Pharmaceutical Updates

Raltegravir “Warnings and Precautions” Updated

The integrase inhibitor drug raltegravir (Isentress) was approved by the United States Food and Drug Administration (FDA) in 2007 and is the only integrase inhibitor currently approved for HIV treatment. Merck Pharmaceuticals, the maker of the drug, recently updated the “Warnings and Precautions” section of the package insert to reflect reports of life-threatening skin reactions and severe hypersensitivity reactions.

The update does not mention the number of reports documenting these reactions, however. Although side effects and adverse reactions can occur with any drug, clinical trials found raltegravir to be safe and well tolerated among large numbers of study participants.

The skin conditions and hypersensitivity reactions added to the package insert include severe rash, rash with an accompanying fever, general malaise or fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis (such as “pink eye”), facial edema (swelling of the face), hepatitis, eosinophilia (build-up of an abnormally high number of white blood cells called eosinophils), and angioedema (hive-like swellings under the skin).

“Delay in stopping Isentress treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction,” the updated package insert advises. That said, abruptly stopping an antiretroviral drug without adding a new one may allow the virus to reproduce and develop resistance to HIV medicines.

This update underscores the importance of good patient-provider communication. Conversations about possible side effects and drug reactions, as well as frank discussions of current and past health issues and family medical history, can go a long way toward preventing unwanted drug effects and choosing the best possible course of treatment.

New Combo Pills on the Way?

In October, pharmaceutical company Gilead applied to the FDA for approval to market the “Quad” pill, which, if approved, would offer people living with HIV a new complete drug regimen in a single, once-daily pill.

Each class of antiretroviral drug works at a specific stage in HIV's lifecycle; for example, integrase inhibitors prevent HIV’s genetic material from integrating with that of the host cell, thereby stopping the virus from making new copies of itself and infecting other cells in the body.

To stop HIV in its tracks at more than one stage, a complete antiretroviral regimen must include medicines from more than one drug class (see page 2 for a full list). To date, the FDA has approved only two products—Atripla and Complera—that pack a complete treatment regimen into a single pill that is taken only once a day.

The Quad pill contains four different antiretroviral compounds: tenofovir (Viread) and emtricitabine (Emtriva), both already approved nucleoside/nucleotide reverse transcriptase inhibitors that can be taken together in the fixed-dose Truvada pill; elvitegravir, an experimental integrase inhibitor; and cobicistat, an investigational “boosting” agent that raises the levels of elvitegravir in the blood enough to allow once-daily dosing.

Also in late October, Gilead and pharmaceutical company Bristol-Myers Squibb announced their partnership to develop and market a once-daily pill that combines cobicistat with the already-approved protease inhibitor atazanavir (Reyzataz).

Only one “booster” is currently approved for HIV treatment (ritonavir; brand name Norvir), making the approval of an alternative boosting agent a welcome prospect. Simplified treatment regimens, as well, represent a welcome trend in antiretroviral drug development; research has shown that lower “pill burdens” (the number of pills taken per day) and less frequent dosing improves adherence to treatment—that is, the fewer the pills and the less frequently people have to take them, the more likely folks are to keep up with their meds. Good adherence, in turn, helps keep viral load down, avoid the development of drug-resistant HIV, and get the most out of any treatment regimen.
Clinical Research Opportunities

Studies are listed with brief descriptions only; additional inclusion and exclusion criteria may apply. For more information, please contact the study site directly.

Alameda County Medical Center
Adult Immunology Clinic, Highland Hospital
1411 East 31st Street
Oakland, CA 94602
510-437-4299

- IRISS Study: A study exploring ways to help individuals cope with a new HIV diagnosis. Study involves nine interviews over one year. Must speak English or Spanish and be recently diagnosed with HIV. Compensation is $20–$50 per visit.

East Bay AIDS Center (EBAC)
3100 Summit Street, 2nd Floor
Oakland, CA 94609
510-869-8490
http://altabates.com/clinical/aids_scvs.html

- ING111762 (SAILING study): An advanced, randomized, double-blind study assessing the safety and efficacy of 50 mg of the experimental ARV GS1349572 taken once daily compared with 400 mg of the integrase inhibitor raltegravir taken twice daily, both administered with an investigator-selected background ART regimen, over 48 weeks in HIV-positive adults. Must have taken ARVs before but have no prior integrase-inhibitor use.

