Combination ART: are two drugs as good as three?

Vyacheslav Prokofyev/Getty Images

Published Online
January 5, 2018
http://dx.doi.org/10.1016/S0140-6736(18)30008-4

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(17)33095-7

The first 10 years of the development of antiretroviral therapy (ART) were characterised by a series of studies that led to the conclusion that triple therapy was the minimum required to induce and maintain full suppression of HIV replication. Early reports of using monotherapy with a nucleoside reverse transcriptase inhibitor (NRTI) had shown only transient decreases in p24 antigen and arrest of HIV disease progression.[1] Studies of dual NRTI therapy showed more robust responses, but again these responses were temporary and unsustained in most individuals in the studies.[2]

The breakthrough came in 1996, at the XI International AIDS Conference in Vancouver, Canada, during which a set of studies that included antiretroviral drugs in two new classes (HIV protease inhibitors and non-NRTIs) added to two NRTIs were reported and had dramatic responses. Using the newly available and far more sensitive molecular amplification technology,[3] the studies showed that these triple combination ART regimens could suppress and maintain HIV replication in plasma to very low concentrations, at which selection of resistance did not occur.[4,5] This outcome was accompanied by reconstitution of CD4-positive T cells and arrest of HIV disease progression. The triple ART era was born.

Since then, the use of three drugs has been the dominant framework in bringing new ART combinations to market. Nonetheless, there have been hints that the use of two drugs might be sufficient. For example, the ACTG 5142 study[6] examined the use of efavirenz and ritonavir-boosted lopinavir, both given either as triple therapy combined with two NRTIs or together as dual therapy as an NRTI-sparing strategy. The time to virological failure was longer in the efavirenz group than in the lopinavir-ritonavir group but was not significantly different to the NRTI-sparing group. It should be remembered that the use of three drugs was not successful in the case of triple NRTIs. The ATCG 5095 study[7] found that the triple combination of abacavir plus zidovudine plus lamivudine was substantially inferior to a triple combination of efavirenz plus two or three NRTIs. In retrospect, perhaps the pertinent lesson from these studies was that successful combination ART should be selected from drugs from two independent ART classes rather than simply containing three drugs.

Over the past 6 years, numerous studies examining various dual ART combinations in either viraemic patients or as a switch strategy have been done, many of them in underpowered pilot studies. A systematic review and meta-analysis[8] of a set of selected randomised trials found that efficacy did not differ between the use of two and three drugs ART (excluding a-priori studies that included maraviroc as a component; most regimens contained a protease inhibitor). However, the analysis suggested that dual therapy was associated with selection of greater degrees of resistance at virological failure and poorer performance in people with a baseline viral load of more than 100 000 copies per mL.

In 2017, outcomes of some well powered studies shed more light on the risks and benefits of dual versus triple therapy as a switch strategy for people who have successfully achieved and maintained full virological suppression on conventional triple therapy. Results of the LATTE-2 study[9] showed that the use of a two-drug ART regimen of 4-weekly injectable cabotegravir and rilpivirine successfully maintained virological suppression in people with HIV who had achieved full virological suppression using three drugs (oral cabotegravir plus abacavir-lamivudine). After 96 weeks of injectable therapy, no participant receiving the 4 weekly injections had virological failure.[9]

In *The Lancet*, Josep M Llibre and colleagues report on the SWORD 1 and 2 studies.[10] These studies represent two identical randomised controlled, open-label, non-inferiority studies that examined a switch to oral dolutegravir and rilpivirine in participants who had at least 24 weeks of full virological suppression using conventional triple therapy. After 48 weeks, 95% (485 of 511) of participants who maintained the triple therapy and 95% (486 of 513) of participants who switched to dual therapy continued to have successful virological suppression (adjusted treatment difference of −0·2%, 95% CI −3·0 to 2·5), demonstrating non-inferiority within a predefined margin of −8%. These results make a convincing case for the use of dual therapy as a maintenance strategy.

The question of whether dual therapy can be used in people with viraemia (either in those patients naive to ART or having had virological failure) remains

open. The GEMINI 1 and 2 studies (NCT02831673 and NCT02831764) in which triple therapy comprising dolutegravir plus tenofovir disoproxil fumarate and emtricitabine is being compared with dolutegravir and lamivudine as initial ART in people with a screening viral load of 500 000 copies per mL or lower have been enrolled and are underway. Other possibilities deserve exploration. For example, the use of tenofovir alafenamide combined with a once-daily integrase inhibitor would form a compact two-drug regimen that would effectively treat both HIV and hepatitis B, a good option for people living in low-income and middle-income countries. The once-weekly nucleoside translocation inhibitor in early human development (MK-8591) combined with a drug from another class offers another intriguing future possibility.[11] All in all, 30 years since the emergence of ART, the potential pipeline for a variety of effective dual therapy options appears rich.

Mark A Boyd, David A Cooper
Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, SA 5112, Australia (MAB); and Kirby Institute, University of New South Wales, Sydney, NSW, Australia (MAB, DAC)
mark.boyd@adelaide.edu.au

MAB reports personal fees from Janssen-Cilag and ViiV Healthcare, and personal fees and grants from Gilead Sciences and Merck, Sharpe and Dohme, outside the area of work discussed here. DAC declares no competing interests.

1 Pedersen C, Cooper DA, Brun-Vezinet F, et al. The effect of treatment with zidovudine with or without acyclovir on HIV p24 antigenaemia in patients with AIDS or AIDS-related complex. *AIDS* 1992; **6:** 821–25.
2 Darbyshire JH, Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348:** 283–91.
3 Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis* 1998; **177:** 40–47.
4 Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; **337:** 725–33.
5 Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* 1998; **279:** 930–37.
6 Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358:** 2095–106.
7 Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004; **350:** 1850–61.
8 Achhra AC, Mwasakifwa G, Amin J, Boyd MA. Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis. *Lancet HIV* 2016; **3:** e351–60.
9 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2018; **390:** 1499–510.
10 Llibre JM, Hung C-C, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2017; published online Jan 5. http://dx.doi.org/10.1016/S0140-6736(17)33095-7.
11 Matthews RP, Schürmann D, Rudd DJ, et al. Single doses as low as 0·5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days. 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017. TUPDB020.