



Next-Generation NNRTIs: Etravirine and Rilpivirine

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“Even in patients with the most resistant virus, our goal now is full suppression of HIV replication,” said Joseph Eron, MD, during a plenary session at the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Dr. Eron, Principal Investigator of the AIDS Clinical Research Group at the University of North Carolina, Chapel Hill, observed that in industrialized nations, up to 10% of HIV positive individuals receiving medical care have triple-class drug-resistant virus.

With the power to revitalize the failing regimens of people with drug-resistant HIV, promising new agents in novel antiretroviral classes—such as CCR5 antagonists and integrase inhibitors—naturally generated much excitement at the conference, held July 22–25 in Sydney, Australia. But investigational drugs in a decade-old class, non-nucleoside reverse transcriptase inhibitors (NNRTIs), received a fair share of attention, with two particular new agents enjoying most of the limelight: etravirine—recently approved by the FDA under the brand name “Intelence”—and rilpivirine (TMC278).

Why Do We Need More NNRTIs?

Introduced in the 1990s, the three initially approved NNRTIs—nevirapine (Viramune), delavirdine (Rescriptor), and efavirenz (Sustiva, Stocrin)—are now widely used in combination antiretroviral therapy thanks to their potency, long half life, and low pill burden, as well as their general tolerability. In fact, the current treatment guidelines published by the U.S. Department of Health and Human Services list the NNRTI efavirenz as a preferred drug for first-line regimens in HIV positive adults. However, the advantages offered by first-generation NNRTIs are offset by widespread resistance mutations and potentially serious toxicities.

The three older NNRTIs have a low genetic barrier to resistance: a single mutation in the virus can eliminate susceptibility to all three drugs. Resistance mutations can, of course, develop in response to incomplete adherence to an NNRTI-containing regimen, but primary resistance—in which a treatment-naive individual is infected with an al-

ready drug-resistant form of HIV—is a growing concern. According to data from the U.S. Centers for Disease Control and Prevention, the prevalence of NNRTI-resistant HIV in treatment-naive individuals more than doubled between 1996 and 2006, increasing from 5% to more than 10% in a single decade.

In addition to resistance, serious side effects represent a major limitation of first-generation NNRTIs. Although the class as a whole is generally well tolerated, some bothersome and even potentially deadly toxicities have been reported for efavirenz and nevirapine.

Perhaps most infamous are the central nervous system effects associated with efavirenz; these range from impaired concentration to dizziness, sleep disorders (including unusual dreams and nightmares), severe depression, and (albeit rarely) contemplated or attempted suicide. Efavirenz has also been linked with birth defects and is therefore not recommended for treatment of women in the first trimester of pregnancy or women of childbearing age who do not use reliable contraception.

NNRTIs in Development

Several NNRTI drug candidates are currently in clinical development:

AGENT	COMPANY	TRIAL PHASE
Rilpivirine (TMC278)	Tibotec	IIb
BILR 355 BS	Boehringer Ingelheim	II
Calanolide A	Sarawak MediChem	II
MIV-150	Medivir/Chiron	II
UK 453,061	Pfizer	II
RDEA806	Ardea	I

Nevirapine, while used extensively and successfully in pregnant women to prevent mother-to-child transmission of HIV, has been linked with skin rash and potentially fatal liver toxicity. Severe hypersensitivity reactions, including rash and elevated liver enzymes, have led both manufacturer Boehringer Ingelheim and the U.S. Food and Drug Administration (FDA) to warn patients and practitioners about the risks associated with including nevirapine in first-line regimens for women with CD4 cell counts above 250 cells/mm³ and men with counts above 400 cells/mm³.

The strengths and limitations of first-generation NNRTIs set a clear standard for next-generation drug candidates: new NNRTIs must—at minimum—demonstrate a higher genetic barrier to resistance, be potent against HIV that already harbors resistance mutations to current NNRTIs, have a superior side effect profile, and offer the same long half life, low pill burden, and ease of coadministration seen with existing NNRTIs. So, how does the next generation of “non-nukes” compare?

Leading the Next Generation: Etravirine and Rilpivirine

Rilpivirine and the recently approved etravirine, made by Tibotec Pharmaceuticals, were designed specifically to meet the drug-resistance challenges posed by a rapidly evolving viral target.

NNRTIs work by binding to amino acids within a “pocket” contained on the reverse transcriptase enzyme, interfering with the enzyme’s function and forestalling the first phase of HIV replication within the host cell. Resistance to NNRTIs occurs when mutations inside the pocket prevent the drugs from binding there, or when a single mutation (known as K103N) alters the opening of the pocket sufficiently to block NNRTIs from entering.

New NNRTIs were designed to get around these resistance mechanisms through “conformational flexibility”: both etravirine and rilpivirine are able to alter their shape and position (through processes scientifically termed “wiggling” and “jiggling”) in order to enter and bind to the pocket on reverse transcriptase in HIV that carries first-generation NNRTI resistance mutations. The benefits of this flexibility, as well as the new drugs’ improved side effect profiles, are evident in promising results from advanced clinical trials.

