Stopping antiretroviral therapy

Whatever the reasons for stopping ART, pharmacological and virological issues must be considered in order for a clinician to give guidance, says S. Taylor et al review article published in AIDS on August 20th 2007. Anti-HIV activity relies on the presence of all components in the regimen; resistance develops more readily when replicating virus is exposed to only one or two drugs. The half-life of each antiretroviral is therefore critical.

Stopping strategies

1. Simultaneous stop

2. Staggered stop

3. Switch or exchange stop

4. Protected stop

1. The simultaneous stop

Early treatment guidelines recommended patients to stop all agents at once to ensure they were not taking mono or dual therapy by only discontinuing one agent in the regimen. Generally, for 'balanced' regimens comprising two short half-life NRTI plus a PI (boosted or unboosted) or else two long half-life NRTI/ NtRTI (i.e. emtricitabine and tenofovir) plus NNRTI this strategy is likely to be correct.

The 'simultaneous stop' may, however, be problematical when using longer half-life NNRTIs with short half-life NRTIs. Here the imbalance in half-lives is considerable. As nevirapine and efavirenz can persist at resistance-inducing concentrations for 2 weeks or more here the 'simultaneous stop' strategy is not advisable.

More problematical is stopping regimens containing longer half-life NRTI/NtRTI (i.e. emtricitabine and tenofovir) in combination with boosted protease inhibitors. This may lead to functional dual or single agent therapy if these agents are stopped together. In this situation, a different method of stopping may be more appropriate. When longer half-life NRTI/NtRTI are combined with nevirapine or efavirenz the matching of half-lives may support a simultaneous stop. We recognize that individual variation in drug metabolism means that matching half-lives of all agents in the regimen is difficult. Clinical data are required to determine whether the simultaneous stopping of these agents will lead to resistance. This is important as fixed dose combination tablets become available.

2. The staggered stop

In attempting to overcome the potential for resistance development with nevirapine or efavirenz and short half-life drugs, some guidelines suggest a 'staggered stop. Here the long half-life drug is discontinued before stopping the other agents in the regimen. Three days were initially suggested, but then at least 5 days were recommended and some said that 5 days appeared too short. The correct duration still remains a matter of
We recommend that nevirapine (after multiple doses) should be stopped at least 7 days (perhaps even 2 weeks) before other shorter half-life drugs, or a different stopping strategy should be employed. Fidler et al. showed that when stopping efavirenz 5-7 days before a predominantly zidovudine/lamivudine-containing regimen, no NNRTI resistance was documented at week 4 after stopping treatment. Others (Back D, Sadiq ST, Weston R) have demonstrated that in some individuals the half-life of efavirenz can be greater than 100 h, and efavirenz concentrations can persist at resistance-selecting concentrations for 2 weeks or more. There are clearly ethnic differences in drug handling so it may be more appropriate to stop efavirenz at least 2 weeks before other shorter half-life drugs, or adopt a different stopping strategy.

The 'staggered stop' approach is problematical if another agent in the regimen has a long half-life, e.g. efavirenz, tenofovir, or lamivudine. In that situation, if efavirenz was stopped 2 weeks before the other two agents, the shorter half-life of lamivudine relative to tenofovir would potentially give functional tenofovir monotherapy.

3. The replacement or exchange stop

In this strategy the drug with the longest half-life is exchanged for a drug with a higher genetic barrier to resistance and a shorter half-life (e.g. lopinavir/ritonavir) for a period of time before the other agents and the new agent are stopped simultaneously. The advantage is that continued viral suppression is likely as the discontinued drug passes through the zone of resistance selection. Four weeks is probably advisable with this strategy to maintain viral suppression. The extended period will allow clearance of the NNRTI at the time of stopping other drugs. This method is likely to work when NNRTI are combined with the shorter-acting NRTI. Nevertheless, it may still be problematical with long half-life NRTI/NtRTI, i.e. functional monotherapy with either tenofovir or emicitabine.

4. The protected stop

In an attempt to provide a universal stopping strategy, we are currently investigating the 'protected stop', in which single agent lopinavir/ritonavir is given on the day patients stop all of the other ART agents. The regimen then continues for 4 weeks before stopping. The rationale comes from single agent lopinavir/ritonavir studies in which maintaining viral suppression was achieved with the minimal development of resistance. The potential for resistance developing in the short time of single agent therapy is small, thus preserving future treatment options. Clinical data are, however, required before this can be recommended as a standard strategy.

Reference