Kaiser Permanente Clinical Trials Unit
4141 Geary Boulevard, Suite 219
San Francisco, CA 94118
415-833-3487

- Gilead 0130: A 48-week head-to-head comparison of the boosting agents cobicistat and ritonavir. Participants will also take tenofovir/emtricitabine and atazanavir. Must have had no prior ART. NS
- Quad Switch Study 1: A 48-week study for those on an ART with two NRTIs and one NNRTI (i.e., tenofovir/emtricitabine/efavirenz or abacavir/lamivudine plus nevirapine) with undetectable viral load. Participants will switch to the fixed-dose, single-pill Quad formulation (elvitegravir/cobicistat/tenofovir/emtricitabine). NS
- Quad Switch Study 2: A 48-week study for those on an ART with two NNRTIs and one PI with undetectable viral load. Participants will switch to the fixed-dose, single-pill Quad formulation. May begin the study on any qualifying ARV regimen, including older regimens containing zidovudine/lamivudine or lopinavir/ritonavir. NS
- Gilead 118: A 96-week study to evaluate the safety of the single-tablet Quad formulation. Must have borderline kidney function (GFR 50–75), and have had no prior ART.
- Viking: A “salvage” study for people with HIV and limited treatment options. Participants will receive the investigational integrase inhibitor dolutegravir plus an optimized ART regimen. Must have detectable virus with resistance to all available drug classes, including raltegravir resistance.

- Cobicistat study: A 96-week study to evaluate the impact of the investigational booster drug cobicistat on kidney function. Participants will switch from using ritonavir to

Metropolis Medical Group
Please note new address:
851 Hyde Street, Suite 301
San Francisco, CA 94109
415-292-5477 ext. 487
http://metropolismedical.net

All studies provide free labwork, study drugs, and compensation between $500 and $750.
- BMS AI467003: A 48-week study comparing a standard ART regimen (atazanavir, ritonavir, and tenofovir/emtricitabine) with an NRTI-sparing regimen (atazanavir, ritonavir, and raltegravir). Must have had no prior ART. NS
- Gilead 130: A 48-week head-to-head comparison of the boosting agents cobicistat and ritonavir. Participants will also take tenofovir/emtricitabine and atazanavir. Must have had no prior ART. NS
- Quad Switch Study 1: A 48-week study for those on an ART with two NRTIs and one NNRTI (i.e., tenofovir/emtricitabine/efavirenz or abacavir/lamivudine plus nevirapine) with undetectable viral load. Participants will switch to the fixed-dose, single-pill Quad formulation (elvitegravir/cobicistat/tenofovir/emtricitabine). NS
- Quad Switch Study 2: A 48-week study for those on an ART with two NNRTIs and one PI with undetectable viral load. Participants will switch to the fixed-dose, single-pill Quad formulation. May begin the study on any qualifying ARV regimen, including older regimens containing zidovudine/lamivudine or lopinavir/ritonavir. NS
- Gilead 0115: A study exploring ways to help individuals cope with a new HIV diagnosis. Study involves nine interviews over one year. Must speak English or Spanish and be recently diagnosed with HIV. Compensation is $20–$50 per visit.

Other Classes
- enfuvirtide (T-20) Fuzone
- maraviroc Selzentry
- raltegravir Isentress

Fixed-Dose Combinations
- lamivudine/abacavir Epizicom
- tenofovir/emtricitabine Truvada
- efavirenz Atripla
- tenofovir/emtricitabine/raltegravir Complera
- zidovudine/lamivudine Combivir
- zidovudine/lamivudine/abacavir Trizivir

The following table lists the generic names, abbreviations, brand names, and dosages of some of the ARVs used in the studies:

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME</th>
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<tbody>
<tr>
<td>abacavir</td>
<td>Ziagen</td>
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<tr>
<td>didanosine</td>
<td>Videx</td>
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<tr>
<td>emtricitabine</td>
<td>Emtriva</td>
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<tr>
<td>lamivudine</td>
<td>Epivir</td>
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<td>stavudine</td>
<td>Zerit</td>
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<td>tenofovir</td>
<td>Viread</td>
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<td>zidovudine</td>
<td>Retrovir</td>
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<tr>
<td>delavirdine</td>
<td>Rescriptor</td>
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<td>efavirenz</td>
<td>Sustiva</td>
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<td>etravirine</td>
<td>Intelence</td>
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<td>Viramune</td>
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<td>rilpivirine</td>
<td>Edurant</td>
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ABBREVIATIONS

