HIV Prevention, Testing, and Treatment

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Prevention

Surely, an ounce of prevention is worth a pound of cure (especially when there is no cure!). We know that HIV is transmitted only by:

(a) transfusion of HIV-contaminated blood products,
(b) sharing of intravenous drug injection apparatus with an HIV-infected user,
(c) having unprotected sex with an HIV-infected person, or
(d) from an HIV-infected mother to her newborn child either during pregnancy/delivery or via breast feeding.

Currently, blood products in this country are screened for HIV and other pathogens using the Nucleic Acid Amplification Test, NAT\(^1\). The best estimates for risk are that one in 2,000,000 units of blood is tainted with HIV. That’s only 0.00005% likelihood of infection (much, much less than dying in an automobile crash). Even with these microscopic odds, infection is possible. On July 20, 2002 the CDC announced that two patients in Florida were infected by tainted blood. It was discovered that the donor had been infected a mere ten days prior to giving blood. This is well within the 20-day screening window for this test. Since the introduction of NAT for screening, only three patients have been infected with HIV.

The use of condoms during sex has already been emphasized. Estimated pregnancy rates during perfect use of condoms, that is for those who report using the method exactly as it should be used (correctly) and at every act of intercourse (consistently), is 3 percent at 12 months. The most frequently cited condom effectiveness rate is for typical use, which includes perfect and imperfect use (i.e. not used at every act of intercourse, or used incorrectly). The pregnancy rate during typical use can be much higher (10–14%) than for perfect use, but this is due primarily to inconsistent and incorrect use, not to condom failure. Condom failure—the device breaking or slipping off completely during intercourse—is uncommon for those condoms that have been tested and approved by the FDA.

In Thailand, the promotion by the government of 100% condom use by commercial sex workers led to a dramatic increase in the use of condoms (from 14% in 1990 to 94% in 1994); an equally dramatic decline in the nation-wide numbers of bacterial STD cases (from 410,406 cases in 1994 to 27,362 cases in 1997); and reduced HIV prevalence in Thai soldiers.

Extensive laboratory testing has found that bacteria and viruses, including HIV, do not pass through intact latex condoms, even when they are stressed and/or stretched. The best research data have been obtained from serodiscordant couples (one HIV+ and the other HIV−) and they indicate a transmission rate of at most one percent. Thus, properly used condoms are estimated to be 99% effective for disease protection. Using a 0.30% probability of transmission for unprotected sex, this reflects a transmission rate of 0.003% during protected sex. This translates to odds of transmission of about 1 in 16,000. Unfortunately, recent surveys tell us that (a) most teenagers do not know how to properly use a condom, and (b) a rather large percentage use no protection at all. A common misconception is that because the female is taking birth control pills there is no need for a condom. This is absolutely NOT true!!!

Latex allergies are very rare among the general population. While 1–2 billion condoms are used per year in the US, the FDA received only 44 reports of allergic reactions associated with condom use between October 1988 and the end of 1991. The Centers for Disease Control and Prevention in Atlanta estimates that the population risk of an allergic reaction to latex is 0.08% and the nature of the reaction tends to be very mild. Concerns about latex allergies should not inhibit sexually active people who are at risk of exposure to pregnancy and STDs using condoms, since the risks associated with unprotected sexual contact are far greater than those from exposure to latex. By the way, the female condom (Reality®) is made of mylar, which is a bit noisy. In March of 2009, the FDA approved another (much less expensive, softer, and quieter) female condom, with the brand name FC2.

Recent research has shown rather conclusively, that sexual transmission of HIV is halved for men that are circumcised. In fact, the long term clinical trials were stopped because the evidence was so overwhelming. This has lead to a rush of adult men going to free circumcision clinics in central Africa.

\(^1\) The NAT testing procedure was made mandatory for blood banks in 1999. It specifically tests for HIV-1 and hepatitis C.
Current thinking is being directed toward further improving the safety of sex by the use of antimicrobics (microbicides), externally applied lotions or gels that either kill microbes or prevent them from infecting the host. The goal is to make their use as effective as the use of a condom. Several options are currently undergoing testing.

1. Dextrin sulfate seems to be an effective vaginal antimicrobial that does not disrupt genital epithelium and it is not systemically absorbed. Its efficacy remains unknown.

2. An extract of blue-green algae, called cyanovirin-N is undergoing tests and seems promising.

3. BufferGel is a mild, detergent-free, non-irritating, oil-free lubricant made of Carbopol 974P. It maintains the acidity of the vagina (pH = 4) against the alkalinizing properties of semen. It inhibits pregnancy, HIV transmission, human papilloma virus (HPV), herpes simplex virus (HSV), and chlamydia infections without causing either tissue damage or loss of vaginal microflora.

4. PRO-2000 is a nontoxic, well-tolerated gel that inhibits HIV entry. Initial and secondary findings have been positive, although a 2% solution in a gel has been shown to be ineffective (2/2008), research on a lower concentration of ½% continues with positive results.

5. Mandelic acid condensation polymer (SAMMA) is nonmutagenic, nonirritating, not cytotoxic to lactobacilli found in the vagina, contraceptive, inhibiting to the growth of bacteria causing gonorrhea, and, in preliminary trials, has prevented infection by HIV-1, HHV-1, HHV-2, and Chlamydia trachomatis. A patent has been issued and full clinical trials have begun.

6. VivaGel has been granted accelerated review since it is effective against herpes and seems not to have any harmful side effects.

7. A gel made from the antiretroviral drug tenofovir has been shown to be effective is killing HIV. During the initial clinical trial with 84 women, most participants reported at least one mild adverse reaction, which was independent of HIV status, sexual activity, and gel concentration. Further research is continuing in New York and India.

None of these products are currently FDA-approved for prevention of transmission of HIV.

Published test tube research has shown that there are other commercially available candidates suitable for further testing: Astroglide, Vagisil, and ViAmor.

An analysis of tissue from the cervix and vagina of women who had hysterectomies has been published. It was found that HIV infects macrophages below the epithelium. Furthermore, this was enhanced by immune activation. Epithelial cells were not infected and did not seem to have a role in transferring the virus across the epithelium. Of course, any trauma that could damage the epithelium would enhance transmission. The scientists tested various viricides that can be applied topically. Gramicidin and PRO-2000 blocked HIV infection by 71% and 97%, respectively. If these results hold up to further scrutiny, women will have an option, over which they have control, which may have a significant impact on transmission.

Unfortunately, it has been found that the spermicide nonoxynol-9 (N9) not only does not fully prevent infection by HIV, but may very well enhance it. In the research, although the infection rate was higher in the N9 treatment group, it was not statistically significant. Other studies have reported disruption of the genital epithelium by N9. Further research has reinforced this recommendation against using this chemical during intercourse and several groups have demanded that condom manufacturers no longer use the substance, because of its enhanced risk for viral transmission. Some manufacturers have already complied with these requests.

Drug “works” can be sterilized using a simple bleach solution. Nevertheless, sharing needles is a very bad idea. Also, infected blood remaining in an unsterilized syringe can harbor viable virus for up to seven days under optimal conditions.
Testing for Experimentation
Testing Modalities

Anyone who is to undergo a medical procedure must give her or his informed consent. Informed consent consists of:

1. Full and complete disclosure of all relevant information to the patient.
2. The patient must be legally competent to make an informed decision.
3. The patient must understand everything that was explained.
4. The patient’s decision must be purely voluntary and free of all duress.
5. The patient must make the decision whether to undergo the procedure or not.

More than half of the states allow testing without consent, but only if certain preconditions are met. Some of these conditions are:

(a) patient or her/his designee is unable to either give or withhold consent,
(b) the test results are essential to determine the form of treatment,
(c) the test is needed to protect the health of health care personnel or others,
(d) a minor patient has parental consent.

