FEATURE

Advances in HIV Treatment Discussed

Written by Brian Hoyle

Mark Wainberg, PhD, McGill University, Montreal, Quebec, Canada, discussed advances in the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). Since the introduction of the reverse transcriptase inhibitor azidothymidine (AZT) in 1987, there has been a steady pipeline of drugs gaining approval for use in the United States and elsewhere. The latest drug to gain approval, in 2013, was the integrase inhibitor dolutegravir. The list of available nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-NRTIs, protease inhibitors, inhibitors of viral entry, and integrase inhibitors is now lengthy (Table 1).

Over the first decade of antiretroviral trials, the disappointing results of monotherapy and encouraging results of therapy with 2 or more drugs were published [Fischl MA et al. *N Engl J Med.* 1987; Eron JJ et al. *N Engl J Med*. 1995; Hammer SM. *N Engl J Med.* 1996; Gulick RM et al. *N Engl J Med.* 1997; Cameron DW et al. *Lancet.* 1998]. The development of highly active antiretroviral therapy incorporating multiple antiretroviral drugs including 2 NRTIs and a protease inhibitor (or inhibitors) was a breakthrough. In the past decade, single-tablet formulations have become available [Cassetti I et al. *HIV Clin Trials.* 2007; Wilkin A et al. *AIDS Res Hum Retroviruses.* 2012; Rockstroh JK et al. *J Acquir Immune Defic Syndr.* 2013; Zolopa A et al. *J Acquir Immune Defic Syndr.* 2013].

There are currently several recommended regimens, all of which use the backbone tenofovir + emtricitabine in combination with a third agent. The NRTI regimen incorporates efavirenz with this backbone. The protease inhibitor regimen incorporates either atazanavir boosted with ritonavir or darunavir boosted with ritonavir with this backbone. The integrase strand transfer inhibitor–targeted regimen incorporates raltegravir, elvitegravir boosted with cobicistat, or dolutegravir with the backbone.

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In British Columbia, Canada, where a concerted HIV and AIDS treatment effort has been underway for decades, the response to antiretroviral therapy has been encouraging, with a viral load < 50 viral copies/mL evident in 65% of the examined population in 2000 and 87% in 2008 [Gill VS et al.*Clin Infect Dis.* 2010]. In the United States, the increased use of protease inhibitors was mirrored by a declining number of deaths [Palella FJ et al. *N Engl J Med.* 1998]. New HIV therapies remain a priority.

Recent developments in integrase inhibitors are heartening. Dr Wainberg discussed the results of the multicenter Trial Comparing GSK1349572 50 mg Once Daily to Raltegravir 400mg Twice Daily [SPRING-2; NCT01227824], a phase 3 parallel-group noninferiority study. The double-blind, double-placebo trial compared dolutegravir with raltegravir in patients who had not previously received antiretroviral treatment. The patients were randomized (1:1) to receive at least 1 dose of dolutegravir (50 mg once daily, n = 411) or raltegravir (400 mg twice daily, n = 411), plus 2 NRTIs (tenofovir + emtricitabine or abacavir + lamivudine). Prespecified 96-week secondary end points included proportion of patients with HIV-1 RNA < 50 copies/mL, CD4 cell count changes from baseline, safety, tolerability, and genotypic or phenotypic resistance. After week 96, in the nonrandomized phase, all patients could receive dolutegravir + either one of the NRTI combinations.

Throughout treatment up to week 48, once-daily dolutegravir was noninferior to twice-daily raltegravir in treatment-naïve patients with HIV-1 (virologic success at 96 weeks was 88% for dolutegravir and 85% for raltegravir) [Raffi F et al. *Lancet.* 2013]. Significantly more patients receiving dolutegravir displayed < 50 copies/mL of HIV-1 RNA from week 2 to week 48, with the difference especially evident from week 2 to 16. At week 48, the difference in response was + 7.4% (95% CI, 2.5 to 12.3; $P = .003$). Virologic suppression occurred faster in those receiving dolutegravir, with 63% of subjects fully suppressed by week 24. It was concluded that the once-daily dosing without the need for a pharmacokinetic booster makes dolutegravir-based therapy an attractive treatment option for HIV-1-infected treatment-naïve patients.

