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VIROLOGICAL AND IMMUNOLOGICAL OUTCOMES IN A COHORT OF PATIENTS FAILING INTEGRASE INHIBITORS

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BACKGROUND: Although integrase inhibitors are highly effective in the management of drug-resistant HIV, some patients fail to achieve durable viral suppression. The long-term consequences of integrase inhibitor failure have not been well defined.

METHODS: We identified 13 individuals who exhibited evidence of incomplete viral suppression on a regimen containing an integrase inhibitor. Genotypic and phenotypic resistance testing was performed at Monogram Biosciences.

RESULTS: Baseline CD4+ T-cell count and plasma HIV RNA levels were 66 cells/mm³ and 4.78 log₁₀ copies/ml, respectively. Patients were followed for a median 12.7 months. Despite evidence of integrase inhibitor failure, patients appeared to have a persistent immunological benefit, with a median change in CD4+ T-cell count of +37 and +71 cells/mm³ at month 3 and month 6 of documented failure, respectively. Integrase inhibitor failure was often associated with the emergence of genotypic and phenotypic resistance, although three individuals with partial adherence lacked evidence of resistance. The G140S/Q148H pattern and T97A/Y143R patterns were each associated with high-level phenotypic resistance (>400-fold change in IC₅₀). One individual harbouring a virus with an isolated N155H mutation (41-fold change in IC₅₀) discontinued raltegravir while remaining on a stable background regimen. Plasma HIV RNA levels remained stable in the absence of raltegravir (suggesting limited residual antiviral activity), but subsequently increased 10fold as genotypic/phenotypic evidence for raltegravir resistance waned (suggesting a significant fitness defect).

CONCLUSIONS: Although experience from clinical trials suggests that the majority of patients receiving the newer antiretroviral agents do well, there remains a subset of individuals for whom these

drugs will not work because of preexisting resistance or non-adherence. There may, however, be a residual clinical benefit despite lack of viral suppression. This benefit may be due in part to alterations in viral fitness, as suggested by changes after removal of raltegravir in a single individual. Notably, this latter observation is consistent with observations from the SIV-infected macaque model, where removal of integrase inhibitors in animals harbouring the N155H mutation was associated with initial stable viraemia followed by rapid increase in viraemia as the mutations waned.

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