There are several forms of testing.

1. Voluntary testing: the patient agrees to a test where the results will be known to the patient and the tester, who is under no obligation to withhold the results.
2. Voluntary confidential testing: the patient agrees to a test where the results will be known to the patient and to the tester, who cannot divulge the information to anyone else.
3. Voluntary anonymous testing: the patient agrees to a test where the results will be known only to the patient. The tester knows the patient only as a code number.
4. Mandatory testing: the patient is required to be tested as a precondition for participation in some activity, e.g., giving blood. This may be anonymous, confidential, or neither. Participation in the activity is at the patient’s option. The patient may choose to forgo the activity to avoid the test.
5. Compulsory testing: the patient must submit to be tested irrespective of her/his wishes, e.g., in some states people convicted of various sexually related crimes are ordered to be tested.

Fundamental Notions of Testing

According to the CDC, in 1996 somewhere between 2 and 2.5 million HIV antibody tests were administered in publicly funded programs. Of these fully 60% were retests and the remaining 40% were tests given for the first time. That was the good news. The bad news is that 26% of those testing HIV+ and 33% of those testing HIV− never returned for their results. That leaves quite a few people—more than half a million—walking the streets that don’t know they are HIV+.

At least 70% of the HIV+ people in the developed countries know their HIV status. On the other hand, at least 90% of the HIV+ people in the developing countries do not know their HIV status. The incidence rates reflect these figures!

The stage of infection at which a person presents themselves for testing seems to be later for heterosexuals than homosexual and bisexual men. About 45% of the heterosexual women and men presented when their CD4+ count was below 200—they had full blown AIDS—whereas 38% of the homosexual and bisexual men had a CD4+ count that low.

No form of testing is perfect. Every test can introduce both:

- false positives (testing positive when you are really negative) and
- false negatives (testing negative when you are really positive).

It is essentially impossible to construct a test procedure for which there are neither false positives nor false negatives in all testing situations. Instead, one designs a test either for screening or confirmatory validation. A screening test must catch as many positives as possible, even at the expense of a large number of false positives, whereas a confirmatory test should rarely give a false negative. For these reasons, tests are characterized by their sensitivity and specificity, together with their predictive values as defined below.

\[
\text{Sensitivity} = \text{probability of testing positive when you are HIV+} \\
\text{Specificity} = \text{probability of testing negative when you are HIV−} \\
\text{Positive predictive value} = \text{probability of being HIV+ knowing you tested positive}
\]
Negative predictive value = probability of being HIV– knowing you tested negative

The sensitivity and specificity are the numbers of most interest to test designers and manufacturers. But, the number of interest to an individual being tested is the positive predictive value (PPV). It tells you how likely you are of being positive once you test positive. A high PPV assures you that the results of the test are reliable, while a low PPV indicates the need for further testing. Some comparative values of these parameters indicate their relationship to each other when we assume that the subpopulation to which the person being tested belongs has an HIV prevalence rate of 0.5% (that means about 1 in 200 people in the population are HIV+; very nearly our national infection rate). The values of sensitivity and specificity in the shaded columns were what was seen in the early HIV tests in the late 1980s. Think about the possibility of being tested and told you are HIV+ when the likelihood of that being true is less than 10%.

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>.990</th>
<th>.990</th>
<th>.990</th>
<th>.995</th>
<th>.995</th>
<th>.999</th>
<th>.999</th>
<th>.999</th>
<th>.990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>.900</td>
<td>.950</td>
<td>.990</td>
<td>.900</td>
<td>.950</td>
<td>.995</td>
<td>.900</td>
<td>.950</td>
<td>.999</td>
</tr>
<tr>
<td>PPV</td>
<td>.047</td>
<td>.090</td>
<td>.332</td>
<td>.048</td>
<td>.091</td>
<td>.500</td>
<td>.048</td>
<td>.091</td>
<td>.834</td>
</tr>
</tbody>
</table>

When sensitivity is 0.995, specificity is 0.995, and the incidence rate of HIV is 0.4% (not at all unreasonable numbers), then the results of testing 100,000 people would break down as follows. We classify whether they test positive or not and whether they are positive or not.

<table>
<thead>
<tr>
<th></th>
<th>Test +</th>
<th>Test –</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>398</td>
<td>2</td>
<td>400</td>
</tr>
<tr>
<td>HIV–</td>
<td>498</td>
<td>99,102</td>
<td>99,600</td>
</tr>
<tr>
<td>Total</td>
<td>896</td>
<td>99,104</td>
<td>100,000</td>
</tr>
</tbody>
</table>

The total number of HIV+ people is (0.004)*(100,000) = 400. The number of those that will test positive is (400)*(0.995) = 398. The number of HIV– people that test positive is (0.995)*(100000 – 400) = 498, and the other number follows by subtraction, 99600 – 498 = 99102.

Notice that in this scenario, there are more false positives than true positives for this (high) caliber test. The idea behind a screening test is to be sure that as few positives as possible get through undetected. This forces the relatively higher rate of false positives.

Viewed from another perspective, suppose we have a test, which has a sensitivity of 0.999 and a specificity of 0.996 (a really high quality test). The PPV as a function of the prevalence rate for the subpopulation to which the person being tested belongs is given below.

<table>
<thead>
<tr>
<th>HIV prevalence rate</th>
<th>0.1%</th>
<th>0.3%</th>
<th>0.5%</th>
<th>1.0%</th>
<th>2.0%</th>
<th>5.0%</th>
<th>10.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>.20</td>
<td>.43</td>
<td>.56</td>
<td>.72</td>
<td>.84</td>
<td>.93</td>
<td>.97</td>
</tr>
</tbody>
</table>

It should be clear from this table that the riskier your behaviors, the higher the incidence rate of your subpopulation, and the more likely that a positive screening test which says you are positive is giving you a correct result.

Screening Tests

There are several types of HIV-1 tests: Enzyme-Linked Immunoassay (ELISA), Enzyme Immunoassay (EIA), various types of blot tests, immunofluorescent tests, and viral load tests that measure the number of copies of viral RNA present in the blood. The enzyme-based tests, which test for HIV antibody, have high sensitivity and only moderate to high specificity. The blot tests search for many types of proteins (and there is not a uniform standard as to what constitutes a positive test) and have lower sensitivity, but higher specificity. The viral RNA tests are highly sensitive and highly specific. There are also separate tests for both the p24 and p31 antigens, which are characteristic of HIV. Each of these usually requires more than a day to complete at a laboratory, so that the person being tested must return to get her/his results.

2 Similar results come out of screening tests for illegal drugs. The thought of being wrongfully branded a drug user by an overly sensitive test is a constant and vexing problem.

3 Offered by the European company Waldheim Pharmazeutika GmbH, hence little used in this country.

4 Also called viremia.
Bear in mind that upon infection with any pathogen, there is a lag time (the “window period”) before antibody is produced. For HIV, that could be as long as several months.

The window period extends from initial infection until HIV-specific antibodies reach a detectable level.

The process of generating detectable antibody is referred to as seroconversion. A person who has seroconverted to HIV+ status is said to be seropositive. Only after seroconversion will any antibody test show a positive result—other than a false positive.

Couples of the same serostatus are said to be seroconcordant. Couples with differing serostatues are serodiscordant.

False positives to antibody tests may occur at disproportionately high rates in:
- injection drug users;
- people who have recently been given injections of gamma globulin;
- those recently immunized against influenza or hepatitis B;
- women who have had several children;
- people with liver disease;
- people who have had autoimmune disorders, rheumatological diseases, DNA viral infections, various cancers, leprosy, malaria, infection with Epstein-Barr virus, or alcohol induced hepatitis.