Table 1. Antiretroviral Drugs Available in 2014

NRTIs	Zidovudine (ZDV, AZT)	Stavudine (d4T)
	Didanosine (ddI)	Lamivudine (3TC)
	Tenofovir (TDF)	Abacavir (ABC)
	Emtricitabine (FTC)	
Protease inhibitors	Saquinavir (SQV)	Indinavir (IDV)
	Ritonavir (RTV)	Nelfinavir (NFV)
	Fosamprenavir (FPV)	Tipranavir (TPV)
	Lopinavir/r (LPV/r*)	Atazanavir (ATV)
	Darunavir (DRV)	
Entry inhibitors	Enfuvirtide (T-20; fusion inhibitor)	Maraviroc (MVC; CCR5** antagonist)
Integrase inhibitors	Raltegravir (RAL)	Elvitegravir (EVG)
	Dolutegravir (DTG)	
Non-NRTIs	Nevirapine*** (NVP)	Efavirenz (EFV)
	Delavirdine (DLV)	Etravirine (ETR)
	Rilpivirine (RPV)	

NRTI, nucleoside/nucleotide reverse transcriptase inhibitor.

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On May 1, 2015, the following data were changed: *ATV to LPV/r; **CCR5 to CCR5; ***Nevirdine to Neviapine.

Table 2. Resistance to Integrase Strand Transfer Inhibitors in Treatment-Naïve Patients

	Resistance Mutations	
Treatment	**Major[a]**	**Minor**
Raltegravir[b]	Y143 N155H Q148	Multiple
Elvitegravir[c]	T66I* E92Q N155H Q148	Multiple
Dolutegravir[d]	None	None

[a]Detected by genotyping in treatment-naïve patients failing therapy

[b]Data sources: Cooper DA et al. *N Engl J Med.* 2008; Sichtig N et al. *J Antimicrob Chemother.* 2009; Canducci F et al. *AIDS.* 2009; Hatano H et al. *J Acquir Immune Defic Syndr.* 2010.

[c]Data sources: Sax PE et al. *Lancet.* 2012; DeJesus E et al. *Lancet* 2012.

[d]Data sources: van Lunzen J et al. *Lancet Infect. Dis.* 2012.

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*On May 1, 2015, T661 was changed to T66I.

The conclusion seems realistic given the absence of resistance to dolutegravir to date, as compared to raltegravir and elvitegravir in 2 other clinical trials also conducted in treatment-naïve patients (Table 2).

The SAILING (ING111762) trial reported dolutegravir superiority to raltegravir at 48 weeks in 715 treatment-experienced but integrase inhibitor–naïve subjects randomized to dolutegravir (50 mg once daily; n = 354) or raltegravir (400 mg twice daily; n = 361) along with investigator-selected background therapy [Cahn P et al. *Lancet.* 2013]. At 48 weeks, dolutegravir was associated with significantly superior virologic success (> 50 copies/mL of HIV-1 RNA; 71% for raltegravir vs 64% for dolutegravir; $P = .003$), with similar adverse effects to raltegravir.

Among the known mutations governing integrase resistance, R263K was present in 2 individuals in whom treatment failed in the SAILING trial. The R263K mutation has been demonstrated during in vitro culture of HIV-1 subtype B in the presence of dolutegravir and confers low-level resistance. Dr Wainberg and colleagues speculate that the reason for the absence of resistance may be the greatly diminished fitness that is associated with the R263K resistance pathway.

The good news of no appreciable in vivo resistance to dolutegravir to date is without precedent. Clinical resistance has occurred to every HIV drug developed so far. It remains to be seen if dolutegravir will be the sole exception. The implication for dolutegravir is that patient adherence to therapy will be crucial.

Strategies to purge reservoirs of HIV, which are a current bane of HIV eradication strategies, include the use of histone deacetylase inhibitors, farnesyl transferase inhibitors, antigenic approaches, and immunologic approaches. It remains unclear exactly when the viral reservoir is established during acute infection and the extent to which it is susceptible early in antiretroviral therapy. A recent study involving rhesus monkeys has clarified the time frame for reservoir seeding [Whitney JB et al. *Nature.* 2014]. In the model, antiretroviral therapy begun within 3 days after infection with simian immunodeficiency virus was effective in quelling the infection. Viral rebound did occur when therapy was stopped. The results suggest that therapy needs to be initiated very soon after infection and continued in this model as soon as possible to determine whether it may be less prone to problems of nonadherence than other anti-HIV drugs.