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About HIV Treatment ALERTS!

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The CFA also publishes **Research Initiative/Treatment Action!** (RITA!). **RITA!** is a literature-review journal that covers issues in HIV research and policy. This and other publications are available on The CFA website or can be requested by mail (see contact information below). CFA publications are supported in part with unrestricted funding from AIM Investments, CFP Foundation, Gilead Sciences, and GlaxoSmithKline.
This year, the 15th Conference on Retroviruses and Opportunistic Infections (CROI) occurred with much less fanfare than in recent years. Enthusiasm for this year’s meeting was diminished largely because of the ups and downs the research community has experienced with existing drugs and with the lack of newly developed ones to fight HIV. Also disappointing was the news from Merck that its vaccine, MRKAd5, was unsuccessful at stopping HIV in negative, high-risk volunteers (Abstract #88LB). The result of this slowdown in drug development was to shift the focus of the meeting back to the laboratory and to rethinking how the virus works inside the human body.

The conference was different in yet another way. Although most presentations at CROI have traditionally been devoted to clinical science, this time there were more sessions that focused on the biomedical prevention of HIV/AIDS. Researchers are beginning to realize that while there will always be a need to alleviate the health consequences of HIV infection, there is also a need for alternate ways to stop or control the virus. As reported in the Winter 2007/2008 issue of RITA!, entitled Biomedical Prevention of HIV/AIDS: What We Can Do to Control This Epidemic, Dr. Kevin De Cock, director of the World Health Organization’s HIV/AIDS Division, reminded us that we cannot stop the epidemic by using medicine alone because most HIV-infected people around the globe do not have access to anti-HIV treatment and because such treatment is moving slowly from industrialized to developing nations. His most important message was that we cannot separate prevention from treatment, a view that was supported by the many discussions at CROI surrounding this issue.

The Space Age: A New Frontier

Now that researchers seem to have run out of new drugs, at least for the time being, there are some who are exploring uncharted territory—the stuff of science fiction novels and TV dramas like Star Trek. Small groups of scientists, mostly in Europe, are using technology from the fields of
physics, chemistry, biology, and engineering to find new ways to enhance the performance of existing anti-HIV drugs. Terms like “gene therapy” and “nanotechnology” were mentioned in several presentations at CROI. But before we explore these potential advances in HIV treatment, let’s see what’s new in our understanding of how HIV interacts with the body’s defensive cells.

Retrovirus/Host-Cell Interactions

When talking about viral infections, such as HIV, infected cells are known as host cells because of the role they play as host to the infectious agents. The research field of virus/host-cell interactions investigates the ways in which the natural defensive mechanisms of host cells interact with the infectious processes of viruses. Host cells in humans have developed a number of proteins that help fight against viral infection and replication. Unfortunately, HIV has found ways to get around these defensive proteins by using something called viral accessory, or helper, genes. Although the purpose of these accessory genes was not clearly understood at first, it is now becoming clear that they play a key role in evading a cell’s defenses.

Dr. Paul Bieniasz, of the Aaron Diamond AIDS Research Center in New York, gave an overview of the findings of a human cellular protein-CD317-that prevents newly formed viral particles from being fully released from infected cells (Abstract #114). Scientists know that certain host cells can slow down the release of newly formed retrovirus particles. Although not all host cells can do this, researchers have discovered that when the viral accessory gene vpu is removed from HIV, the virus cannot replicate. Evidence has also shown that some cell proteins—dubbed "tetherins"—have the ability to force new retrovirus particles to simply attach to the cell surface rather than invade it. The HIV accessory protein, vpu, tries to resist being attached or tethered.

Dr. John Guatelli, at the University of California, San Diego, also experimented with the CD317 protein which appears to play this tethering or attaching role (Abstract #104a). Cells that express this protein are able to inhibit the release of HIV. Whereas there are no immediate therapeutic implications to these findings, Dr. Bieniasz said that future work will continue to explore the range of viruses against which tetherin is...
active, the precise mechanisms by which tetherin inhibits viral replication, and the mechanisms by which the HIV vpu protein opposes tetherin.