A rare case of a false negative viral load test has been recorded for an HIV+ man with an active, simultaneous cytomegaloviral infection.

The various EIA and ELISA tests can use different reagents to react with and measure the concentrations of: carcinogenic antigen (CEA), sex hormone binding globulin (SHBG), h-insulin-like growth factor binding protein-1 (IGFBP-1), luteinizing hormone (h-LH), thyroid stimulating hormone (hTSH), prolactin, or human chorionic gonadotrophin (hCG). Most of these tests cost around $15–$50. Another test of this form is OraSure which does not use blood but rather oral fluids, saliva, and transmucosal fluid, and it can serve as both a screening and a confirmatory test depending on the reagents used. Its sensitivity is 99.9%.

To improve the patient return rate for screening testing and cut down on the number of people who test positive but never learn their test results, several companies have developed rapid screening tests. The OraQuick test was approved in November of 2002. Using blood from a finger prick, it can provide reliable results in as few as 20 minutes. The previously approved rapid test was the Single Use Diagnostic System for HIV-1, but it was not popular among public health clinics because of difficulties implementing it. Many of the rapid tests return results in anywhere from 10 minutes to one hour. Preliminary data indicate that their sensitivity and specificity are as good as the regular enzyme antibody tests. Hopefully, their introduction will decrease the number of HIV+ people who do not know their HIV status, thus increasing the use of safer sex precautions and resulting in a subsequent decrease of the incidence rate of the disease.
The manufacturer's information for the OraQuick HIV test.

Calypte Biomedical Corp. has formed Sentinel Testing. This involves a rapid turn-around time (3 days after receipt at their lab facilities) for testing of HIV–1 antibody, chlamydia DNA, and gonorrhea DNA using urine! Its sensitivity exceeds 99.9%.

Bio-Rad Labs announced a new HIV assay that can detect the virus (not just antibodies) earlier than other tests. The company’s Genscreen Plus HIV Ag/Ab kit detects both antibody and antigen in a blood sample with a sensitivity of 99.9%. The test can detect all forms of HIV-1 groups M and O, plus all forms of HIV-2. Although approved in France, the company has yet to apply for FDA approval.

As of March 2009, there were 15 commercial HIV-1 antibody tests, 6 commercial HIV-1,2 antibody tests, 1 commercial HIV-2 antibody test, 5 HIV-1 antigen tests, and 19 HIV RNA test that have full FDA approval. A full and up-to-date listing is available at the FDA website.

Confirmatory Tests

The most widely used confirmatory tests have been of either the Western Blot or immunofluorescent types. Blot testing screens for a large number of HIV proteins. HIV is cultured in human cells, which are then ground up and placed on a gel. An electric current is applied and the lightest proteins move the farthest and the heaviest move the least. The result is a series of narrow bands corresponding to the protein molecular weights. Bands corresponding to p17/18, p24/25, p31/32, gp41, p51/52/53, p55, p64/65/66, gp110/120, and gp160 can be detected. Sometimes indeterminate results are obtained at various bands. Additionally, testing methods, reagents, and test criteria are not standardized. Various companies and organizations define a positive Western Blot test differently. Costs are typically $150+ and the time required is ordinarily from 12 to 24 hours at the shortest.

The immunofluorescent tests can detect either antigen or antibody. A control preparation of antibodies labeled with a fluorescent dye is added to a sample. This test has the added advantages of taking about 90 minutes to do in a doctor’s office and has no indeterminate outcomes.

Not all HIV-1 tests will respond properly to either type O HIV-1 infections or HIV-2 infections. Special tests have been designed for patients suspected of having these conditions.

A qualitative nucleic acid assay for HIV-1 RNA has been approved by the FDA and will go on the market in November of 2006 under the brand name Aptima. It will be able to test for viral RNA well before a humoral immune response begins.

The currently available viral load tests, which detect proviral DNA (from which the RNA numbers can be easily inferred), are: AmpliCor, which uses PCR; Quantiplex, which is a banded DNA testing method; and Nucleic

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5 This means that p17 and p18 cannot be easily distinguished
6 The most conservative approach is to define a positive as showing determinate results for p17, p24, gp41, gp120, and gp160.
7 measured in virions per mL. One mL is the same as 1000 mm³.
8 This stands for Polymerase Chain Reaction which is a process that makes copies of genetic material.
Acid Sequence Based Amplification (NASBA) of HIV-RNA. These are a bit pricier, than either ELISA or EIA, at about $160+. Only the Amplicor test is FDA-approved for general use in the US, although many large-scale research groups use the Quantiplex test.

Both the dynamic range and lowest detectable level have been improving. The range of standard viral load tests can go from 400 to 50,000 copies per mL. The lowest currently detectable viral load is 20 copies in so-called ultrasensitive screening, but accuracy at this level is unknown and variability below 400 may be as high as a factor of five! For advanced AIDS cases, tests are frequently “detuned” to provide an extended dynamic range above 50,000 copies. Viral load tests for proviral DNA currently have sensitivity exceeding 99%, while such tests for HIV-RNA have sensitivity ranging from 95% to 98%.

A research group from Johns Hopkins led by T. Sterling developed a test for the p24 antigen of HIV that is highly correlated with outcomes predicted by CD4+ counts and viral loads. The fundamental difference is that this test costs between $20 and $30 versus $80 to $90 for a CD4+ count and $150 to $160 for a viral load test. An additional advantage is that this antigen test kit is more easily stored.

On February 5, 2001, BioTech Imaging Inc. announced a new test for immune cells that are actively producing HIV. The gp120 Tagger Cell Expression Kit is currently undergoing clinical trials. If successful, this test would shed an entirely different light on the production and number of virions in the body as the current PCR Amplicor test counts only viral RNA in the peripheral blood.

Viral load tests are not designed as screening tests even though they have very high sensitivity. A team has reported three misdiagnoses of HIV by these tests (in addition to one other such case). Nevertheless, that remains a very low false positive rate.

If you were going to be tested for HIV, there are several steps to follow. Everyone begins with a screening test, usually ELISA or EIA. If you are not someone who engaged in risky behaviors, e.g., unprotected sex with multiple partners, intravenous drug use sharing needles, etc., then if you test negative, that would be that. On the other hand, if you had engaged in risky behaviors and tested negative, you would be advised to (a) come back for another test in six months to one year and (b) change your behaviors. Anyone who tests positive would be strongly urged to take a second screening test. If that test were also positive, then a confirmatory test would be given. In all cases and for all people, testing should be preceded and followed by counseling. It is imperative that the patient be given all the facts associated with her/his test and test results.

Virus Replication Capacity

Not all versions of HIV were created equal. Like people, some strains are more fit than others. By “fit,” we mean that some viruses are more capable of replication. The less fit the virus, the lower its replication rate and the slower the disease will progress with a slower decline in the CD4+ count and a slower increase in the viral load.

Fortunately, there is a test of replication capacity—in the US, the test is made by ViroLogic and has been available since June 2002. This test is most useful in showing when a virus is becoming resistant to the drug regimen used by the patient. As the virus develops resistance, viral fitness usually—but not always—decreases, and the drug regimen should be changed. Current research is ongoing.

Treatment

Generally, diseases are initially treated by an aggressive induction therapy, which is designed to lower the number and virulence of causative pathogens in the body. Once the reproduction rate of the pathogen is below a predetermined threshold, the dosages of drugs are lowered to levels of so-called maintenance therapy, designed to keep the level of the pathogen low and manageable by the immune system. If the infection resurges, then a major change in medication is called for and salvage therapy begins.

