (12.2 vs. 7.7%, adjusted odds ratio=1.54, P<0.001) despite a similar prevalence of antibody to HBV core antigen (56.3 vs. 52.4%) in the two settings. Overall, HBsAg positivity was associated with male sex (adjusted odds ratio=1.54, P<0.001) but not with age, WHO disease stage, or CD4 cell count. HBeAg was detected among 37% of HBsAg-positive patients, with higher rates among those with advanced WHO stage (P=0.02). Also in HBsAg-positive patients, HBV DNA was undetectable in 21%, detectable but below the level of quantification in 14%, and quantifiable in 65%. A total of 96% of HBeAg-positive and 70% of HBeAg-negative patients had detectable HBV DNA; 92 and 28% of patients, respectively, had HBV DNA viral load more than 2000IU/ml.

CONCLUSION:
High rates of HBV coinfection were observed, highlighting the importance of ensuring that coinfected patients receive an antiretroviral regimen, whether first-line or not, that is active against both viruses.

The virological durability of first-line ART among HIV-positive adult patients in resource limited settings without virological monitoring: a retrospective analysis of DART trial data. Dolling DI, Goodall RL, Chirara M, Hakim J, Nkurunziza P, Munderi P, Eram D, Tumukunde D, Spyer MJ, Gilks CF, Kaleebu P, Dunn DT, Pillay D; DART Virology Group. ***BMC Infect Dis.*** ***2017 Feb 21;17(1):160. doi: 10.1186/s12879-017-2266-3.***

BACKGROUND:
Few low-income countries have virological monitoring widely available. We estimated the virological durability of first-line antiretroviral therapy (ART) after five years of follow-up among adult Ugandan and Zimbabwean patients in the DART study, in which virological assays were conducted retrospectively.

METHODS:
DART compared clinically driven monitoring with/without routine CD4 measurement. Annual plasma viral load was measured on 1,762 patients. Analytical weights were calculated based on the inverse probability of sampling. Time to virological failure, defined as the first viral load measurement ≥200 copies/mL after 48 weeks of ART, was analysed using Kaplan-Meier plots and Cox regression models.

RESULTS:
Overall, 65% of DART trial patients were female. Patients initiated first-line ART at a median (interquartile range; IQR) age of 37 (32-42) and with a median CD4 cell count of 86 (32-140). After 240 weeks of ART, patients initiating dual-class nucleoside reverse-transcriptase inhibitor (NRTI) -non-nucleoside reverse-transcriptase (NNRTI) regimens containing nevirapine + zidovudine + lamivudine had a lower incidence of virological failure than patients on triple-NRTI regimens containing tenofovir + zidovudine + lamivudine (21% vs 40%; hazard ratio (HR) =0.48, 95% CI:0.38-0.62; $p < 0.0001$). In multivariate analyses, female patients (HR = 0.79, 95% CI: 0.65-0.95; $p = 0.02$), older patients (HR = 0.73 per 10 years, 95% CI: 0.64-0.84; $p < 0.0001$) and patients with a higher pre-ART CD4 cell count (HR = 0.64 per 100 cells/mm^3, 95% CI: 0.54-0.75; $p < 0.0001$) had a lower incidence of virological failure after adjusting for adherence to ART. No difference in failure rate between the two randomised monitoring strategies was observed ($p= 0.25$).

CONCLUSIONS:
The long-term durability of virological suppression on dual-class NRTI-NNRTI first-line ART without virologicalmonitoring is remarkable and is enabled by high-quality clinical management and a consistent drug supply. To achieve higher rates of virological suppression viral-load-informed differentiated care may be required.

Not Taking it Will Just be Like a Sin": Young People Living with HIV and the Stigmatization of Less-Than-Perfect Adherence to Antiretroviral Therapy. Bernays S, Paparini S, Seeley J, Rhodes T. ***Med Anthropol 2017 Apr 5:1-15. doi: 10.1080/01459740.2017.1306856.***

Abstract
Global health priorities are being set to address questions on adherence to HIV antiretroviral therapy in adolescence. Few studies have explored young people's perspectives on the complex host of social and relational challenges they face in dealing with their treatment in secret and their condition in silence. In redressing this, we present findings from a longitudinal qualitative study with young people living with HIV in the UK, Ireland, US, and Uganda, embedded within the BREATHER international clinical trial. Drawing from Goffman's notion of stigma, we analyze relational dynamics in HIV clinics, as rare spaces where HIV is "known," and how young people's relationships may be threatened by non-adherence to treatment. Young people's reflections on and strategies for maintaining their reputation as patients raise questions about particular forms of medicalization of HIV and the moralization of treatment adherence that affect them, and how these may restrict opportunities for care across the epidemic.