**Gene Therapy**

We humans have between 50,000 and 100,000 genes that regulate how the cells in our bodies behave. These regulatory genes work like a switch: they can either “turn on” or “turn off” nearly every function that a cell is capable of performing. Gene therapy takes advantage of this regulatory switch by introducing foreign genetic material into a person's cells so that it can turn specific cellular functions on or off. In the case of HIV, turning off certain T-cell functions may help protect T-cells from becoming infected with HIV or from becoming host cells that produce new virus once infected. Gene therapy can also be used to turn on certain T-cell functions, possibly causing HIV-infected cells to self-destruct or to begin producing a weakened form of HIV that standard HIV medications can then attack.

Since a gene cannot be directly inserted into a person's cells, it must be delivered using a vehicle, called a “vector.” The vectors most commonly used in gene therapy are viruses. Because viruses cause disease, they have a unique ability to recognize or target specific cells in the body and insert their DNA into those cells. For a virus to be used as a vector, the disease-causing genes in the virus must be replaced with those that can help make the body’s immune cells resistant to infection with the virus.

**VRX496**, developed by VIRxSYS Corporation (Abstract #753a), is the first gene-therapy agent to use HIV as a vector. As with any viral vector, the disease-causing genetic material of HIV had to be removed, leaving only the outer shell (envelope) of the virus. The envelope was then fitted with therapeutic material called antisense, a molecule that is the mirror image of the gene that makes the virus produce new envelopes. When the modified T-cells are infused back into the patient's blood, the antisense gene is permanently incorporated into the cellular DNA. When the virus starts to replicate inside the host cell (T-cell), the antisense gene stops the envelope gene from working, thereby shutting down HIV replication.

Dr. Vladimir Lukashov, from the Netherlands, reported the results of a study conducted by VIRxSYS Corporation in which 9 HIV-infected patients were given a single intravenous infusion of their own immune cells (T-cells) that had been modified using the antisense therapeutic gene. Two months after the infusion, 8 of the 9 patients had undetectable viral loads and their T-cell counts remained steady or increased. Dr. Lukashov’s group was able to detect the gene-modified cells for up to 3 years, suggesting that genetically modified cells do not die quickly and may have long-lasting therapeutic benefits in the body. VIRxSYS Corporation is now conducting a Phase II study in which patients will receive 6 infusions rather than just 1. The clinical trial is designed to evaluate the safety of multiple infusions and to test the effect of infusions on the ability of the patients' immune systems to control
HIV after they stop taking their standard HIV treatment. The hope is that this treatment approach may ultimately allow patients to stay off HIV treatment for extended periods of time.

**Nanotechnology**

Another new and exciting frontier being explored in the fight against HIV is nanotechnology. **Nanoparticles** are ultramicroscopic polymers that are already being used in cancer research to deliver chemotherapy drugs directly to tumors, thereby improving the usefulness of the drugs while potentially limiting their side effects. Using the same technology, researchers are working to simplify HIV therapy by packing HIV molecules into tiny polymer bundles that slowly release a drug when they are injected into the body. The goal is to develop an injectable highly active antiretroviral therapy (HAART) that patients could take only once a month. As was evident in several presentations at CROI, nanoparticles are also being used to develop long-acting antiretrovirals—and possibly other medications used to treat HIV-positive people—that may be administered at even longer intervals.

Dr. Gerben van t’Klooster, from Belgium, discussed how the company Tibotec has experimented with nanoparticles containing **rilpivirine** (also known as TMC278; see the June 2007 issue of *HIV Treatment Alerts* for additional information), a nonnucleoside reverse transcriptase inhibitor (commonly known as NNRTIs or “non-nukes”) (Abstract #134). The simple, once-daily 75 mg dosing of rilpivirine makes it an ideal candidate for study as a long-acting antiretroviral agent.

Tibotec has conducted preliminary research of rilpivirine-containing nanoparticles in rats, dogs, and humans. In all these study subjects, the enhanced drug was injected either **subcutaneously** (under the skin) or **intramuscularly** (into a muscle). Once the drug-containing nanoparticles are injected, they are slowly broken down and gradually release their rilpivirine payload. In dogs, the concentration of rilpivirine remained high in the blood for up to 3 months, and the release of rilpivirine from the nanoparticles was completed between the third and sixth month after the injections. In HIV-negative human volunteers, peak blood levels of rilpivirine were documented approximately 3 days after doses that ranged from 200 mg to 600 mg were injected. Blood concentrations of the drug fell off by 60% by day 14, after which a slow gradual decline was noted. Dr. van t’Klooster said that his group would continue experimenting with long-lasting rilpivirine formulations...
and possibly with other long-lasting antiretrovirals to combine with it.

