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Contents

I ANTI-HIV AGENTS

A. Good news for HAART users

In high-income regions such as North America, Western Europe and Australia, highly active antiretroviral therapy (HAART) has been available since about 1996. In these regions, HAART's impact has been dramatic. For instance, once-dreaded AIDS-related infections are now uncommon in HIV positive people who are aware of their health status, keep regular appointments with their health care team and adhere to treatment.

HAART works by suppressing production of HIV. In turn, with reduced exposure to new viruses and toxic viral proteins, the immune system is able to gradually repair itself. But the immune system does not return to a pristine pre-HIV state. Also, HAART does not cure HIV infection, so taking therapy is a lifelong activity. Despite these caveats, HAART has helped save many lives.

Researchers in Canada, Western Europe and the United States have been compiling databases containing health-related information on HIV positive people under care. Their analyses suggest that, overall, life expectancy since HAART has been considerably increased. However, the benefits of HAART are not evenly distributed and vary according to different factors such as gender and risk behaviour.

Study details

Researchers in Canada, including those at the B.C. Centre for Excellence in HIV/AIDS and the Southern Alberta Clinic, collaborated on a massive international database project where they pooled their collective databases, amassing

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information on a total of 43,355 HIV positive people. Such a giant database becomes a powerful statistical tool for finding and confirming trends among these people.

The study team focused on the time between January 1, 1996 and December 31, 2005. They divided participants into three groups corresponding to their initiation of HAART in the following time periods:

- 1996 to 1999: about 19,000 people
- 2000 to 2002: about 14,000 people
- 2003 to 2005: about 11,000 people

Because of the way the researchers reported their data, we are unable to provide the usual composite profile of an average participant.

Results—Overall

Over time, researchers noted certain trends, such as the following:

- starting therapy at an older age
- starting treatment earlier in the course of HIV disease
- more women starting HAART

Results—Survival

Over the study period, survival of HIV positive people who used HAART increased significantly, particularly for young people. Other trends were as follows:

- women were more likely to survive than men
- injection drug users (IDUs) had lower survival rates compared to women and men who were not IDUs

The research team speculates that the following factors might explain these differences between women and men, and between IDUs and people who were not IDUs:

- adherence issues
- inadequate or unequal access to care and treatment
- co-infection with hepatitis C virus
- high rates of nicotine addiction
- low income

The researchers were unable to take these issues into account when doing their study but these factors point the way forward for future research on survival trends.

Results—Deaths

A relatively small proportion of participants (about 5%) died during the study. Many of these deaths were AIDS-related. However, there were also deaths from causes unrelated to AIDS, including the following:

- cancers
- cardiovascular diseases
- kidney-related complications
- liver-related complications
- suicide

This last point may bear further scrutiny. HIV infects immune cells within the brain. These infected cells release toxic proteins that damage brain cells. In turn, this damage can result in problems with memory, thinking clearly, emotional control, coordinating muscles and movement, and other brain-related issues. In extreme cases, HIV-related brain damage results in dementia.

Fortunately, now that HAART is available, HIV-related dementia is uncommon, at least in high-income countries. But the relatively high rates of death due to so-called accidents or suicide in this study were "alarming," according to leading Australian researcher Dr. David Cooper. Perhaps one of the reasons for the high rate of suicide is because of HIV's effect on the brain in some people. To be certain, brain researchers need to investigate this.

Counting up the years

Still, overall, the study was good news for many HAART users. Here are some overall examples for males, as cited by researchers:

- An HIV positive man who begins HAART at age 20 can expect to live for an additional 43 years to age 63.
- An HIV positive man who begins HAART at age 35 can expect to live for another 32 years to age 67.

For females, the researchers gave these examples:

- An HIV positive woman who begins HAART at age 20 can expect to live for an additional 44 years to age 64.
- An HIV positive woman who begins HAART at age 35 can expect to live for another 32 years to age 67.

