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I ANTI-HIV AGENTS

A. Starting therapy: study finds guidelines linked to level of immunity

The immune system has a number of ways of dealing with HIV-infected cells:

- It can physically destroy the cells.
- It can release chemicals that block the ability of infected cells to produce new viruses.

This second function is largely performed by a type of immune cell called CD8+ cells. These cells can produce antiviral chemicals that are non-toxic to healthy cells and have the potential to clear HIV from infected cells. Although much research is underway to identify the chemicals produced by CD8+ cells, so far no research team has been able to find out what they are. However, at least one research team suspects that by releasing these antiviral compounds, CD8+ cells may also play a role in preventing HIV infection in some people exposed to the virus.

Researchers at the University of California at San Francisco (UCSF) have been working for more than a decade to try to identify and understand how the naturally produced antiviral substances work. In one study, they found that the immune system is usually able to maintain production of the antiviral compounds for the first 10 years after a person becomes HIV positive. In general, by the time HIV positive people develop AIDS-related symptoms and levels of CD4+ cells fall, production of antiviral substances has also decreased.

In their latest study, the UCSF researchers studied 20 healthy subjects who had been HIV positive

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for at least 10 years. The purpose of the study was to find out if there was any link between production of natural antiviral substances by CD8+ cells and CD4+ cell counts.

Study details

Researchers recruited 20 male subjects who were free from symptoms of AIDS. Eighteen of the 20 subjects had never used anti-HIV therapy nor was anyone currently receiving such treatment. Technicians analysed blood samples from subjects for CD4+ cell levels and the ability of CD8+ cells to produce antiviral substances.

Results

In general, researchers found that subjects could be divided into two groups:

- those with fewer than 300 CD4+ cells
- those with more than 300 CD4+ cells

Key findings from the study were as follows:

- Subjects with higher CD4+ cell counts were more likely to have higher CD8+ counts than subjects with low CD4+ cell counts.
- The amount of virus in the blood (viral load) of subjects with high CD4+ counts was relatively low (4,000 copies) compared to subjects with low CD4+ cell counts (26,000 copies).
- Subjects with more than 300 CD4+ cells produced significantly less antiviral substances than subjects with lower CD4+ cell counts.
- There was a trend for subjects who had low levels of antiviral substances to have high viral loads.

In this study, researchers found that the immune systems of healthy HIV positive subjects who had fewer than 300 CD4+ cells were significantly less able to suppress HIV than similar subjects who had more than 300 CD4+ cells. These findings provide, according to the research team, “immunologically based evidence” that supports current treatment guidelines. The findings may also be another factor to weigh when making decisions about the timing of anti-HIV therapy.

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II ANTI-CANCER AGENTS

A. Recurring cervical growths

HIV positive women are at increased risk for the development of abnormal growths on their cervix. These growths are caused by infection with human papilloma virus (HPV), a sexually transmitted infection. In some cases, the growths regress or shrink without treatment. In other cases, the growth may become cancerous. Regular Pap smears and gynecologic examinations are therefore an important part of health care for HIV positive women.

Abnormal cervical lesions can be dealt with in a number of ways, including the following:

- laser therapy
- zapping with an electric current
- surgery

However, abnormal growths on the cervix can recur. To compare the recurrence rates among HIV positive and HIV negative women, researchers in Forth Worth, Texas, conducted a study. They found that recurrence rates were significantly greater in HIV positive women.

Study details

Researchers reviewed medical records of 43 HIV positive and 103 HIV negative women, all of whom had been diagnosed with abnormal growths on their cervix. Subjects who had cancer or who had previously undergone a hysterectomy were not included in this study. All subjects who had abnormal growths detected on their cervix (either by Pap smears or biopsy) were initially treated with laser therapy, liquid nitrogen or surgery. Other measures, such as hysterectomy or “cold knife” surgery, were only used if less-invasive therapy failed.

Forty of the 43 HIV positive women were taking combination anti-HIV therapy. Their average CD4+ count was 340 cells. Viral loads were available from the records of 30 subjects. In 19 subjects, the average viral load was about 19,000 copies, while in the remainder it was below the 500 copy mark. Data was collected between January

1996 and December 2000. All subjects were monitored for at least two years.