Tibotec is not alone in its exploration of the potential cooperative interaction between nanotechnology and HIV drug development. Researchers at Creighton University in Omaha, Nebraska (Abstract #743), reported that their test-tube studies involving nanoparticles containing the NNRTI efavirenz (Sustiva®) and the protease inhibitors lopinavir (Kaletra®) and ritonavir (Norvir®) were successful at maintaining adequate drug levels for up to 30 days. They also performed experiments to show that the nanoparticles were quickly captured by human macrophages, a kind of immune system cell.

In another experiment conducted at Creighton University (Abstract #745), scientists succeeded in loading indinavir (Crixivan®) into nanoparticles, then getting bone marrow-derived macrophages to soak them up. These cells were then injected into HIV-infected mice that had developed HIV-related brain swelling. The altered cells naturally gravitated toward the cells that were being destroyed as a result of the HIV-related inflammation. More importantly, the injected cells were not found in the healthy areas of the brain. This model suggests that there might be a way to improve the ability of certain drugs to cross the blood-brain barrier to the sites in the brain where they are most needed.

**Back to Earth: A Continuing Journey**

Although results from drug updates were not nearly as exciting as last year, there was still encouraging news at CROI about some of the drugs that have been recently approved and that were the focus of last year’s conference, such as vicriviroc, maraviroc, and raltegravir (see the June 2007 issue of HIV Treatment Alerts). Furthermore, there are some new drugs in the existing classes of antiretroviral drugs that are in the very early stages of development and look promising.

Dr. Barry Zingman, from the Montefiore Medical Center in the Bronx, New York, reported on a clinical trial investigating the efficacy, safety, and strength of the chemokine receptor (CCR5) antagonist vicriviroc (Abstract #39LB). In this study, 116 subjects received 20 mg of vicriviroc, 30 mg of vicriviroc, or placebo once daily in combination with a new ritonavir-boosted optimized background therapy (OBT) that consisted of 3 or more drugs, including a protease inhibitor. At the start of the study, the average viral load was above 32,000 copies and the average T-cell count increased 210. After 48 weeks of treatment, viral loads had dropped to less than 1000 copies for all of the three different treatment arms of the study; the average T-cell count an average of 100 cells. These findings suggest that 20 mg or 30 mg of vicriviroc given once daily with ritonavir-containing OBT is able to control HIV in treatment-experienced subjects. Phase III trials are ongoing.

MOTIVATE 1, in the United States and Canada, and MOTIVATE 2, in Europe, Australia and the United States, are Phase III studies evaluating the effectiveness and safety of maraviroc (Selzentry™), another recently approved CCR5
antagonist, in treatment-experienced patients. Dr. David Hardy, of the David Geffen School of Medicine at the University of California, Los Angeles, presented the data on both studies (Abstract #792). About 90 patients whose HIV infection had become resistant to 3 other classes of anti-HIV drugs and who had viral loads above 5,000 copies were placed in 1 of 3 treatment groups: once-daily maraviroc plus OBT, twice-daily maraviroc plus OBT, or placebo plus OBT. After 48 weeks of treatment, researchers found that once-daily or twice-daily maraviroc plus OBT controlled HIV and protected the immune system significantly better when compared to placebo plus OBT.