| NS | New study in this issue, or update to an existing study |
| ARV | Antiretroviral |
| ART | Antiretroviral therapy |
| > | Greater than |
| < | Less than |
| ≥ | Equal to or greater than |
| ≤ | Equal to or less than |
| EAP | Expanded access program |
| PI | Protease inhibitor |
| NRTI | Nucleoside/nucleotide reverse transcriptase inhibitor |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
• Hepatitis C virus (HCV) treatment study: A 48-week study of an investigational HCV treatment. Must have both HIV and GT1 HCV infection and be on a stable ART regimen (either tenofovir/emtricitabine/efavirenz or tenofovir/emtricitabine plus ritonavir), with undetectable viral load. May either have had no prior HCV treatment or have experienced a past treatment failure on pegylated interferon/ribavirin.

• Kowa Lipid Study: People with HIV and elevated cholesterol will receive an investigational statin (cholesterol-lowering) drug or Pravachol. Must either be currently taking a statin drug or have elevated LDL (>130). Study lasts one year.

• Eradication Strategies Study: A one-time, large-volume blood draw for investigation of compounds that could lead to eradication of “dormant” HIV. Must have been on HIV treatment for many years with no detectable virus. Single study visit.

• The ASSURE Study: An ART regimen simplification strategy study for people taking Truvada, atazanavir, and ritonavir to assess whether stopping ritonavir is an option when switching from Truvada to abacavir/lamivudine. Two in three participants will switch.

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San Francisco Department of Public Health AIDS Office
25 Van Ness, Suite 500
San Francisco, CA 94102

- BUMP: A group of studies to test the feasibility of providing medication to individuals who want to reduce their meth use. Participants will be paid $10–$35 per study visit. 415-554-9013, http://sfbump.com.

- Project ECHO: A study to assess whether a behavioral intervention designed for HIV-negative gay and bisexual men who use alcohol and other substances changes participants’ thoughts, attitudes, and beliefs while they are using substances and helps them reduce their sexual risk. 415-554-4233, http://echosf.com.

Stanford AIDS Clinical Trials Unit
1000 Welch Road, Suite 202
Palo Alto, CA 94304
650-723-2804
http://actu.stanford.edu/

Compensation is provided for travel and meals for most studies.

- A double-blind study of an investigational once-daily CCR5 inhibitor (BMS-663068) followed by an open-label period of taking a recommended dose. Must be HIV positive and have used ARVs before, with a CD4 count >50 cells/mm³ and viral load >1,000 copies/mL. Compensation is $50 per visit and $500 for each pharmacokinetic analysis performed (for participants who qualify).

- Study of “zinc finger nuclease” (ZFN) proteins: ZFNs can be used to delete the gene for CCR5, a protein on the surface of some blood cells that allows HIV to enter. CD4 cells are extracted from participants’ blood and modified by ZFNs to resist HIV infection by removing the CCR5 gene. Additional modified cells are then made and re-infused back into participants. Researchers hope these genetically modified cells will be resistant to HIV infection and will reproduce additional HIV-resistant CD4 cells in the body. Participants must have a viral load >1,000 copies/mL and either no prior ART and a CD4 count of >500 cells/mm³ or ART “failure” and a CD4 count >250 cells/mm³.

- A5280: A study evaluating high-dose vitamin D and calcium in people starting ART, to see how those meds may affect bone health. Must have had no prior ART. NS

- A5286: A study to evaluate the ability of the antibiotic drug rifaximin to reduce bacteria in the gut. For those on ART for longer than two years, with a CD4 count <350 cells/mm³ and an undetectable viral load for more than one year. NS

- A5303: A study evaluating a standard HIV medication combination compared with an experimental combination containing maraviroc. Must have a viral load ≤1,000, be hepatitis B–negative, and have had no prior ART. NS

- A5275: A study to see whether the cholesterol-lowering drug atorvastatin can reduce inflammation in HIV-positive individuals who have an undetectable viral load and normal LDL cholesterol levels and are on a boosted-Pi-containing ARV drug regimen.

- A5281: A study examining an experimental therapeutic vaccine designed to boost the immune system. Must have a CD4 count >500 cells/mm³ and a viral load <200 copies/mL on ART for more than six months.

- POEM Study: A five-year study to monitor the safety of long-term use of maraviroc in a large and diverse patient population. Those without R5 tropism will not be given maraviroc but will be observed in the study.