For injection drug users, the figures were good but not as good as those for people who did not inject drugs, as follows:

- An HIV positive IDU who began HAART at age 20 can expect to live for an additional 33 years to age 53.
- An HIV positive IDU who begins HAART at age 35 can expect to live for another 23 years to age 58.

These calculations are estimates from a large group and individual results can vary considerably based on some of the factors previously listed (co-infections, adherence and so on). However, bear in mind that in the time before HAART a person had an average of about 10 years between the time of infection and the development of AIDS. So HAART has made a huge difference.

Still, although HAART has clearly extended survival, the improvement in survival results in a lifespan that is only about 67% of what an average HIV negative person is likely to experience. So much work remains to be done to understand why this is the case. It is possible that the differences in survival between HAART users and healthy HIV negative people are due to HIV's damage to the immune system before treatment is initiated.

In the future, as HAART continues to become safer and more tolerable, it is likely that studies will explore the possibility of starting therapy at higher CD4+ cell counts.

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II ANTI-CANCER AGENTS

A. Kaposi's sarcoma—past and future

One of the hallmarks of AIDS, particularly in the early years of the pandemic, was the appearance of skin tumours called Kaposi's sarcoma (KS). During the 1980s, KS was very common in people with AIDS. Indeed, in those years, sometimes the only initial signal of immune dysfunction was KS.

Nearly three decades later, KS is now relatively uncommon in high-income countries. Yet reports have recently emerged of KS outbreaks in these countries in both HIV positive and HIV negative men who have sex with men (MSM).

To gain some insight into the possible future of KS, it may be useful to take a closer look at KS in the time before AIDS.

Last century

During most of the 20th century, in the time before AIDS, KS was a relatively uncommon skin tumour in the high-income regions of North America, Western Europe and Australia.

When everything changed

In the late 1970s, medical records suggested that a small but growing outbreak of immune deficiency–related diseases had occurred almost simultaneously in North America, Haiti, Western Europe and Central and East Africa. The people who developed these problems were previously healthy and relatively young adults who were not taking drugs to suppress their immune systems. Further research suggested that some factors that these people acquired (rather than a factor with which they were born or inherited)—such as an infection with a novel germ—made them susceptible to immune deficiency.

The KS that occurred in these and in future cases of acquired immune deficiency was not restricted to the feet or legs but could strike anywhere on the body. Moreover, in some cases, KS tumours would grow inside people, in lymph nodes or near vital organs/systems such as the lungs, heart and intestine. In such situations, KS lesions would block blood or lymph vessels, causing fluid to build up and degrading affected organs and eventually the whole person. In this period of time, treatments for this aggressive form of KS were generally not effective.

Affected people also had to contend with life-threatening infections. By the early 1980s, these cases of immune deficiency–related diseases were called AIDS. In 1983, French scientists were able to isolate the cause of AIDS, a virus we now call HIV.

In the United States and Western Europe, new cases of KS began to decline in the mid-to-late 1980s, and now KS is not as common as it once was. (Indeed, there was a time when half of all AIDS cases in the US had KS.) The reasons for this change are not clear. Some researchers speculate that perhaps a reduction in unsafe sexual behaviour was responsible, yet this does not seem to be the case.

Another feature of KS that remains unexplained is the odd geographic distribution of KS cases. For instance, KS was and still is more likely to be found in the coastal cities of New York, Los Angeles and San Francisco than in cities far away from the coast. And even within coastal cities, there were differences in the distribution of KS (Nathaniel Pier MD, *personal communication*).

In Canada, in the urban centres that were the original focus of the AIDS epidemic (Montreal, Toronto and Vancouver), the proportion of men with AIDS-related KS was greater than in other parts of Canada.

The cause(s) of KS

Researchers studying KS lesions have been able to isolate viruses from the herpes family, so they suspected that one of these viruses could be the cause of KS. In the mid-1990s, one team zeroed in on a virus called HHV-8 (human herpes virus-8), or KSHV (Kaposi's sarcoma herpes virus), and suggested that it was the cause of KS tumours.