Dr. Sarah Pett, of Australia's National Centre for HIV Epidemiology at the University of New South Wales, reported the results of a small 10-day monotherapy study of a new experimental ritonavir-boosted CCR5 antagonist, SCH532706 (Abstract #38). The study included 12 individuals, 4 of whom were treatment-naive and 8 of whom were treatment-experienced but off therapy for at least 3 months. At the baseline evaluation, the average T-cell count among the subjects was 385 and the average viral load was 32,000 copies. Participants received 60 mg of SCH532706 twice daily that was boosted with 100 mg of ritonavir once daily; this regimen was taken for 10 days. As with some protease inhibitors, ritonavir boosts the blood level of SCH532706 and makes it last longer in the body. After 10 days, there was a 14-day “wash out” period during which no anti-HIV drugs were taken; participants then started standard combination antiretroviral therapy. At day 10, the average viral load had dropped to 1500 copies and the T-cell count had increased by 59 cells. Based on these findings, the researchers concluded that SCH532706 is safe, well tolerated, and suitable for once-daily dosing as part of a ritonavir-containing antiretroviral regimen.

Dr. David Cooper, of the University of New South Wales in Sydney, Australia, presented 48-week data from a study testing the effectiveness of the integrase inhibitor raltegravir (Isentress™), in combination with OBT (Abstract #788). The data come from BENCHMRK-1 (Protocol 018), an ongoing multicenter, Phase III study being conducted in Europe, Asia/Pacific, and Peru. Patients whose anti-HIV therapy had become ineffective because of resistance to several classes of antiretroviral drugs were treated either with 400 mg of raltegravir or with placebo, both administered in combination with OBT. Among the 352 patients participating in the study, T-cell counts were 140 and 105 and viral loads were around 40,000 copies at the beginning of the study. After 48 weeks, 74% of the patients who received raltegravir has viral loads less than 400
copies, 65% had viral loads less than 50 copies, and T-cell counts had increased by about 120. In the placebo group, only 36% had viral loads less than 400 copies, 31% had viral loads less than 50 copies, and T-cell counts had only increased by about 49. This indicates that raltegravir plus OBT produced superior antiretroviral and immunological responses when compared to OBT alone.

**Uprooting Some Perennial Problems**

Despite these promising breakthroughs, researchers and clinicians are not forgetting the hard realities of living with HIV infection in favor of experimenting with the new, high-tech treatments. They continue to work with their patients to prevent the serious problems that both HIV and anti-HIV therapy can cause, in addition to finding ways to improve quality of life.

**Consequences of Treatment Interruptions: Heart Disease and Other Adverse Events**

The SMART Study was a large, international trial that enrolled more than 5,000 patients with T-cells counts over 350. The results of this study have been discussed at all of the HIV/AIDS conferences over the past 2 years. Researchers involved in this study discovered, quite by accident, that delayed or interrupted treatment (drug conservation) caused a greater risk of AIDS or death than immediate, continuous treatment (viral suppression) and that stopping treatment led to serious illnesses such as liver, kidney, and heart disease. Dr. Wafaa El-Sadr, of the Harlem Hospital Center and Columbia University in New York, reported the final results from this study at this year’s CROI (Abstract #36). She looked at outcomes after the trial was modified in 2006, when all of the participants in the drug-conservation group were encouraged to switch to continuous therapy. The good news is that the harmful effects of interrupting antiretroviral therapy are reduced, although not entirely reversed, after treatment is restarted.

In the same study, before January 2006, there were 172 total instances of opportunistic disease or death due to any cause. In addition, there were 104 adverse heart, kidney, or liver events, with a higher risk for these events among the patients in the drug-conservation group. After the study was modified in January 2006, there were 131 total occurrences of opportunistic disease or death. Although the risk was significantly reduced, it was still higher among the patients in the treatment-interruption group when compared with the continuous-therapy group. Risks for opportunistic diseases, death from all causes, and heart, kidney or liver diseases were also reduced, but patients who had had problems related to these conditions before January 2006 still had a “residual excess risk” even after they had resumed continuous therapy.

The researchers believe that this persistent excess risk results from a lower-than-average T-cell count and a higher detectable viral load, in part because some patients did not resume continuous
therapy as recommended. Importantly, T-cell recovery was slow after resuming treatment, even among the patients who experienced a rapid reduction in viral load. The researchers concluded that their findings support a recommendation not to interrupt antiretroviral therapy based on T-cell level, as was done in the SMART Study, since “antiretroviral therapy interruption is associated with long-term consequences beyond the period of treatment interruption.”

