Future of nonnucleoside reverse transcriptase inhibitors

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The nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs) are small molecules that bind to HIV-1 RT at a site distinct from the DNA polymerase active site of the enzyme and block retroviral reverse transcription via an allosteric mechanism of action (1). Nevirapine (NVP) was the first NNRTI approved in 1996 by the US Food and Drug Administration for the treatment of HIV-1 infection, followed by delavirdine in 1997, efavirenz (EFV) in 1998, etravirine (ETV) in 2008, and rilpivirine (RPV) in 2011. For almost 20 y NNRTIs served as the cornerstone of combination antiretroviral therapy (cART). Indeed, most first-line cART included one NNRTI (typically NVP, EFV, or RPV) in combination with two nucleoside/nucleotide RT inhibitors. Just last month, RPV and the integrate inhibitor dolutegravir were approved as the first once-daily, single-pill, two-drug regimen for the maintenance treatment of virologically suppressed HIV-1 infection. ETV can be included in salvage cART for the treatment of HIV-1-infected ART-experienced individuals, including those with prior NNRTI exposure. NNRTIs have also been used to prevent HIV-1 infection. NVP has been used to prevent mother-to-child transmission (2), the MTN-020/ASPIRE and RING trials demonstrated that a vaginal ring containing the NNRTI dapivirine can prevent HIV-1 infection in women (3, 4), and a completed phase II clinical trial, HPTN 076, recently assessed the safety and acceptability of a long-acting formulation of RPV for preexposure prophylaxis (PrEP) (5). In the development pipeline, doravirine (MK-1439) is in phase III clinical trials for the treatment of HIV-1 infection (6), while the urea-PETT derivative MIV-150, formulated as microparticulate gel, is in a phase I study to evaluate safety, pharmacokinetics, pharmacodynamics, and acceptability (7).

Limitations of Approved NNRTIs

Despite the success of NNRTIs in both the treatment and prevention of HIV-1, this antiviral drug class has reached a critical juncture, with an unclear future. All NNRTIs bind to the same pocket in HIV-1 RT, and the genetic barrier to NNRTI resistance is low. Typically, EFV, NVP, and RPV require only a single mutation to reduce clinical efficacy. Furthermore, nearly all of the resistance mutations are located within or adjacent to the NNRTI-binding pocket, and there is little evidence to suggest that any one mutation confers resistance to only a single agent. As such, there is a high level of cross-resistance within the NNRTI class (8). Transmitted NNRTI resistance is also becoming a major issue (9), particularly in low- and middle-income countries (LMIC), and could significantly impact both treatment and prevention strategies. Furthermore, in 2015, the US Department of Health and Human Services downgraded Atripla (EFV + tenofovir disoproxil fumarate and emtricitabine), a widely used first-line cART regimen, from “recommended” to “alternative,” and it is likely that its use will also be phased out in other countries, including LMIC, in the next 5–10 y. Where does this leave the NNRTI class? Is it possible to develop a new generation of NNRTIs, with improved antiviral activity and resistance profile, that rekindles the enthusiasm for their use in treatment and prevention strategies?

A New Class of Potent NNRTIs

In PNAS, Kudalkar et al. (10) describe the activity, both in vitro and in a humanized (Hu-PBL) mouse model of HIV-1 infection, of a new class of very potent catechol diether-based NNRTIs. The lead compound (compound I) exhibited robust antiviral activity in HIV-1-infected T cells (EC<sub>50</sub> ~2 nM), demonstrated synergistic antiviral activity with antiretrovirals from other drug classes, and was shown in a prior study to have remarkable in vivo safety and pharmacokinetic properties (11). In HIV-1–infected humanized mice compound I potently suppressed plasma viral loads and prevented CD4+ T cell loss. Importantly, the authors also demonstrated that compound I was amenable to formulation in poly(lactide-coglycolide) nanoparticles which slowly released the inhibitor over a 3-wk time period and provided sustained antiviral activity in the HIV-1–infected Hu-PBL mice. Collectively, these studies highlight that compound I could be considered a promising late-stage preclinical candidate and tantalizingly suggest that the catechol diethers could be one future of the NNRTI class.

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In PNAS, Kudalkar et al. (10) rightly propose that compound I may be a promising NNRTI to evaluate for PrEP. However, what additional developments and/or research are needed to fully assess its potential for use as a PrEP agent? As described above, the long-acting formulation of compound I was effective over a 3-wk period. There is clearly room for improvement here, considering that pharmacokinetic data from a phase I study suggest that long-acting RPV administered every 8 wk could sustain plasma and tissue drug levels necessary for preventing HIV-1 infection (12). We also need to understand the pharmacokinetic and pharmacodynamic activities of compound I in both ectocervical and colonic tissues. For example, Dezzutti et al. (13) reported that higher levels of RPV are needed in female genital tract tissue compared with gastrointestinal tract tissue to prevent HIV-1 infection in vitro. Finally, and perhaps most importantly, we need to comprehensively understand the resistance and NNRTI cross-resistance profiles of compound I, particularly against transmitted drug-resistance variants such as K101E, K103N, Y181C, and G190A, which are prevalent in all geographic regions and HIV-1 subtypes (9).

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