FORGIVENESS OF ANTIRETROVIRAL REGIMENS: IN VITRO HIV-1 VIRAL BREAKTHROUGH WITH 2-DRUG VERSUS 3-DRUG REGIMENS SIMULATING VARIABLE ADHERENCE TO TREATMENT

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Background: Guidelines for treatment of HIV-1 infection recommend an integrase strand transfer inhibitor (INSTI) plus 2 nucleoside/tide reverse transcriptase inhibitors (NRTIs). Recently, controlled clinical studies have reported on the efficacy and safety of an INSTI+ 1 NRTI. To estimate regimen "forgiveness" for triple therapy versus 2-drug combinations, *in vitro* experiments monitoring viral breakthrough (VB) and resistance development were conducted under conditions simulating drug exposures at full adherence or suboptimal adherence to treatment. In addition, the role of pre-existing minority drug resistant variants was assessed.

Methods: MT-2 cells infected with wild-type HIV-1(IIIb) or HIV-1with low-level (0.01-10%) pre-existing FTC/3TC-resistant M184V were cultured in the presence of fixed doses of bictegravir+emtricitabine+tenofovir alafenamide(BIC+FTC+TAF) or dolutegravir+lamivudine(DTG+3TC) and monitored for VB by cytopathic effect for up to 5 weeks. Constant drug concentrations were set at their human plasma-free adjusted clinical trough concentrations (Cmin) or fixed at simulated Cmin after missing 1 to 4 consecutive doses. Emergent HIV-1 variants were characterized using standard genotyping methods.

Results: Using drug concentrations corresponding to full adherence and wild-type HIV-1, 0/24 replicates showed VB with either BIC+FTC+TAF or DTG+3TC through 5 weeks in culture. Drug concentrations corresponding to two consecutive missed doses showed no VB with BIC+FTC+TAF through week 5 whereas 23/24(96%) had VB with DTG+3TC as early as 2 weeks.. At breakthrough, HIV-1 lacked drug resistance mutations when analyzed by population sequencing. Additional studies using a broader range of missed doses, other drug combinations, and pre-existing low-level M184V are on-going.

Conclusions: These preliminary *in vitro* results suggest that the higher potency provided by BIC/FTC/TAF may provide better long-term suppression of HIV-1 replication and therefore more robust prevention of potential drug resistance development compared to DTG/3TC.These results highlight the importance of a third agent to prevent viral replication and evolution, particularly in the real world where imperfect drug adherence is frequent.

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