Another reason why heart disease is still a hot topic is that the population of HIV-infected persons is getting older. This is a good thing, but it comes with its own baggage. Aging itself puts people at higher risk for heart disease. Given the evidence that anti-HIV treatments can increase cholesterol (a risk factor for heart disease) and that HIV infection itself can increase the risk of heart disease, the threat of heart problems is greater than it would be even for the average middle-aged or elderly adult.

One of the early observations from the SMART study was that people who stopped therapy were more likely to have heart attacks. When these results were reported, researchers and clinicians alike were shocked. General wisdom said it should be the other way around—people on therapy should have more heart attacks because of the cholesterol changes caused by anti-HIV drugs. Since this early observation was made, clinicians have been looking for the reason why stopping therapy would increase the risk of heart attacks. One thought is that when the viral load goes up, inflammation or immune activation occurs that then could cause coronary plaques (blood clots) to form in the coronary arteries, the arteries of the heart. Dr. Lewis Kuller, of the University of Pittsburgh in Pennsylvania, decided that D-dimer, a laboratory test that measures how easy it is for blood to form clots, might be a useful measure of heart attack risk in HIV-infected persons (Abstract #139). Having a high D-dimer level seems to cause more clotting, which is not a good thing because clots in the coronary arteries are what cause heart attacks. The researchers found that when anti-HIV therapy is stopped, the D-dimer level went up. Furthermore, the higher a patient's viral load rose, the higher the D-dimer level was. Based on these results, it seems that anti-HIV drugs not only keep viral load suppressed but they also keep the D-dimer level down. In other words, the anti-HIV drugs are making it harder for a person to form bad clots. When treatment is stopped, however, the risk for forming clots returns.

Apparently, not being on anti-HIV therapy at all also increases an HIV-infected person's D-dimer
level. There are long-standing data that show that untreated HIV-positive people are more likely to develop clots in their veins, which may help to explain why clotting occurs more easily in untreated HIV-infected persons. If this is the case, should anti-HIV therapy be started earlier because of these issues? For example, if there is a strong family history of heart disease, or if an HIV-infected person has certain other risk factors—such as smoking, high blood pressure, diabetes, and high cholesterol—then untreated HIV could be another factor that increases the risk for heart disease.

In conclusion, it is better, at any age, to have HIV infection treated than not treated and to have an undetectable viral load than a detectable one. Although the current guidelines do not recommend that all HIV-infected persons should receive anti-HIV therapy, a person with a T-cell count below 350 should still be treated. Given the potential for adverse health events, all HIV-infected persons would be better off having a suppressed viral load.

Bone Problems

One of the major health issues that has plagued HIV-infected individuals for a long time is bone problems. Fortunately, researchers continue to examine the relationship between HIV-related bone loss (osteoporosis), bone density loss (osteopenia), and bone death (osteonecrosis). Several studies that examined the relationship between bone conditions and HIV disease were reported at this year’s CROI.

Two studies looked at the reasons for the loss of bone mineral density (BMD) in people taking anti-HIV drugs for the first time, also called first-line therapy. The study presented by Dr. Todd Brown, of Johns Hopkins University in Baltimore, Maryland, enrolled 155 individuals who had never taken anti-HIV drugs (Abstract #966). The volunteers took either lopinavir plus ritonavir (Kaletra) or efavirenz (Sustiva) together with zidovudine (Retrovir®) and lamivudine (Epivir®) for 24 to 48 weeks. After 48 weeks, all the volunteers were switched to Kaletra monotherapy through to 96 weeks. Every 24 weeks, the volunteers had bone scans done to measure bone density. Similar decreases in BMD were seen in both groups; these decreases continued at about the same rate throughout the monotherapy period. Because both groups were so similar in the amount of BMD lost after starting HIV therapy, it apparently is not related to the anti-HIV drugs used. This finding suggests that others factors, such as changes in immune function or the activity of HIV in the body, could be causing the loss of BMD.