Etravirine: The DUET Studies

DUET-1 and DUET-2, a pair of randomized, double-blind, Phase III trials, compared 200 mg etravirine twice daily with placebo in treatment-experienced participants, who also received optimized background therapy (OBT) that included the relatively new protease inhibitor (PI) darunavir (Prezista) plus a boosting dose of ritonavir (Norvir), as well as investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Eligibility requirements included documented NNRTI resistance and three or more PI resistance mutations. The mean baseline CD4 cell count in both studies was approximately 100 cells/mm³, and more than 30% of participants had a viral load greater than 100,000 copies/mL at study entry. The majority of participants in DUET-1 and DUET-2 were male (86% and 93%, respectively) and white (61% and 63%, respectively).

After 24 weeks of therapy, a significantly greater proportion of volunteers in the etravirine arm than in the placebo group achieved a viral load of less than 400 copies/mL (74% vs 51% in DUET-1, 75% vs 54% in DUET-2). Significantly more participants taking etravirine also saw their viral load fall below 50 copies/mL (56% vs 39% in DUET-1, 62% vs 44% in DUET-2). Etravirine appeared to be most efficacious in the absence of other active agents: in participants with no active drugs in their OBT, the difference in virological response was 47% vs 9% in DUET-1 and 44% vs 7% in DUET-2. Participants in the etravirine arm also saw greater CD4 cell increases.

Both trials found etravirine to be well tolerated, with reported side effects similar to placebo. Rash was more common in the etravirine arm compared with the placebo group (20% vs 10% in DUET-1, 14% vs 9% in DUET-2), although most reported rashes were mild and short-lived. No differences were noted between the etravirine and placebo arms regarding other side effects, including CNS and psychiatric problems (such as sleep changes, anxiety, and depression), liver toxicities, and lipid elevations.

The DUET trials also better defined the etravirine resistance profile, identifying 13 NNRTI resistance mutations associated with diminished response to the study drug;

however, at least three of these mutations were needed simultaneously for virological response to be significantly reduced. Importantly, K103N—the mutation most commonly associated with efavirenz or nevirapine resistance—does not appear to number among the etravirine resistance mutations so far identified, possibly accounting (at least in part) for the drug's potency against virus that is not susceptible to first-generation NNRTIs.

Rilpivirine

In vitro studies of rilpivirine indicate that the drug candidate is active against NNRTI-resistant strains of HIV—including many with double or triple mutations. Like etravirine, rilpivirine appears to have a higher genetic barrier to resistance compared with older NNRTIs.

The *in vivo* anti-HIV activity of rilpivirine was initially established by two short-term Phase IIa trials, TMC278-C201 and TMC278-C202. Both randomized, double-blind studies administered 25 mg, 50 mg, 100 mg, or 150 mg rilpivirine once daily for seven days. Study TMC278-C201 compared rilpivirine or placebo monotherapy, while TMC278-C202 assessed the effects of replacing a PI or first-generation NNRTI with rilpivirine for participants on failing regimens.

By day eight, participants receiving rilpivirine in both trials saw greater decreases in viral load than did those in the placebo arms, and no new NNRTI resistance mutations were observed in either study. The study drug was also found to be well tolerated, the most common adverse events (AEs) being primarily grade-1 or -2 headache, drowsiness, nausea, and fatigue. (See sidebar below for more about AE grading scales.)

A Phase IIb dose-ranging trial, TMC278-C204, assessed the safety and efficacy of 25 mg, 75 mg, or 150 mg rilpivirine once daily compared with efavirenz in treat-

ment-naive individuals. Participants were screened for NRTI- and NNRTI-susceptible virus and had to enter the study with a viral load greater than 5,000 copies/mL. One-third of the study population was female, less than half was white, and the median age was 35 years.

After 48 weeks of treatment, no statistically significant differences in efficacy were seen between the three rilpivirine doses: between 77% and 81% of participants in the rilpivirine groups achieved a viral load of less than 50 copies/mL. (In the efavirenz arm, a comparable 81% of participants achieved this viral load.)

As in the Phase IIa studies, rilpivirine was found to be generally well tolerated at all doses, and the drug was associated with fewer reported cases of CNS complications (including headache, dizziness, and drowsiness), abnormal dreams or nightmares, vertigo, and rash. Changes in lipid parameters were also generally smaller in the rilpivirine arms: total cholesterol increased by 5 mg/dL, compared with 31 mg/dL in the efavirenz group, while triglyceride levels dropped by 10 mg/dL in rilpivirine-treated individuals and rose by 18 mg/dL in those taking efavirenz. The ratio of total cholesterol to high-density lipoprotein cholesterol declined study-wide, with no statistically significant difference between the rilpivirine and efavirenz arms.

Implications for Treatment

Between them, etravirine and rilpivirine are in more than a dozen ongoing clinical trials. Rilpivirine's 45-hour half life permits once-daily dosing, and a 75-mg dose is being assessed for use by treatment-naive individuals. Etravirine requires twice-daily administration and was approved for the treatment-experienced population. The higher barrier to resistance, efficacy against drug-resistant virus, and generally better tolerability of etravirine and rilpivirine make them promising candidates for both first-line and "salvage" therapy.

