Is interruption of HIV therapy always harmful?

M. Youle

Royal Free Centre for HIV Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

Human immunodeficiency virus (HIV) infection is associated with progressive immune damage leading to AIDS. Since the advent of combination antiretroviral chemotherapy clear morbidity and mortality benefits have been shown. Reversal of clinical disease and improvement in health status has resulted in a massive change in the epidemiology of HIV and AIDS and is seen as a remarkable therapeutic success story. However, these benefits have been accrued in spite of increasing evidence of long-term drug toxicity and with difficulty in compliance in taking this therapy.

In other disease areas, such as oncology, intermittent therapy has been utilized to deal successfully with the paradigm of effective, but highly toxic, treatment, and remains the standard of care. To date, this approach has not drawn support from those treating HIV. Treatment interruption has now been evaluated in two specific, but very different, scenarios in HIV disease. In the first, several investigators have interrupted therapy for short periods in small numbers of subjects (n < 20) who had previously shown suppression of HIV to below levels of detection by currently available assays (plasma HIV RNA <20–50 copies/mL). Sharp rises in HIV viraemia occurred within weeks of stopping therapy and a concomitant reduction in accrued immune benefits (in terms of CD4+ lymphocyte count) was found in all tissues evaluated. Although in all these studies reintroduction of the same therapy resulted in resuppression of HIV in all subjects, subsequent acquisition of mutant virus was noted in four of the ten subjects in one study. The impact of treatment interruption on the risk of subsequent acquisition of resistance is uncertain. The aim of these studies was to evaluate the viral dynamics and consequences of interrupting treatment and a relationship did appear to exist between baseline immune status, as measured by CD4+ T-lymphocyte levels, with greater rebound in those subjects with <100 cells/mm^3 before therapy.

The second scenario where the effects of treatment interruptions have been evaluated is in subjects who were failing antiretroviral therapy with a rising viral load on treatment. In the Royal Free Centre cohort of 63 such patients there was a median rise in CD4+ of 120 cells/µL and a viral load fall of 3.08 log_{10} copies/mL over 28 weeks, with 62% of subjects achieving a fall in viral load to <50 copies/mL and 82.5% <400 copies/mL. The Frankfurt cohort showed lower rates of surrogate marker response but the subjects had greater previous exposure to antiretrovirals. Although no controlled clinical data exist, these pilot studies both showed favourable changes in HIV resistance patterns over the period of treatment interruption in most of those studied. Subjects who had resistance assays performed on HIV from peripheral blood samples whilst on their failing drug regimens had significant numbers of mutations associated with drug resistance in the areas of the HIV genome encoding both reverse transcriptase and protease. These genetic changes were less after a period of off therapy as measured by both genotypic and phenotypic assays. There appeared to be a relationship between the rise in viral load after stopping therapy and the subsequent changes in detectable mutants. When salvage therapy with multiple antiretroviral agents (median five drugs) was started in these subjects, a significant proportion of individuals achieved suppression of HIV to <50 copies/mL. This outcome was linked to the length of time off therapy; for every month since stopping the failing regime a subject was 15% more likely to suppress HIV (P < 0.049). In addition, when genotypic resistance was assessed at weeks 2, 4 and 8 after reintroduction of antiretroviral therapy, persistent and continued reduction in measurable mutant HIV was observed (H. Devereux, C. Loveday, M. Youle, C. Sabin, A. Burke, M. Johnson, unpublished data). However, during the period off therapy, significant drops occurred in CD4+ cell counts; these fell back to pre-therapy levels in the majority of those studies at late stage disease, and this would suggest that during such treatment interruptions, careful monitoring should be performed and consideration given to prophylaxis against opportunistic infections at appropriate levels of immunosuppression.

Precedent exists in other viral diseases for reversion of mutant viruses to wild-type after treatment interruption.
and for the successful reintroduction of the same antiviral therapy after a period off therapy. Presumably the selective pressure of the agents results both in the development of resistance owing to ongoing viral replication and, after removal of therapy, in the reversion to wild-type strains. The presumption, by HIV researchers, but not by all virologists, that a rapid re-emergence of resistant HIV quasi-species would preclude a benefit from stopping and then restarting therapy, is not borne out in the therapy of other viruses. The current paradigm is that treatment of HIV must be continuous and lifelong. This is based on present knowledge of HIV dynamics under therapy and the perception that cessation of that therapy would lead to reversion of clinical status to baseline and, subsequently, a detriment to the individual. But modelling of viral kinetics suggests that to prevent resistance to HIV emerging in the long term would require suppression to levels of <1 copy/mL, which may not be achievable with current therapy options.

Intermittent treatment or pulse therapy has distinct attractions for patients and healthcare providers, with potential for reduce toxicity, improved tolerance (and, therefore, compliance) and lower cost. The ability to recycle drugs that have ceased to work and to reduce overall exposure to antiretroviral agents, is invaluable with a restricted palette of drugs. These first pilot studies of interrupting HIV treatment appear to challenge the assumption that only harm would occur and to support the evidence that the virus is more forgiving than has previously been realized. Investigation of the changes in mutant viral strains at the clonal population level needs to be carried out in subjects failing therapy to delineate further the potential for re-emergence of resistant strains. What is clear, however, is that to continue the mantra of ‘life-long suppression of HIV at all costs’ may no longer be acceptable or realistic.

References