Stanford University Medical Center
300 Pasteur Drive, A342
Stanford, CA 94305
650-724-3792

- A study of pregabalin to treat painful HIV-related neuropathy. Must be 18 or older and have had neuropathy for at least three months; must not have used pregabalin before. Participants will receive research-related medical care and medication at no cost and will be reimbursed for study-related expenses.

UCSF/360: Positive Care Center
400 Parnassus Avenue, 4th Floor
San Francisco, CA 94110
http://php.ucsf.edu/rsrch_trials.shtml#anc2

- ACTG 5272: A study to evaluate the presence of human papilloma virus (HPV) in saliva after ART initiation and explore the association of oral sex practices and any changes in the
presence of oral warts. Must have had no prior ART. Each study visit offers $20 compensation (except screening visit). 415-353-2463, option #1 for additional information.

- PiHDL levels in African American men age 50 and older: A study to compare the prevalence of PiHDL serum levels in older African American men with and without HIV. The comparison may increase the knowledge base of risk factors for developing coronary artery disease and lead to improved screening tests. The study takes 75 minutes. Must be African American, male, and 50 or older; may be HIV positive or negative. Must not be using a lipid-lowering agent. If HIV positive, viral load must be undetectable. Compensation is $35.

- OHARA ACTG 5254: A study designed to assess the accuracy of clinical diagnoses of HIV-related mouth diseases made by medical researchers compared with those made by oral-medicine-trained dentists; describe the relationship between HIV viral load in blood and HIV viral load in saliva; and assess the relationship between Candida levels in the mouth and clinical diagnosis of oral candidiasis. The study takes 90 minutes. Must be 18 or older and HIV positive with a CD4 count ≤200 cells/mm³; may be male or female. Must not have used a systemic antifungal during the past 60 days. Compensation is $20. 415-353-2463, option #2 for screening.

UCSF/San Francisco General Hospital
1001 Potrero Avenue, Ward 4C
San Francisco, CA 94110

- SCOPE Study: An observational study recruiting: (1) “elite controllers” (HIV positive with viral load <2,000 copies/mL and not taking ARVs), (2) antiretroviral-naive individuals (those with no prior ART), (3) long-term non-progressors (HIV positive for more than 10 years and with a CD4 count >500 cells/mm³ without taking ARV drugs), and (4) HIV-negative “control” participants. Study involves an interview and blood draw every two to four months. Compensation is provided. 415-476-4082, ext. 155 or 139.

- Mesalamine Study: A randomized, controlled trial adding the anti-inflammatory drug mesalamine to current ART in people with a low CD4 cell count despite undetectable viral load. Study will assess whether decreasing inflammation in the gut improves immune function. Compensation is provided. 415-476-4082, ext. 104 or 139.

Other UCSF Studies

- CIT2 Study: A study evaluating how ART affects the brain and central nervous system. Must be about to start or change ARVs under a doctor’s supervision and willing to undergo three MRI scans, spinal taps, blood draws, physical exams, and extensive neuropsychological testing over a four-to-six-month period. 415-206-4328.

- OPTIONS Project: A study for individuals recently exposed to HIV and experiencing acute retroviral syndrome (e.g., flu-like symptoms), those who have been infected with HIV within the past six months, and those who are HIV negative and having unprotected sex with men. Compensation and counseling are provided. 415-502-8100, www.ucsf.edu/options.

- HIV Negatives Study: A study examining how some men can be exposed to HIV yet not become infected with the virus. For men who have unprotected sex with men and are currently HIV negative or untested. Compensation and counseling are provided. 415-502-8100.

- A blood-draw study to find the CD8 cell anti-HIV factor (CAF) that naturally protects infected people from disease. Must not be on ART or must have been on treatment for less than one year. 415-476-4071.

- The DUO Project seeks male couples for interviews. One or both partners must be HIV positive and on ART. Compensation up to $120 per couple. 877-386-6292 (toll free) or 415-597-9322.

- A study of the interaction of alcohol and ARVs, for people about to start or restart HIV medications. Compensation up to $575. 415-206-3364.

- IRISS Study: A study exploring ways to help people cope with a new HIV diagnosis. Includes nine interviews over a year and a half. Must speak English or Spanish and have been recently diagnosed with HIV. Compensation is $20–$50 per visit. 415-353-4299.

Veterans Affairs
Palo Alto Health Care System
3801 Miranda Avenue, Suite 132
Palo Alto, CA 94304
650-496-2510

- HIV & Hepatitis C or Hepatitis C Study: A one-time blood draw for those who have spontaneously cleared hepatitis C virus without treatment.