With a full antiretroviral pipeline and valuable new agents on the market—including drugs in novel antiretroviral classes—the need for strategic treatment planning cannot be overemphasized; putting together a new regimen or revitalizing an old one is more complicated than plucking the newest drug off the pharmacy shelf. Conferencegoers in Sydney were repeatedly encouraged to include (whenever possible) two or more active drugs in a regimen when adding a novel agent, to increase the likelihood of fully suppressing HIV and averting resistance mutations that could otherwise knock out new treatment options. As succinctly put by Cal Cohen, MD, Research Director of the Community Research Initiative of New England, "it's not just picking active drugs; it's picking *active regimens*."

Reilly O'Neal is the editor of *BETA*.

Grading Adverse Events

Clinical trials use a variety of grading scales to classify adverse events (AEs). Here is a commonly used grading scale:

Grade 1: Mild (AE did not require treatment)

Grade 2: Moderate (AE was resolved with treatment)

Grade 3: Severe (AE interfered with normal activities and required professional medical treatment)

Grade 4: Life-threatening or disabling

Grade 5: Fatal

Drug-Drug Interactions

Interactions between investigational agents and other drugs are elucidated in pharmacokinetic (PK) studies.

For example, PK analyses have shown that rilpivirine reduces blood levels of certain antibiotics used to treat tuberculosis (TB), which may limit its use among individuals with HIV/TB coinfection.

Rilpivirine also appears to reduce blood levels of norethindrone, an oral contraceptive drug marketed in the form of Ortho-Micronor and Nor-QD (among others), and is therefore not recommended for use by women taking some contraceptive pills.

Studies of etravirine have found no effect on metabolism of oral contraceptives. Unlike efavirenz and nevirapine, etravirine has also been found to have no clinically relevant interaction with methadone, suggesting that the new agent may be a useful addition to the regimens of HIV positive individuals on methadone maintenance therapy.

Further research will help define the PK of next-generation NNRTIs and guide their use in conjunction with other medications.

Selected Sources

Bennett, D. and others. Prevalence of mutations associated with antiretroviral drug resistance among recently diagnosed persons with HIV, 1998–2000. 9th Conference on Retroviruses and Opportunistic Infections (CROI). Seattle. February 24–28, 2002. Abstract 372.

Cahn, P. and others. Pooled 24-week results of DUET-1 and -2: TMC125 (etravirine; ETR) vs placebo in 1203 treatment-experienced HIV-1-infected patients. 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago. September 17–20, 2007. Abstract H-717.

Das, K. and others. Strategic flexibility of the non-nucleoside RT inhibitor TMC278 explains its potency against drug-resistant mutants. 16th International HIV Drug Resistance Workshop. St. Michael, Barbados. June 12–16, 2007. Abstract 31.

Goldman, B. ICAAC 2007: Key HIV research—interviews with Cal Cohen, MD, MS, and Eric Daar, MD. September 20, 2007. Available at www.thebody.com/content/confs/icaac2007/art43256.html.

Katlama, C. and others. DUET-2: 24 week results of a phase III randomised double-blind trial to evaluate the efficacy and safety of TMC125 versus placebo in 591 treatment-experienced HIV-1 infected patients. 4th International AIDS Society (IAS) Confer-

ence on HIV Pathogenesis, Treatment and Prevention. Sydney. July 22–25, 2007. Abstract WESS204-2.

Lazzarin, A. and others. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *The Lancet* 370:39–48. July 7, 2007.

Madruga, J.V. and others. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *The Lancet* 370:29–38. July 7, 2007.

Mills, A. and others. DUET-1: 24 week results of a phase III randomised double-blind trial to evaluate the efficacy and safety of TMC125 vs placebo in 612 treatment-experienced HIV-1 infected patients. 4th IAS Conference. Abstract WESS204-1.

Pozniak, A. and others. 48-week primary analysis of Trial TMC278-C204: TMC278 demonstrates potent and sustained efficacy in ART-naive patients. 14th CROI. Abstract 144LB.

Ruxrungtham, K. and others. The metabolic profile of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). 4th IAS Conference. Abstract TUAB105.

Schöller-Gyüre, M. and others. Pharmacokinetic and pharmacodynamic study of the concomitant administration of methadone and TMC125 in HIV-negative volunteers. *Journal of Clinical Pharmacology*. January 14, 2008 (Epub ahead of print).

Schöller-Gyüre, M. and others. No effect of TMC125 on the pharmacokinetics of oral contraceptives. 8th International Congress on Drug Therapy in HIV Infection. Glasgow. November 12–16, 2006. Abstract P277.

Vingerhoets, J. and others. Impact of baseline NNRTI mutations on the virological response to TMC125 in the phase III clinical trials DUET-1 and DUET-2. 16th International HIV Drug Resistance Workshop. Abstract 32.

Wheeler, W. and others. Antiretroviral drug-resistance mutations and subtypes in drug-naive persons newly diagnosed with HIV-1 infection, United States, March 2003–October 2006. 14th CROI. Abstract 648.

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