If an HIV patient develops an opportunistic infection, it must be treated immediately and aggressively. In fact, when the CD4 markers fall low enough to indicate the possibility of such an infection, medication in prophylactic dosages is usually given as a preventive measure. Thus, patients are often taking medications when they have no symptoms of disease other than HIV disease. For instance, when a patient’s CD4+ count falls below 400, s/he is considered a candidate for development of *Pneumocystis jiroveci* pneumonia. A prophylactic dose of the antibiotic combination trimethoprim and sulfamethoxazole (TMP-SMZ) is usually started at one tablet of 150 mg TMP/800 mg SMZ once a day with a full glass of water.
A clinical marker of infection by HIV has been the CD4+ T cell count, which has been supplemented by the viral load. CD4 counts are not very predictive of the onset of opportunistic infections and frank AIDS9, but the viral load is a fairly good predictor. Therefore, people undergoing treatment are given frequent viral load tests. Depending on the hospital or physician, a viral load below either 1,000 or 10,000 is considered to be stable. Viral loads between 10,000 and 100,000 mean there is a risk of disease progression and/or opportunistic infections. Viral loads in excess of 100,000 indicate an increased risk of progression to AIDS10. Oddly enough, women tend to develop AIDS at lower viral loads than men, but equally strangely, women have a longer life expectancy once infected.

Drug design is a function of the virus's life cycle. If any one step in that cycle can be broken, then the disease can be controlled. Drugs could be designed to prevent: (a) attachment to a T cell by disabling the protein gp120, or either of the co-receptors CCR5 or CXCR4, (b) fusion of the virus with T cells, (c) reverse transcriptase from being used to transcribe HIV RNA to ssDNA, (d) HIV’s dsDNA from being integrated into the host's DNA using the enzyme integrase, (e) HIV DNA from being transcribed into viral RNA which becomes the genome of the newly made HIV virions, (f) protease from cleaving viral proteins so that new virions can be assembled, and (g) maturation of the newly formed virions (if immature, the resulting virions will remain noninfectious). There are currently four approved (plus several experimental) classes of anti-HIV drugs;

1. **Nucleoside analogue reverse transcriptase** inhibitors (NRTIs or “nukes” in the vernacular), which block the action of the enzyme reverse transcriptase and prevent the virus from transcribing HIV RNA to ssDNA,
2. **Non-nucleoside analogue reverse transcriptase inhibitors** (NNRTIs or non-nukes), which bind directly to reverse transcriptase to prevent its action, and
3. **Protease inhibitors** (PIs), which block the action of the enzyme protease that is used by HIV to cleave proteins into shorter, more useful pieces for reassembly into new mature virions.
4. **Fusion Inhibitors**, which prevents the virus from fusing with the membrane of the T cell.
5. **Entry Inhibitors**, which prevent the virus from entering the membrane of a T cell.
6. **Integrase inhibitors**, which prevent the action of integrase in integrating the viral genome to the cellular genome.
7. **Coreceptor inhibitors**, which prevent viral attachment to a cell.

There is a new class of experimental drugs called **pyrophosphate analogues**, which also block the action of reverse transcriptase. Several coreceptor blockers are also being studied. Clinical trials are ongoing for new fusion inhibitors and positive results have been published.

**As an aside**, you might be wondering how the FDA goes about approving a drug. After initial testing (using animal models or possibly humans), the sponsoring company or research group must perform a series of human tests in three different phases. Phase I clinical trials consist of administering the drug to a group of healthy volunteers in order to determine the mechanisms by which the drug is absorbed, metabolized, and excreted. Phase II clinical trials are designed to determine the efficacy of the drug; volunteers are randomly assigned to treatment and control groups. The treatment group is given the drug and the control group is usually given either a placebo (an innocuous substance with no medicinal effect) or a similar drug. Phase III clinical trials are large scale and usually randomized and blinded. They are meant to determine effectiveness, benefits, and any adverse reactions. Those drugs that pass all three phases can be submitted to the FDA for approval. Sometimes there are also Phase IV trials to monitor long-term effectiveness and impact on patient quality of life, the cost effectiveness relative to traditional and competing therapies, and also to assess the value of the drug with respect to its competitors. Once this sequence is complete, the results are submitted to the FDA for scrutiny and possible approval.

**Monotherapy**, the use of a single drug, is strongly advised against because of the very strong (almost certain) possibility of the development of resistance to the drug by the virus as it mutates. It is recommended that patients take at least a two- or three-drug “cocktail,” possibly including one drug from each of two or three of the major categories. This is called **Highly Active Antiretroviral Therapy** or **HAART**. These treatments can drop the viral load by three and four logs11. Currently, the trio of zidovudine (ZDV), 3TC, and efavirenz is considered to be the best choice for patients who have no experience with antiretroviral medication.

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9 Remember, the CDC defines AIDS among HIV+ patients as having a CD4 count under 200 and/or a specific opportunistic infection such as PCP, wasting syndrome, KS, etc. when you are HIV+.
10 Early after infection, when the viral load is at a maximum and the patient is most infectious, counts in the millions are not uncommon.
11 A log is a factor of 10. Thus, two logs is a factor of 100, three logs a factor of 1000, and four logs a factor of 10,000.
Although HAART has led to decreased viral loads and increased CD4+ counts, there is evidence of continued viral replication in the brain.

Additionally, HIV has managed to develop mutations that resist many of these drugs. When adverse side effects dictate a lowered dosage, the viral load can rise significantly, and drug resistance can increase. Then the drugs may have little effect on the HIV, and an alternative drug regimen is required.

There are three types of drug resistance that can develop:

- **genotype resistance**: the virion mutates (its genome changes) in the presence of the drug.
- **phenotype resistance**: there is an decrease in sensitivity of the virus to the drug, and
- **cross-resistance**: the virion develops a resistance to many drugs within the same functional class.

There are FDA-approved tests for all three types of resistance. Such testing should be done prior to the onset of therapy in order to prevent the introduction of drugs to which the infecting virus may be resistant. The use of such drugs could enhance the resistance of the virus and cause a resurgence in viral load.

The administration of ZDV orally during pregnancy, intravenously during delivery, and to the baby for a short time after delivery can significantly reduce the transmission rate from a high of 16–20% down to at most 6–8%. An experiment done on Thai women indicated that a shorter regime of ZDV is nearly as effective. Other research done in Africa indicates that a much shorter course of nevirapine may be equally effective and significantly cheaper ($15 versus $75), but there are some serious questions concerning this study and this remains highly controversial.

One study tested the trophoblastic outer layer of the placentas of several positive women. No trace of HIV RNA was found, indicating that except in unusual circumstances, HIV is not transmitted to the fetus during pregnancy. More likely transmission occurs slightly before or during the birth process. Thus, adding the requirement that at 34 weeks of pregnancy, delivery is to be done by Cesarean section (after drug treatment) further reduces the risk of transmission to as low as 2%. The current hope is that by following the “best practices,” vertical transmission will be kept to near-zero minimum.

Many patients receiving HAART do not initially respond as well as they should and require changes in their treatment. In fact, 15% of those given PIs must change medications because of the drugs’ side effects. An additional 15% do not respond to PIs at all. Recent numbers indicate that many patients who have been previously successfully treated using PIs are no longer responding to the drugs. For these reasons, initial treatment regimens strive to be PI-sparing.

The optimal or **durable response** is to lower viral load below detection by ultrasensitive test, i.e., < 40 copies/mL, and raise the CD4 count. Factors that decrease the chances of a durable response are:

1. low baseline CD4 count,
2. high initial viral load,
3. prior long-term use of a NRTI or PI, and
4. poor treatment adherence.