Dr. Claudine Duvivier, of the Hopital Pitie-Salpetriere in Paris, France (Abstract #967), presented another study that also looked at BMD loss in people taking anti-HIV drugs for the first time. The study followed 71 people over 48 weeks and examined the BMD in the hip and spine. One of 3 regimens was given: NNRTI (efavirenz or nevirapine [Viramune®]) plus a protease inhibitor (lopinavir/ritonavir or indinavir [Crixivan®]); a protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors (also

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known as NRTIs or “nukes”); or an NNRTI plus 2 NRTIs. After 48 weeks, there was marked loss of BMD for all 3 treatment groups. For the regimens that included a protease inhibitor, there was a greater loss of BMD in the spine. Bone scans taken at the start of the study, and before anti-HIV therapy was initiated, revealed that about a third of the volunteers already had some degree of osteopenia and that 2 had osteoporosis. This finding suggests that HIV contributes to the loss of BMD in people taking anti-HIV drugs.

In a study that looked at the role of HIV therapy and loss of BMD in patients who had been taking HAART, Dr. Silvia Guillemi, of the University of British Columbia in Vancouver, Canada, followed 299 patients over 2.5 years (Abstract #969). Results showed that 2 out of 3 patients had abnormal bone scans: 54% had osteopenia and 13% had osteoporosis. Several factors contributed to low BMD in all of the volunteers, including older age, low body mass index, ethnicity, and low T-cell counts. For men, low physical activity and drinking alcohol also contributed to low BMD. Interestingly, the data in general did not show a relationship between taking anti-HIV therapy and losing BMD, except for the HIV drug tenofovir (Viread®). Unlike the other study, protease inhibitors were not shown to contribute to bone loss.

Altogether, these studies stress the need for more research on the underlying causes for BMD and other bone disorders in people living with HIV. They also underscore the need for patients to work with their doctors to monitor bone issues while on anti-HIV therapy, even at the start of therapy. Getting a baseline bone scan before starting therapy, and then regular tests afterwards, can help identify the start of bone loss. Also, addressing other health issues that can contribute to decreased BMD may help prevent some of the loss over time. Such issues include low body mass index, lack of physical activity, older age, alcohol use, and low T-cell count.

Hepatitis

One topic that is receiving more and more conference coverage is hepatitis because of the large number of people who are infected with both HIV and the hepatitis C virus (HCV). Over 100 of the abstracts presented at this year’s CROI addressed different aspects of coinfection with HIV, HCV, and viral hepatitis. This helped focus attention on the importance of diagnosing, monitoring, and appropriately treating coinfected patients.

It is well-known that progression to cirrhosis of the liver occurs faster in patients with chronic
HCV infection who are also HIV-positive when compared with individuals who are infected with only HCV. Without treatment, half of coinfected patients will show liver cirrhosis an average of 25 years after acquiring HCV infection. As a result of these findings, recent guidelines from the United States Department of Health and Human Services recommend earlier initiation of anti-HIV therapy in HIV/HCV-coinfected patients. But there is a Catch-22 in treating both conditions. That is that prolonged exposure to protease inhibitors, NRTIs, or both, can contribute to the progression of cirrhosis. Thus, while high blood levels of HCV and more advanced stages of cirrhosis are associated with poorer recovery from HCV in coinfected patients, taking certain combinations of anti-HIV drugs can also worsen the problem. Several studies presented at CROI this year supported the concern that serious liver events are more common in HIV/HCV co-infected patients who have cirrhosis. Researchers from Spain (Abstract #1059) found that liver disease is the main cause of death in this group while a group from Italy (Abstract #1084) concluded that co-infected patients with cirrhosis were at increased risk of AIDS-related cancers.

Other research (see AIDS 2007;21(9):1073-1089) indicates that insulin resistance seems to occur more frequently in HIV/HCV-coinfected patients who are taking anti-HIV drugs than in patients who are monoinfected with HIV. Therefore, combining ribavirin, which is used to treat HCV infection, with zidovudine, didanosine (Videx®), or stavudine (Zerit®) should be avoided because of an increased risk for anemia, worsening of liver function, or severe weight loss. Furthermore, abacavir (Ziagen®) negatively affected the response of coinfected patients to hepatitis C therapy when compared with tenofovir.