But more recent research suggests that while HHV-8 may be necessary for the formation of KS, there are likely other co-factors that may play a role in triggering the development of KS lesions. These co-factors could include the following:

- drugs that weaken the immune system, such as corticosteroids, and other drugs used in transplant recipients
- environmental factors (perhaps prolonged exposure to volcanic soils)
- other viruses
- genes
- other, as yet unknown factors

HAART and KS

The introduction of HAART made many previously stubborn cases of KS regress, usually after at least one year of therapy. Some researchers suspect that HAART has made KS even less common today. They speculate that a revitalized immune system is able to keep HHV-8 replication under control. In turn, this could explain why KS lesions are less common. Still, in cases where HAART has failed or been interrupted, KS can reappear.

Is this the future?

Doctors in San Francisco have reported a cluster of KS cases in HIV positive men. The men were all taking HAART and their CD4+ counts were above the 300-cell mark. This level of cells should protect them from many AIDS-related complications. Moreover, their viral loads were less than 300 copies—suggesting a relatively low level of HIV production. Some of the men had been taking HAART for as many as seven consecutive years.

Yet KS lesions still appeared on their skin. The doctors were unable to explain why this occurred. Also, doctors in London, UK, reported KS lesions in their patients whose viral loads were below the 50-copy mark and who had similar levels of CD4+ cells. They also could not explain why these cases had occurred. Clues as to why these men developed KS appear in our next story.

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B. More about KS

KS is divided into four types depending partly on ethnicity and geography, as follows:

Classic KS

This rare disease tends to occur in men of Mediterranean or Jewish heritage who are 50 years or older. Skin lesions usually appear on the feet or upper legs. This form of KS is generally benign.

Endemic KS

This occurs in Africa and affects men and women across a broad range of ages, from young children to elderly people. This form of KS can affect the lymphatic system and internal organs, and as a result can be lethal.

Immune-suppressed KS

People who have received organ transplants need to have their immune system suppressed so it does not attack or reject the new organ. In such cases where the immune system is deliberately weakened, KS can occur.

AIDS-related KS

This form of KS affects mostly men, and, in rare cases, women who have sex with bisexual HIV positive men. KS is uncommon in people who inject street drugs. KS lesions may first appear anywhere on the skin and later grow near internal organs and lymph nodes.

About HHV-8

Worldwide, HHV-8 infection is more common than KS. As a result, researchers suspect that there are co-factors that play a role in the development of this form of cancer.

HHV-8 is relatively common in parts of Central and East Africa, and researchers estimate that about 15% of people in North America are infected with this virus. It is likely that in North America and Western Europe gay and bisexual men have higher rates of infection—perhaps about 25% are infected. Among MSM, the virus is probably spread by contact with saliva during sex. HHV-8 is less commonly found in other bodily fluids (such as semen).

In children, infection with HHV-8 can cause a red, itchy rash associated with fever. This virus is probably spread by contact with saliva from an infected adult.

HHV-8 infection seems to turn cells in the skin, blood and lymph vessels into KS tumours.

Tests for HHV-8 are available but researchers are not certain how to interpret the results. For instance, some of these tests can detect antibodies to HHV-8 and others can detect proteins of HHV-8. But exactly what these tests mean is unclear. So, for now, testing for HHV-8 is usually a research tool.

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C. KS in HIV negative men

Studies in Western Europe and the United States suggest that about 25% of gay men are infected with HHV-8. In contrast, in women and in men who are not MSM, rates of infection are less than 5%.