On the other side of the coin, there are currently no universally reliable indicators that can assure when treatment will succeed in all possible cases.

Rather than the “hit early and hit hard” philosophy espoused in the late 1990s, federal health officials are recommending delaying treatment as long as possible. The intent is to prevent the cumulative toxicity that can cause major physiological changes in the body.

**Approved Drugs**

The tables below lists the drugs that currently (12/2011) have FDA approval. The abbreviations used are:

- **qd** = *quaque die* = once a day,
- **bid** = *bis in die* = twice per day,
- **tid** = *ter in die* = three times per day,
- **q8h** = every 8 hours,
- **wf** = with food,
- **wwof** = with or without food.

<table>
<thead>
<tr>
<th>Reverse Transcriptase Inhibitors: Nucleoside/Nucleotide Analogues</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage</th>
<th>Considerations and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovir</td>
<td>zidovudine (ZVD or AZT)</td>
<td>300 mg bid, wWof</td>
<td>Joint pain, nausea, headache, weakness, insomnia; bone marrow suppression, anemia, decrease in granulocytes, anemia, anorexia, wheezing, cough.</td>
<td></td>
</tr>
</tbody>
</table>

12 Currently, genotype resistance testing ranges from $800–$1000 and phenotype testing $250–$750.

13 CD4+ count below 350 and viral load above 55,000 using PCR or 30,000 using branched-DNA.
**Reverse Transcriptase Inhibitors: Nucleotide Analogues**

Viread   tenofovir  400 mg, qd, wwof; give 2 hours before or 1 hour after ddI  Nausea, diarrhea, decrease in neutrophils, headache, liver problems, may interact with other antiviral drugs. In particular, it can raise ddI levels and increase risk of side effects

**Reverse Transcriptase Inhibitors: Non-Nucleoside Analogues**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage</th>
<th>Considerations and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viramune</td>
<td>nevirapine (NVP)</td>
<td>200 mg bid, wwof</td>
<td>Lead-in dose is 200 mg once daily for two weeks. Rash, hepatitis. The rash can develop into the severe Stevens-Johnson syndrome that may require surgery and skin grafts.</td>
</tr>
<tr>
<td>Rescriptor</td>
<td>delavirdine (DLV)</td>
<td>2*200 mg bid mixed into water, wwof</td>
<td>Take one hour apart from ddI and antacids. Rash, headache, and hepatitis.</td>
</tr>
<tr>
<td>Sustiva/Stocrin</td>
<td>efavirenz</td>
<td>600 mg, qd at bedtime</td>
<td>Diarrhea, rash, dizziness, irregular sleep patterns, insomnia, abnormal dreams, depression.</td>
</tr>
<tr>
<td>Complera</td>
<td>25 mg rilpivirine, 300 mg tenofovir, 200 mg emtricitabine</td>
<td>1 qd, wf</td>
<td>Depression, mood changes, lipodystrophy</td>
</tr>
<tr>
<td>Edurant</td>
<td>25 mg rilpivirine</td>
<td>1 25 mg pill/day, wf</td>
<td>Depression, mood changes, lipodystrophy, immune reconstitution syndrome</td>
</tr>
<tr>
<td>Intelege</td>
<td>etravirine</td>
<td>2*100 mg, bid, wf</td>
<td>Skin rashes, nausea, vomiting, diarrhea, abdominal pain, headache, peripheral neuropathy; Stevens-Johnson syndrome is possible.</td>
</tr>
</tbody>
</table>

**Protease Inhibitors**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dosage</th>
<th>Considerations and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crixivan</td>
<td>indinavir</td>
<td>2*400 mg tid on an empty stomach or with low-fat snack &amp; not within 2 hours of ddI</td>
<td>Increase fluid intake to prevent kidney stones. Nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, FRAM, elevated triglycerides and cholesterol levels, glucose intolerance.</td>
</tr>
<tr>
<td>Invirase</td>
<td>saquinavir</td>
<td>5<em>200 mg bid with a meal or up to 2 hours after a meal + 2</em>100 mg ritonovir</td>
<td>May not have antiviral activity when taken on an empty stomach. Nausea, diarrhea, headache, FRAM, elevated triglycerides and cholesterol levels, glucose intolerance.</td>
</tr>
</tbody>
</table>

**Considerations and Adverse Effects**

- Tablets must be chewed; powdered form is available.
- Alcohol should be avoided. Nausea, diarrhea, bloating, pancreatic inflammation, peripheral neuropathy.
- Do not coadminister with ddI. Do not use with antacids. Peripheral neuropathy, mouth inflammation, pancreatic inflammation.
- Do not use with antacids. Peripheral neuropathy may be dose-related.
- Should only be used in combination with other agents. Resistance develops rapidly if used as a monotherapy.
- Skin discoloration of palms and soles of feet. Lactic acidosis, enlarged liver, and liver damage.
- Unexpanded tiredness, diarrhea, nausea, and headache
- Hypersensitivity; fever, rash, headaches, stomach upset, malaise, sore throat, cough, shortness of breath; lactic acidosis.
- Lactic acidosis, liver damage, lowered bone density, kidney impairment.
- Lactic acidosis, kidney impairment and possible bone, central nervous system side effects, potential for birth defects
- Nausea, diarrhea, skin rash, fatigue, GI upset, respiratory symptoms, lactic acidosis, severe liver problems, anemia, decrease in neutrophils, disorders of skeletal muscles.

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14 This class of drugs does not seem to be effective against HIV-2.

15 The drug Fortovase, which is saquinavir with a different coating, has been discontinued by the manufacturer due to significantly decreased demand.
Despite the number of drugs available for treatment, only about seven or eight 3-drug regimens (“cocktails”) are available due to the development of viral resistance.

Not all drug research ends with the development of a new weapon against HIV disease. Drug manufacturers have their fair share of “dry wells.” Many drugs fail to make it through Phase II clinical trials and others are approved but later removed from the market because of significant long-term adverse reactions.

As an example of adverse effects, a study from Australia indicated that 18–76% of the people on protease inhibitors will develop what used to be called **peripheral lipodystrophy**, wherein they lose subcutaneous fat from their extremities and add visceral fat to the trunk, particularly the breasts, the abdomen (called a **“Crix belly”** or **fuzeon** injection 90 mg bid, wwoff; as determined by Monogram Bioscience’s Trofile)

<table>
<thead>
<tr>
<th>Prodrug Name</th>
<th>Dosage</th>
<th>Considerations and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vincent</strong></td>
<td>raltegravir</td>
<td>400 mg bid, wwoff, must be taken with other anti-HIV meds</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td><strong>Dosage</strong></td>
<td><strong>Considerations and Adverse Effects</strong></td>
</tr>
<tr>
<td><strong>Amarina</strong></td>
<td>raltegravir</td>
<td>Nausea, headaches, tiredness, weakness, trouble sleeping, stomach pain, dizziness, depression, suicidal thoughts and actions; rash, severe skin reactions, anxiety, paranoia, low platelet count, diarrhea, liver failure</td>
</tr>
</tbody>
</table>

16 The manufacturer has decided to discontinue production of Agenerase by the end of 2007, due to the success of its other protease inhibitor combination drug Lexiva.
“protease paunch”), or on the back between the shoulder blades (called a “Buffalo hump”). Other metabolic disorders are concomitant with antiretroviral therapy. The study also reported that 16% of the subjects had impaired glucose tolerance, which can lead to symptoms of diabetes. These metabolic abnormalities have not been fully characterized, nor are they restricted to the use of protease inhibitors. Cases have been reported for people on other anti-HIV drugs too. A suggestion was made to call the syndrome FRAM, Fat Redistribution And Metabolism. This is reasonable because there are three separate problems: peripheral lipoatrophy, truncal accumulation of visceral fat, and various metabolic disorders. FRAM has been tied to mitochondrial toxicity of the antiretroviral medications.