Results

In general, regardless of treatment, the recurrence of cervical growths was nearly four times higher in HIV positive women than in HIV negative women. In six HIV positive women, hysterectomy was performed because of recurring cervical growths. In three of the six women, precancerous cells were found to have spread into the vagina. No subject died while in this study.

Researchers found that women who had fewer than 200 CD4+ cells often had a higher rate of recurrence of abnormal growths on their cervix compared to women who had higher CD4+ cell counts.

This study highlights the need for HIV positive women to receive regular gynecologic care. It also reveals the need for therapies that can improve the immune system's ability to control tumours.

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III SIDE EFFECTS

A. Study finds problems with reporting side effects

Drugs are first tested in clinical trials to assess their safety and effectiveness before being approved for sale. However, not all side effects caused by drugs — adverse drug reactions (ADRs) — are identified in clinical trials. Indeed, in one study, a large proportion of ADRs was not detected before drugs were approved for sale.

The limitations of clinical trials to detect *all* serious ADRs has made clear the need for effective systems to confirm and extend the data captured in clinical trials with approved drugs. Such a system in which side effects are monitored *after* a drug has been licensed is called post-marketing surveillance. Because drugs used to treat HIV/AIDS have often been placed on the fast-track for approval, perhaps it is not surprising that the flip-side of this process may be that more side effects are noted once drugs are approved.

Health authorities in Western Europe and North America have different ways of conducting post-marketing surveillance. One aspect of such a system can involve patients who, upon developing ADRs, document and report them. To date, most studies on ADRs apparently do not directly involve reporting from patients to regulatory authorities.

Researchers in Scotland conducted a study designed to develop a method for patients to report symptoms that they believe were caused by a prescribed drug. Although none of the drugs in the study are used to treat HIV infection, it may be useful reading for regulatory authorities who are interested in improving the current system for capturing data on ADRs. The researchers also checked patients' medical records to compare symptoms recorded by the their physicians. According to the researchers, their results suggest that "patients do not report all symptoms they suspect to be ADRs to their general practitioner (GPs) and GPs do not record all symptoms which may be reported to them."

Study details

Standard questionnaires were developed to help capture and classify information about ADRs. The questionnaires were tested in a pilot study and validated. Primary care doctors were contacted and about 2,300 of their patients were enrolled in this study. The drugs that patients were questioned about included four antidepressants, three anti-seizure drugs and two others used for pain relief.

Results

Researchers obtained a response rate of about 36% to their questionnaire. Most respondents were female (66%) and their average age was 51 years old. Half of respondents stated that they were taking between two and four prescribed medicines.

In reviewing 310 medical records and the completed questionnaires, researchers found that in 70% of cases the drug(s) that patients stated they were taking was not recorded in their charts. Other results were as follows:

- Analysis of the completed questionnaires found that 55% of the symptoms reported were "possibly" caused by the drugs studied.
 - About 43% of patients reported that their symptoms were severe or very severe.
 - The researchers found a significant level of under-reporting of ADRs to regulatory authorities.
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The researchers concluded that “patients are most likely to report genuine symptoms which have a high probability of being drug-related.” Moreover, they added that “patient reports of ADRs may be of value for post-marketing surveillance since the symptoms reported were seldom unattributable to drug therapy.”

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B. Male sexual dysfunction and HAART — the confusion continues

The use of highly active antiretroviral therapy (HAART) has extended the survival of people with HIV/AIDS (PHAs) who can adhere to and tolerate these medications. As PHAs live longer, issues related to quality of life begin to have more importance. One of these issues is sexual dysfunction. Most studies in PHAs dealing with this subject have been on males. For details about a study that included both females and males, please see *TreatmentUpdate 120*.

A problem interpreting the results from some of the sexual dysfunction studies is that they do not always take into account certain factors which can cause sexual dysfunction, including the following:

- nerve damage
- less-than-normal levels of testosterone/estrogen
- diabetes
- anxiety
- depression
- nutritional deficits

The number of drugs, both prescription and recreational, that have been linked to sexual dysfunction is large. Below is a brief list of some classes of such drugs:

- drugs for high blood pressure
- drugs for high cholesterol and triglycerides
- antidepressants
- tranquilizers
- anti-ulcer drugs

- hormones
- anticancer drugs
- antiseizure drugs
- recreational drugs — alcohol, cocaine and marijuana

Because of the previously mentioned conditions, as well as the wide variety of drugs that can cause sexual dysfunction, trying to find the cause of this problem in PHAs who are taking many drugs is not an easy task. In this issue of *TreatmentUpdate*, we review two studies on male sexual dysfunction in subjects who were taking HAART. In reading the results of these two studies, it is worth noting that in the time before HAART several studies found a relatively high level of sexual dysfunction — between 53% and 67% — in HIV positive men.