Researchers at two hospitals in Paris have been studying MSM whose KS was detected between 1995 and 2007. All 28 cases of KS were in HIV

negative men. The research team reported details on these men as follows:

- average age – 53 years
- 22 of the men identified as gay
- six of the men described themselves as bisexual
- 89% of the men had KS in the form of small nodules that appeared on the feet or lower legs
- other sites included the face, trunk and penis
- three men had blocked lymph vessels; however, ultrasound and CAT scans did not detect any KS lesions near major organs
- CD4+ and CD8+ cell counts were within the normal range in all the men as were another type of immune cell called NK (natural killer cells). These cells are important in controlling viral infections and tumours. Note that counting cells and assessing their function are two different issues (more about this point later in our story).

Risk factors for KS

About half of the men had the following risk factors for KS:

- having visited or lived in places where HHV-8 or KS were common
- a history of sexually transmitted infections

Immune deficiency is also a risk factor for KS. But CD4+ cell counts performed from the men's blood samples found an average reading of 920 cells—well within the range that is considered normal. However, more subtle conditions that may have suppressed the functioning of the immune system, such as the presence of type 2 diabetes or use of corticosteroids, was noted in only three men. None of the men were taking transplant medications.

Twenty-two patients tested positive for HHV-8, while three tested negative. The test was not performed on blood samples from three patients.

Other problems

Seven patients developed cancers of the lymphatic system (lymphomas) between two and seven years after doctors diagnosed KS. When these cancers were diagnosed HHV-8 was detectable in their blood samples. This is not surprising, as researchers suspect that HHV-8 can trigger the development of lymphoma in lymph nodes and tissues.

Treatment of KS

The course of treatment given to these 28 patients varied considerably. Some received interferon alpha injected into their blood, sometimes along with chemotherapy. Other patients received treatment directed at lesions, such as the following:

- radiation treatment
- surgery
- liquid nitrogen
- laser beams
- the immune-boosting cream imiquimod (Aldara)

The response to therapy was often successful, as there was not any major underlying immune dysfunction.

The question

The French study has underscored the issue of KS in HIV negative men. Based on this study an important question that needs to be asked is:

> Why did these relatively young and mostly healthy gay/bisexual men develop KS?

In attempting to answer this question we may find clues about KS risk factors.

Sex and drugs

The previous French study and others suggest that in high-income regions KS is much more common among men than women. Until the late 1970s, doctors did not routinely ask questions about the sexuality of their patients. However, it is now clear that MSM are at increased risk for KS.

Precisely which aspect of sexual behaviour places men at risk for KS is not clear. However, the KS-associated virus, HHV-8, can be found in saliva. So one theory is that exposure to HHV-8 in saliva through kissing and perhaps oral sex could help spread this virus. However, this idea awaits further study and KS has not been definitely linked to a particular sexual practice.

Recently there have been reports of sero-sorting among HIV positive MSM who have practiced unprotected anal intercourse. This has inadvertently led to outbreaks of hepatitis C virus (HCV), LGV, rectal gonorrhea and possibly syphilis in some MSM. It is possible that this behaviour could also help transmit HHV-8 or other germs or substances that could act as co-factors for the formation of KS tumours.

Also recently, reports from San Francisco and London, UK, have found that KS tumours have occurred among HIV positive MSM who are

taking HAART and who have low levels of HIV replication and moderate levels of CD4+ cells. Unfortunately, details of the sexual behaviours of these men were absent. Also missing were any reports of their substance-using behaviour.

Ethnicity and geography

Only some of the men in the French study had visited or lived in regions where KS is relatively common. These include Mediterranean countries (particularly southern Italy, Greece, Turkey, Israel and northern Egypt) and parts of Central, Eastern and Southern Africa, North and South America and China. The reasons for this may be related to genetic environmental factors.

Shining a light on immunity

Although the French team conducted limited immunologic assessments, these were restricted to CD4+, CD8+ and natural killer cell counts. They did not investigate the functioning of these cells.