The following pictures are taken from the October 29, 1998 issue of the New England Journal of Medicine’s section Images in Medicine.

What you see is someone whose fat levels in the arms and legs have dropped precipitously, while s/he has developed fatty deposits around her/his trunk and abdominal organs. This is not the usual subcutaneous fat that lies below the skin and above the muscles, but rather visceral fat that lies around the vital organs. Some people have a small fat pad on the back of their neck, but the man above has a much more pronounced accumulation. Normal activities like sleeping on one’s back or holding the head erect are significantly impaired by such a protrusion. Sometimes either liposuction and/or surgery are used to remedy the Buffalo hump. Liposuction is not usually a viable option for removal of visceral fat.

A form of growth hormone, Serostim, has been shown to have a statistically significant effect on reducing FRAM-type body habitus symptoms. The flip side to this coin is that Serostim is being counterfeited and sold at a huge markup. Needless to say, the fraudulent version does not have the full therapeutic effect of the real thing.

Reports beginning in 1999 tied antiretroviral therapy (nukes, non-nukes, and PIs) to increases in both cholesterol and triglyceride levels. These increases have been associated with cardiac problems, including heart attacks. Further research has found statistically significant increases in cardiac problems among PI users.

The drugs ddI and/or d4T have been given in combination with hydroxyurea, which enhances their effect, mitigates the effects of drug resistance, and allows somewhat reduced dosages with a concomitant reduction in side effects. Hydroxyurea also inhibits the production of HIV in macrophages, quiescent lymphocytes, and dendritic cells. Intermittent treatment with interleukin-2 (IL-2) appears to counteract the toxic effects of the hydroxyurea, so that CD4+ cell counts are maintained. This is especially beneficial to patients who have failed previous regimens. Mycophenolic acid has a similar effect with abacavir. Recent research indicates that the rheumatic drug leflunomide has a similar effect with zidovudine.

Another drug, resveratrol, seems to have similar effects as hydroxyurea, but with fewer adverse reactions. Efavirenz and abacavir can cross the blood-brain barrier and have been shown to reduce the viral load in the cerebrospinal fluid (CSF). This raises some hope that there is a possibility that AIDS dementia can be arrested and some studies have shown this to be the case.

Abacavir can lead to such severe hypersensitivity reactions that death can result. The reactions usually begin after six weeks of taking the drug and symptoms mimic those of any viral infection, thus making diagnosis difficult. There is a genetic test that can be used to determine if a patient will become hypersensitive and many physicians are using it before prescribing the drug. Once abacavir is discontinued it should not be restarted because of a possible

17 Serostim also adds lean muscle mass. Hence, it has become an underground favorite among bodybuilders.
hypersensitivity reaction which can be life-threatening. One death due to rechallenge with abacavir has been reported in France.

It is known that suboptimal doses of any antiretroviral drug can lead to HIV mutations that can replicate better than the wild type virus. Two phases of evolution of the virus can occur: in the first phase, the HIV changes in only one or two nucleotides and the drug seems to be doing what it was intended to do. In the second phase, there is a five or six nucleotide difference from the wild type virus. This new form does not show increased drug resistance, but it does show an increased efficiency of protease and a concomitant increase in the replicative capacity of the virus. Thus the fitness of the virus improved as a stronger variant was selected for by these changes.

These antiretroviral drugs together with others have had a remarkable effect on HIV-infected patients. There has been a marked drop in the number and intensity of opportunistic infections. The following graph clearly illustrates this decline in number.

![Graph showing opportunistic infection rates](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>PCP</th>
<th>Mycobacterium avium complex</th>
<th>Esophageal candidiasis</th>
<th>CMV retinitis</th>
<th>CMV disease</th>
<th>KS</th>
<th>Extrapulmonary cryptococcosis</th>
<th>Toxoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>2001</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

Some Good News
A 2006 study\(^\text{19}\) of 68,669 New York residents with HIV disease discovered that between the years of 1999 and 2004, 26.3% died of causes other than the virus. Simple arithmetic tells us that 73.7% of the infected group died from HIV disease. Considering that as few as 10 years ago, this infection killed almost everyone who had it, this is very good news indeed.

Of deaths from other causes, 31% were a result of substance abuse, 24% cardiovascular disease, and 20% were non-HIV related cancers. Similar numbers have been found in a study conducted in the United Kingdom.

As Yet Unapproved Drugs

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There are a large number of drugs currently in testing. These drugs fall into several categories that attack the virus at different points in its replicative cycle, some of which are:

- nucleoside analog reverse transcriptase inhibitors
- nonnucleoside analog reverse transcriptase inhibitors
- nucleotide analog reverse transcriptase inhibitors
- protease inhibitors
- integrase inhibitors
- attachment inhibitors
- coreceptor binding inhibitors
- fusion inhibitors
- uncoating protein inhibitors
- capsid protein polymerization inhibitors
- assembly protein inhibitors
- small interfering RNAs

This large array of new approaches to defeating HIV should give cause for hope if even half of the drugs/methods currently under research are brought to the market.

**Drug Interactions**

Another significant problem is the interaction of various drugs (not just anti-HIV drugs). Some work together to enhance their effects and others retard their effects. The number of possible combinations is quite large and great care is needed to avoid worsening current side effects, and/or weakening the antiretroviral activity. Currently, software is available to check on these interactions—at least those that have been reported to the manufacturers and listed with the FDA.

As an example, in December of 2004, a warning was issued not to take the stomach-acid-reducing drug Prilosec while on a regimen of either atazanavir or ritonavir. Such a drug combination reduces the effective dose of the antiretrovirals by a bit more than 75%. Interactions between ritonavir and nasal sprays containing fluticasone can be especially serious.

There are also synergistic effects between drugs and common foods, most notably grapefruit juice—which enhances the effects of many drugs. On the other hand, test tube studies of the widely used (in Africa) herbs African potato and Sutherlandia showed interference with non-nukes and protease inhibitors.

For those suffering from indigestion, it might not be a good idea to take either Mylanta, Rolaids, or Tums, as they can decrease the levels of some HIV medications when taken together. The drug labels carry warnings to this effect.

Some herbs, most notably the widely used mildly antidepressant St. John’s wort, lower the efficacy of many anti-retroviral drugs. Garlic capsules stop the action of saquinavir and it is likely they have the same or a similar effect on other protease inhibitors.

Many websites are available to check such interactions. Software can be downloaded for pocket digital assistants to do these searches for patients and/or physicians.

**Other Drug Notions**

Drugs in the body react and decay to the point where they are no longer effective. A measure of this decay is the **half-life**. A drug with a half-life of one hour will operate at only 50% of its maximum activity after one hour, 25% (= (1/2)^2) after two hours, 12.5% (= (1/2)^3) after three hours, and so on. The longer the half-life of a drug, the less often it needs to be taken. Zidovudine has a half-life of about an hour, while efavirenz has a half-life of seven to eight hours thus allowing a twice-daily dosing schedule. Some experimental drugs have half-lives exceeding 15 hours, so that once daily dosing is possible without using timed release processing.

The ultimate goal of any dosing schedule should be the maintenance of a near constant therapeutic level of the drug. In actuality, the level rises and falls. The lowest level is called the **trough level**. The trough level must be high enough to be therapeutic, lest the virus mutate and develop resistance to the drug. The maximum level should not be so high that side effects become overwhelming.