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C. Sexual dysfunction in men: A report from Boston

Study details

Researchers at a number of care facilities in Boston reviewed medical records of HIV positive men whose data were recorded between January 1993 and November 1998. In searching through the records, the researchers focused on 254 adult males who used protease inhibitors (PIs) and who had the following profile at the start of the study:

- average age – 37 years
- about 82% of subjects had fewer than 200 CD4+ cells
- the same proportion of subjects had viral loads greater than 10,000 copies

The following PIs were used by the proportion of subjects listed:

- indinavir (Crixivan) – 62%
- nelfinavir (Viracept) – 46%

- ritonavir (Norvir) – 46%
- saquinavir (Invirase) – 41%

Importantly, some subjects also had pre-existing conditions which placed them at risk for sexual dysfunction, including the following:

- depression – 35%
- high blood pressure – 14%
- alcohol abuse – 12%
- diabetes – 7%

Results

In reviewing their data, the researchers found that 32% of subjects had been diagnosed with sexual dysfunction. According to the data analysis, here are the key findings:

- When taking into account such factors as age, depression, alcohol abuse, high blood pressure and diabetes, the use of protease inhibitors in general was linked to sexual dysfunction.
- Among specific PIs only ritonavir was significantly associated with sexual dysfunction.
- At first it appeared that the nucleoside analogue 3TC (lamivudine, Epivir) might also have been associated with sexual dysfunction. But when researchers adjusted their data for some subjects having high viral loads between the years 1996 and 1998, 3TC was no longer linked to this problem.

The major drawback of this study is that it involves looking back at information captured for a different purpose, in pre-existing medical records. This type of retrospective study is not as useful as a study designed from the outset to monitor the level of sexual dysfunction in subjects over time.

At the time the subjects would have been using ritonavir; in the late 1990s, the dose of this drug used would have been relatively high — as much as 1,200 mg daily. Currently, in North America, ritonavir is usually prescribed together with another protease inhibitor. In such cases, the dose of ritonavir is usually between 200 and 400 mg daily. It is not clear if these doses would still cause the same degree of sexual dysfunction reported in the Boston study.

This retrospective study found an association between the use of protease inhibitors and male sexual dysfunction. It is noteworthy that testosterone levels were only recorded in the medical records of 8 out of 254 subjects. Since less-than-normal levels of testosterone are not

uncommon in HIV positive men, this lack of testosterone measurement is another possible limitation of the study. Perhaps the most useful outcome of this work is that it provides directions for better research into the causes of male sexual dysfunction in HAART users.

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D. Sexual dysfunction in men: A report from France

Summary

Researchers in Paris, France, conducted a study on 156 HIV positive men who were taking a variety of anti-HIV treatment regimens. The purpose of this study was to find out about the relation between treatment and sexual dysfunction. According to their results, about 71% of subjects experienced “some degree” of sexual dysfunction since they began therapy. However, there appeared to be no link between the use of protease inhibitors (PIs) and sexual dysfunction.

Study details

Researchers divided subjects into the following three groups:

- group A – PI-using subjects
- group B – subjects who had never received a PI
- group C – subjects who had stopped taking PIs for at least one month

The profile of subjects was as follows:

- average age – 41 years
- average CD4+ count – 415 cells

Researchers used a survey with 163 questions to capture information.

Results

In reviewing responses to the questions, researchers found out the following:

- 18% of subjects had experienced sexual dysfunction before becoming HIV positive
- 32% of subjects had experienced sexual dysfunction before they began using anti-HIV therapy

- about 71% of all subjects reported some degree of sexual dysfunction
- subjects with sexual dysfunction were more likely to also have anxiety and/or depression
- the researchers could find no link between the use of PIs and sexual dysfunction
- there was no connection between the presence of the lipodystrophy syndrome and sexual dysfunction

The cause of sexual dysfunction in some men who use HAART remains unclear and will hopefully be the subject of future research. More research also needs to be done on sexual dysfunction in women!

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Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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Credits

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