On the other hand, patients who were only infected with HCV were able to achieve a continued undetectable viral load 6 months after completing hepatitis C treatment, which suggests that stopping the hepatitis C virus slows the progression of liver disease. Little is known, however, about the long-lasting benefits of this treatment response in HIV/HCV-coinfected individuals. The same research group from Spain (Abstract #60) that looked at the rate of death from liver disease in co-infected patients assessed the long-term outcome for HIV/HCV-coinfected patients who had been receiving interferon plus ribavirin treatment for HCV since the year 2000. Thirty-one percent of the 711 coinfected patients receiving therapy experienced a reduction in HCV viral load to undetectable levels. This has led to increased interest in examining whether liver cirrhosis could be improved in HIV-infected patients who have undetectable levels of HCV as time passes, as has already been demonstrated in HCV-monoinfected patients.
**Anemia:** low levels of red blood cells or hemoglobin in the blood, resulting in feelings of tiredness or fatigue.

**Body Mass Index (BMI):** a key index that is calculated by dividing weight by height to determine whether a person is overweight or obese. A BMI of 25 or greater has been associated with a wide range of health risks, such as heart disease.

**Bone Mineral Density (BMD):** a test used to measure bone density (thickness) and to determine the risk of fracture related to **osteoporosis**.

**Boost (boosted):** to elevate the levels of a drug in the body.

**Cholesterol:** a fat-like substance that occurs naturally in all parts of the body and is made by the liver. Too much cholesterol in the body increases a person’s risk of getting heart disease.

**Chemokine receptor antagonists:** this new class of antiretroviral drugs, also known as CCR5 (short for chemokine receptor 5) agonists, blocks HIV from attaching to the chemokine receptor on the T-cell, making it hard for the virus to enter T-cells.

**Cirrhosis:** a slowly progressing disease in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly.

**Coinfection:** the simultaneous infection of a cell by two or more virus particles.

**Coronary plaque:** a buildup of fatty deposits within the wall of a blood vessel in the heart.

**Genetic material:** used to store a person’s biological blueprint in the body.

**Hepatitis:** an inflammation of the liver usually caused by a virus.

**Host Cell:** the cell that hides a virus.

**Immune Activation:** when the body’s immune system is turned on (activated) in response to a foreign invader (i.e., viruses and bacteria).

**Insulin Resistance:** in persons with diabetes, a condition in which the body’s cells have a decreased ability to respond to the action of the insulin hormone. To compensate for the insulin resistance, the pancreas secretes more insulin.

**Integrase inhibitors:** a new class of antiretroviral drugs that block the action of integrase, an enzyme that inserts genetic material from a virus into a person’s cells.
**Intramuscular**: injected into a muscle.

**Intravenous**: injected into a vein.

**Macrophages**: cells within the tissues that originate from specific white blood cells called monocytes. These cells are part of the body’s immune system and attack foreign invaders (i.e., viruses and bacteria) by ingesting them.

**Molecule**: the smallest part of any substance. It has the properties and qualities that are characteristic of that substance and, therefore, can exist alone in a free state.

**Nanoparticle**: a microscopic particle whose size is measured in nanometers. A nanometer is one-billionth ($10^{-9}$) of a meter.

**Opportunistic disease (infection)**: a disease or infection caused by an organism that is usually harmless but becomes activated when a person’s immune system is weakened or damaged.

**Optimized background therapy**: the combination of HIV drugs most likely to increase T-cell count and decrease viral load based on which HIV drugs have been taken in the past and on the results of drug resistance testing.

**Osteopenia**: refers to **bone mineral density** that is lower than normal but not low enough to be classified as osteoporosis.

**Osteoporosis**: a disease that weakens bones by making them thin and fragile, thereby increasing the risk of sudden and unexpected fractures.

**Osteonecrosis**: the destruction (necrosis) of bone tissue, often resulting from a decrease in the supply of blood to the bone.

**Placebo**: a pill or substance that has no effect on the body, such as a sugar pill. It is often compared to a real medication to see what the real effect of the medication might be.

**Polymer**: a chemical substance or mixture of substances produced from the combining of small **molecules**, usually then forming repeated molecular units.

**Protein**: a building block found in all living cells. Proteins makes up many of the substances (enzymes, hormones, and antibodies) the body needs to function.

**Resistance** (resistant): a genetic change that allows HIV to reproduce itself in the presence of an HIV medication.

**Subcutaneous**: injected under the skin.
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