if selected gp41 mutational clusters correlate with viro-immunological outcome. One hundred ninety five sequences of HIV-1 gp41 and clinical follow-up from 77 T-20 treated pts were analyzed from baseline (BL) up to week (wk) 48. Covariation analysis was based on the binomial correlation coefficient and hierarchical clustering. Nine mutations (A30T/L54M/E119Q/S129D/G/N126K/N140I/D239H/T268A) were positively associated with T-20 treatment and correlated with known T-20 resistance mutations. In particular, strong correlation was observed for N140I with V38A and for D239H with Q40H and L45M. Our analysis revealed the existence of 4 clusters of mutations: (1) V38A with N140I, S129G and A30T; (2) N43D with S138A; (3) G36V with N126K; (4) Q40H, L45M with the L54M, E119Q, S129D, T286A and D239H. Co-presence of N140I with V38A was associated ($P < .05$) with a CD4 increase from BL (40 c/μl) of 2-fold (210 c/μl) at week 24 and 4.7-fold (249 c/μl) at week 48 compared with V38A alone, without significant changes in VL. In contrast, the presence of D329H duplicated CD4 loss from BL (124 c/μl) to week 48 (35 c/μl) given by Q40H + L45M ($P = .05$), without significant changes in VL. Moreover, specific polymorphisms at BL were correlated ($P < .05$) with the on treatment development of T-20 resistance mutations. In particular, P213Q and R236Q at BL correlated with development of V38A and N43D, respectively. Our study shows that gp41-mutational patterns under T-20 pressure are more complex than currently known, suggesting that an ordered network of mutations, regulated by natural polymorphisms present before T-20 treatment, modulates positively and negatively the HIV ability to damage the immune system. Their knowledge is important for a correct use of T-20 and for innovative therapeutic strategies.

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Drug Resistance to Tipranavir (TPV) or Darunavir (DRV) According to New Interpretation Algorithms in PI-naïve HIV-1 Infected Patients

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Background: Genotypic interpretation algorithms to newly approved anti-HIV drugs are mainly derived from respective phase II and phase III trials. However, study conditions and patients included might not reflect the situation in routine clinical circumstances. Therefore, interpretation algorithms might be biased depended on patient populations used for evaluation and validation. Current algorithms for interpretation of TPV and DRV include mutations, which are present in naïve patients, especially in patients infected with non-B subtypes. The aim of this study was to analyze the performance of these algorithms in PI-naïve patients.

Methods: The Frankfurt HIV Cohort was searched for genotypes from PI-naïve patients; 1002 samples were analyzed. A score ≥5 out of 10V, 13V, 20MRV, 33F, 35G, 36I, 43T, 46L, 47V, 54AMV, 58E, 69K, 74P, 82LT, 83D, 84V and ≥3 out of 11I, 32I, 33F, 47V, 50V, 54LM, 73S, 76V, 84V, 89V was associated with intermediate resistance to TPV and DRV, respectively. Subtypes were analyzed based on the respective pol-region (not available for all samples).

Results: 510/1002 (50.9%) and 993/1002 (99.1%) samples had a score of 0 for TPV and DRV, respectively. 491/1002 (49.0%) samples had a score of 1–4 for TPV, and 9/1002 (0.9%) samples a score of 1 for DRV. Only 1/1002 (0.1%) showed intermediate resistance to TPV (score of 5), and none to DRV. The proportion of non-B subtypes significantly increased from 0% to 4.5%, 64.6%, 97.2%, 100% and 100% with an increasing TPV score ($p < 0.001$; Kruskal-Wallis Test).

Conclusions: Intermediate resistance to TPV and DRV in PI-naïve patients was detected very rarely, if at all. Based on our data, both algorithms seemed to be practical for the interpretation of TPV and DRV at least in PI-naïve patients. However, an increase in the TPV score was significantly associated with a non-B subtype, which might reflect a bias in patient populations used for evaluation and validation of the TPV algorithm. More clinical data from TPV and/or DRV failing patients not included in studies are necessary to validate current algorithms.

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HIV Interactions With Other Viruses Determine Pathogenesis in Human Lymphoid Tissues

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Critical events in HIV disease occur in lymphoid tissues, often coinfected with other microbes (co-pathogens). To investigate their interactions in these tissues, we studied viral pathogenesis in human tonsillar and gut tissues infected ex vivo with HIV-1 alone or in combination with other viruses, including human herpesviruses (HHV) 6, and 7, vaccinia virus (VV), measles (MV) and human cytomegalovirus (HCMV). As in vivo, both activated and non-activated T cells supported productive viral infection in blocks of human tonsillar tissue infected ex vivo with R5 or X4 HIV-1, although activated T cells determined the "viral load". Productive HIV infection correlated with CD25/HLA-DR expression but not with CD69 expression. HIV infection facilitates this pattern of activation creating new target cells that are efficient at replicating the virus, leading to cell apoptosis Upregulation of cytokines/chemokines in infected tissues is another sign of activation. This is typical of HIV-infected tonsillar tissue, whereas in infected rectosigmoid tissue these chemokines are not upregulated. The lack of such upregulation may contribute to the high vulnerability of the gut to HIV,