The following figure shows the enhancing effect of low-dose ritonavir (RTV) on indinavir (IDV). Medicating with indinavir by itself shows a highly variable concentration that lies just above the effective concentration at its trough level and increases by about a factor of 15 to its maximum level. The addition of ritonavir smooths the curve,
Drug resistance is particularly problematic for the treatment of HIV disease because of the relatively small number of available drug combinations. Viral resistance occurs in 30–50% of the patients on HAART. Once a patient shows a resistance to an NNRTI, it is very likely there will be cross-resistance to all NNRTIs. The Swiss cohort study assigned people on HAART to four groups according to their viral load and CD4 count.

- 40% of the subjects showed a decreasing viral load and an increasing CD4 count (that’s very good);
- 40% showed ongoing viral replication and an increasing CD4 count (fair);
- 5% showed viral suppression with a steady low CD4 count (also fair); and
- 15% were treatment failures, showing high viremia and low CD4 counts (not good).

Study of the mutations has proceeded, insofar as it is now known at what codons the mutations for most of the individual drugs occur. Several rather expensive tests for drug resistance are available20. Such tests are of value for determining which drugs not to give. For instance, a single mutation of the RTI gene of HIV confers a high degree of resistance to 3TC and/or nevirapine, whereas multiple mutations of the protease gene are required for resistance to protease inhibitors.

The difficulty of maintaining a HAART regimen is hard to imagine. An anonymous letter to the editors of POZ magazine (accessible in part at theBody) published way back in July 1998 brings a few of the problems to light.

The portrayal of the HIV positive physician’s assistant, Jeanie Boulet21, on the TV show ER is very unrealistic. She is on Crixivan, the protease inhibitor hardest to take, but has only ever taken one dose on the show. A more realistic picture of Jeanie’s day: Wake up by 5 am. Take Crixivan, take a shower, withstand nausea for at least one hour, take other meds at 6 am. Eat breakfast. Go to work around 7 am. Once there, spend a lot of time at the water fountain or carry around a bottle of water. Lunch at 11 am (barring any emergencies), then take other meds and finish by noon so that at 2 pm she can take her next dose of Crixivan. Jeanie had better hope none of the good-looking residents asks her out to lunch, as she’d have to explain that she has to be finished eating by noon or her dosing for the day will be messed up. The same goes for any dinner dates. When not drinking water, eating meals or taking her reverse transcriptase inhibitors or Crixivan, Jeanie would be on her way to the rest room. Where would she find time to see patients?

It is worth using the data in the previous tables to calculate the number of pills a patient might have to take each day. Suppose the doctor recommends the regimen consisting of ddl, delavirdine, and ritonavir. ddl must be taken twice a day on an empty stomach, four pills of delavirdine must be taken twice a day one hour away from ddl, six pills of ritonavir must be taken twice a day. All tolled, that is 22 pills. Recently released drugs have gotten this down to one or two pills for HIV each day. In addition, the patient would have to take prophylactic medications such as TMP-SMX (one twice a day), isoniazid (one per day), clarithromycin (one or two twice a day), and fluconazole (one four times a day); for an additional five or more pills per day. This daily number of pills one needs to take can be

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20 Such tests take as long as four weeks to complete and genotype testing costs from $250–$750, while phenotype testing costs from $800–$1000 per test.

21 She is no longer part of the program.
absolutely overwhelming. 6 or 8 on the low side to a high of around 60, for those with multiple opportunistic infections. That’s about a small plastic lunch bag filled with medication. Bear in mind, these pills must be timed with respect to meals, feelings of major nausea, and each other. Some must be taken with a high fat meal. By “high fat meal,” they mean a minimum of 28 grams of fat. That’s about half of a normal person’s daily allowance of fat! Despite all these caveats, when it works, HAART can drive viremia down to undetectable levels, < 400 copies/mL. It can even force the viral load below the threshold of the ultra-sensitive tests, < 40 copies/mL.

Back in 1998 scientists reported on the detailed analysis of T cells of patients on highly active antiretroviral therapy, HAART, whose CD4 count rose significantly. The bad news was that this increased count consisted mostly of severely damaged T cells that did not function to their full potential. Only for children (they have fully functioning thymus) were the T cells fully functional. This throws cold water on any hopes of reviving the immune system for HIV patients by using the current crop of drugs. Even worse news was announced on the next day of that same conference. There was a report of an infection with a multiply drug resistant subtype of HIV–1 in a man who was antiretroviral naïve, i.e., he had never had any antiretroviral therapy. Since such an infection can be spread from person to person, it bodes ill for the future of the epidemic when people with a mutated version of the virus are having unprotected sex and spreading a resistant strain of the virus. This is as bad as the 1997 report of a variant of Yersinia pestis with a resistant plasmid, but it too was not unexpected. Since 1998, there have been very many reports of such transmission, including vertical transmission, of these so-called recombinant forms of HIV. In fact, nowadays such forms of the virus are rarely met with surprise.

The crucial question remains, is it possible to completely destroy all the HIV in the body by using HAART? Since early in the infection, before seroconversion, HIV-1 populates latent cellular and anatomical reservoirs, drug therapy cannot affect this population of virions. The virus can enter, gain control of the cellular DNA, and remain somewhat dormant in memory or so-called resting T cells, macrophages, follicular dendritic cells in the lymph nodes, the central nervous system, and possibly the testes. They are seeded with the wild type virus and normally do not contain any mutated strains. At present it is unclear if there are any other latent reservoirs in which HIV can hide. Nor is it known for how long the virus (or provirus) can remain hidden while HAART continues. Some scientists have suggested times on the order of several years. Research (May 1999) suggested that for a reservoir of 100,000 virions it could take HAART as long as 60 years to wipe out the virus! Several suggestions have been advanced for “flushing” the reservoirs to accelerate the viral destruction. A study by Fauci and his colleagues on patients using HAART together with interleukin-2 to flush out the virus was made. Two groups were analyzed; the first received HAART and IL-2, while the other received just HAART. Both groups were taken off HAART and the results were identical. The virus rebounded for both groups. This dealt a critical blow to the concept that the virus can be eliminated from the body using the currently available drugs. Further research has reinforced this pessimistic view. More recent work showed a significant positive effect when IL-2 was used together with HAART.

Adherence to the dosing schedule has also become problematic. Those who fail to maintain their drug schedules can rapidly develop resistant strains of the virus, which can then be transmitted to others. Furthermore, once a patient becomes resistant to a drug, the medical options available for treatment decrease markedly. Currently, we are seeing a significant number of people for whom HAART is no longer effective due to resistance developed because of nonadherence. Research published in November of 2002 reported that patients having problems with fat redistribution and metabolism, FRAM, usually fail to follow their drug regimen because of their negative feelings about their physical appearance in this state.

A current area of research is Structured Treatment Interruption (STI), whereby AIDS patients that have been on HAART and have had an undetectable viral load for a significant period of time are taken off almost all antiretroviral medications. Some people can maintain their low viral load for as long as a year. This gives significant relief from the adverse effects of the medications.

A disturbing epidemiological report said that sexually active patients on protease inhibitors were 2.5 times more likely to engage in unprotected sex, than those not taking PIs. Those being treated with PIs were also more likely to report that they “never” used condoms during intercourse. This result has been reinforced by other research. “Riding bareback” seems to be gaining in popularity among young white gay males. Data from San Francisco indicate that the incidence rate among young gay males has doubled.

Data from the year 2000 showed an increase in the rates of infection among young (age 23–29) urban gay males in the six cities sampled (Baltimore, Dallas, Los Angeles, Miami, New York, and Seattle). The disturbing news was that among this cohort 30% of African-Americans, 15% of Hispanics, 7% of non-Hispanic whites, and 3% of Asian-

22 A Big Mac has 34 gm of fat and a large fries has 26 gm of fat. That’s a “happy meal” your cardiologist would hate.
Americans were infected. Fully 12.3% of urban gay men are HIV+ (with rates ranging from 4.7% in Seattle to 18% in Dallas) and only 29% of them were aware of their serostatus.

Problems associated with medication could be greatly reduced if there were a vaccine against HIV. Unfortunately, the prognosis for a successful vaccine is not very good, due to the high mutation rate for the virus. Past vaccines for various diseases have contained either a killed virus or a live but attenuated virus. Many scientists feel that a live virus vaccine is too dangerous to test. [Would you volunteer for a test with a live virus vaccine?] One suggested live virus vaccine, which was to begin clinical trials, had four of HIV’s nine genes disabled. Researchers who have done this with other viruses had warned of the “certainty” of infection, while others disputed this. Pretrial vaccination of monkeys resulted in their infection, so the trial was canceled. Many other types of vaccines are in clinical trials, but results are not expected for quite some time. Still other research is looking for ways to enhance the immune system’s ability to fight the virus, but no concrete results are available. This is a difficult problem whose solution has so far eluded all that have sought it. A United Nations report projected a minimum of ten years until a usable vaccine is available.

Unlike HIV, it seems that various types of the sexually transmitted Human Papilloma Virus (HPV) are amenable to immunization. An announcement in April of 2005, indicated a 90% successful vaccine, Gardisil, against HPV 16 and 18, which cause 70% of all cervical cancers, and HPV 6 and 11, which cause 90% of all cases of genital warts. Shortly thereafter, a second such vaccine, Cervarix, was shown to be successful in clinical trials. Both vaccines have received full FDA approval. At present, there is a push by Merck, the manufacturer of Gardisil, to have men immunized to prevent genital warts.

Diet

It is surely the height of folly to assume that the anti-HIV medication alone will be sufficient to maintain a Person Living With HIV/AIDS (PLWHA) in a state of health. A patient’s meds are only a microscopic part of their daily oral intake. Eating is fundamental to life and for someone who is HIV+, it needs to be approached with considerably more than the usual degree of care. The disease makes one susceptible to infections with which non-immune-suppressed people rarely have problems. The biochemical mechanisms of the virus deplete the body of certain nutrients; also PLWHA frequently suffer from intestinal malabsorption and/or reduced food intake due to decreased appetite from the gastrointestinal effects of their drug regimen.

The first aspect of nutrition to which an HIV+ person must attend, is the safety of the food and drink they ingest. Most food, when left unrefrigerated, can become the ultimate Petri dish for growing cultures of all manner of bacteria—benign and pathogenic. For this reason, all prepared foods should be carefully covered and refrigerated. Do not store milk- or raw-egg-based foods in the refrigerator for longer than one week. When serving all foods, especially dairy products or egg-based foods, always use a clean serving spoon. Putting a spoon you have used into a food container will contaminate the food and produce major bacterial growth!

Drinking water should be tested for contaminants, in particular, volatile organic hydrocarbons. Facing a viral onslaught is enough of a problem without additional unwelcome chemical additives.

Some nutritionists would insist on using purely organic foods, but this is currently an unproven expense that very few can afford. With the new Department of Agriculture guidelines for organic foods, pricing may change as the market for certified organic foods increases.

One well-established nutritional fact is that many small meals are better than a few big meals. Besides breakfast, lunch, and dinner, one should have a balanced small snack about an hour or so before dinner and another an hour or so before bedtime. The total caloric intake of these five “meals” should not be higher than your usual three meals, unless there has been a recent significant weight loss. If possible, before each major meal, drink one 12-ounce glass of water.

Avoid caffeinated drinks, artificially sweetened foods and drinks, fried foods, refined sugars including high fructose corn syrup (which seems to be added to an astonishing number of prepared foods), and foods high in saturated and/or hydrogenated fats (also called trans fatty acids).

A well-balanced diet derives roughly 40–60% of its calories from carbohydrates, 20–30% from protein, and 20–30% from fats, mostly monounsaturated. A person living with HIV/AIDS should eat potatoes, rice, and pasta sparingly. Instead, they should get their carbohydrates mostly from green vegetables, whole grains, uncooked fruit, and other high fiber foods. Wisdom suggests avoiding products like Ensure because of their high carbohydrate and sugar content.

All meats eaten should be as lean as possible. One needn’t buy the most expensive super lean cuts; rather carefully trim what you buy. As a simple example, when preparing ground beef, drain off all the grease. If they want to be extra careful, flush the well-cooked ground meat with boiling water to remove any remaining grease. For protease inhibitor containing drug regimens, lipid management is of vital importance.
A vegetarian diet is not to be avoided so long as you take sufficient calcium and vitamin B₁₂ supplements.

If appetite does not allow a PLWHA to maintain a healthy diet, the use of supplements may be in order. Protein can be added to many dishes by using either powdered soy- or whey-protein isolates high in branched-chain amino acids. Daily snacks can be made from almonds, walnuts, or flavored lentils. Soy-based drinks are preferable to milk.

Except for ddI (Videx) and efavirenz (Sustiva), all anti-HIV meds can be taken with food. If necessary, eat part of the meal, take the meds, and then finish the meal.

Vitamin supplements may be necessary, but one must take care, because there are so-called Upper Tolerable Limits (UTLs), beyond which there may be some adverse effects. Also, acid-producing supplements should be taken in a form that minimizes the production of digestive acids. For instance, Vitamin C can be purchased in an ester form that is much gentler for the stomach. Vitamin E is available in a dry form as alpha-tocopherol succinate for those who react poorly to oily food.

Some PLWHA have digestive difficulties, leading to either diarrhea or constipation with a dark oily stool. This is usually a result of a decrease in the normal flora in the GI tract. There is a simple remedy—probiotics. These are capsules of carefully prepared species of the bacteria that usually populate the gut. Seek out enteric-coated capsules, so the stomach acids don’t kill all those friendly microbes before they reach their destination. Also, take them with meals only. It is recommended to start with one a day and taper off from there.

As for other supplements, there is some research indicating value to the use of pre-vitamin A as beta carotene, vitamins B₁, B₂, B₁₂, biotin, vitamin C, vitamin D, vitamin E, coenzyme Q10, calcium together with magnesium, selenium, zinc, carnitine, cysteine, and glutamine. The last three amino acids are used to prevent the mitochondrial toxicity associated with many of the antiretroviral meds. Some experts recommend the herb milk thistle, whose active ingredient is silymarin, if liver tests are out of the normal range. In all cases, a registered nutritionist specializing in HIV-disease should be consulted to determine the necessary dosages. Current research has found dietary deficiencies in PLWHA, but it is unclear whether these are markers for disease progression or causes of it. Much remains to be done.

Although a PLWHA may not feel like engaging in major physical activity, exercise is fundamental to wellness for all people. It may be a good idea to combine exercise and meditation in the forms of qigong, taijiquan, and/or hatha yoga. These involve slow, no-, or low-impact moves that can have major positive health benefits.

Higher intensity aerobic exercise, such as bicycling, brisk walking, jogging, etc., is also recommended for those who are able. As usual, one should always start easy and slowly work your way up to the exercise regimen that has been recommended.

There is evidence that religion, in all its forms, may play a role in maintaining or enhancing the well-being of PLWHA.

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23 Too little or too much Vitamin A can be bad for the patient.
24 The latest recommendation is 1000 units of Vitamin D each day.
25 For patients taking amprenavir (a component of Lexiva), additional Vitamin E is not a good idea. This is because a daily dose of the drug contains over 1700 IUs of the vitamin which currently has a UTL of 2000 units.
Calanolide is derived from the bark of tree found in the rainforest in Sarawak, in Malaysian Borneo.