A different team of researchers has investigated the functioning of T-cells in people who are infected with HHV-8, some of whom also have KS. Researchers found that, overall, CD4+ counts were similar in people with and without KS. However, T-cells from people who had KS tumours responded poorly when exposed to proteins from HHV-8. By contrast, in people co-infected with HHV-8 and HIV who did not have KS, the immune responses to HHV-8 proteins were much better.

This experiment has uncovered that people who have KS tumours, regardless of HIV co-infection, have some subtle defect in their T cells. This defect is not revealed when CD4+ cell counts are done. Thus, the immune systems of people with KS tumours are somewhat dysfunctional.

Why this dysfunction occurred is not clear. But the French team was able to rule out HHV-8 viral load as a possible factor.

Clearly, more research needs to be done to better understand how and why KS tumours occur and to uncover subtle defects in immunity of people with this problem.

Also, more research is needed to find out how HHV-8 is spread and if there are any other risk factors for KS tumour formation so that people can take steps to protect themselves.

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D. Liposomal chemo for KS

The use of HAART suppresses HIV production, which allows the immune system to begin repairs. As a result, previously hard-to-treat infections usually begin to respond to therapy and may go into remission.

In HIV positive people with a limited number of KS lesions (less than 10) and no other KS-related complications, research-dermatologists have recently recommended that doctors prescribe HAART. They suggest that the immune recovery associated with HAART will, in the medium- or long-term, cause these limited number of lesions to fade.

For people with more extensive KS or who have KS tumours that are affecting their internal organs, anti-cancer chemotherapy is required.

In the time before HAART, chemotherapy caused some lesions to regress and generally delayed the spread of new lesions and reduced the size of existing ones. However, chemotherapy rarely cured AIDS-related KS.

In the 1990s, new formulations of chemotherapy were developed. These formulations contained chemotherapy inside tiny balls of fat called liposomes. They caused less toxicity and resulted

in better penetration of chemotherapy into tumours.

In addition to trapping drugs inside liposomes, pharmaceutical companies have added PEG (polyethylene glycol) to them. The process of adding PEG to another drug is called pegylation and results in a longer-lasting formulation of the drug. One drug that has been reformulated so that it is both in liposomes and pegylated is called Caelyx, or liposomal doxorubicin.

Short- vs. long-term

While the short-term response to products (whether they are drugs, vaccines or chemotherapy) is well publicized by pharmaceutical companies, patients, their doctors and payers (such as drug formularies and insurance companies) are interested in long-term impacts.

So researchers at several Spanish hospitals reviewed health information collected from their patients with AIDS-related KS between 1997 and 2006 to assess the long-term effectiveness of liposomal anti-cancer therapy. All patients had received pegylated liposomal doxorubicin (PLD; Caelyx) as part of two studies. Their findings suggest that the use of PLD is very effective in moderate-to-advanced KS—relapse rates were low. However, the death rate was relatively high and the reasons for this are explored later in this report.

Study details

Researchers analysed data from two clinical trials. In the first study, they assessed the safety and effectiveness of PLD against AIDS-related KS. In the second study, they assessed the effect of HAART and PLD on KS. For the purposes of the combined study, the researchers looked at the long-term outcomes—KS, survival and complications.

In total, there were 98 participants who were evaluated. Their average profile was as follows:

- 4 females, 94 males
- age – 40 years
- all participants had at least 10 KS lesions on their skin or lesions in the mouth and internal organs; nearly 30% had KS on or near major internal organs/systems such as the lungs and intestine
- CD4+ count – 150 cells
- viral load – 16,000 copies
- all participants were taking HAART
- 75% of participants tested positive for HHV-8

Participants received PLD intravenously at a dose of 20 mg per square metre of skin, once every three weeks. Each of these dosing periods is called a cycle. On average, participants received nine cycles of PLD. Some participants were monitored for up to eight years.

Results—Initially

Response to therapy varied, but a substantial proportion of participants (75%) achieved some degree of benefit as follows:

- 48 people (49%) recovered from KS
- 27 participants (28%) had a partial recovery—lesions shrank by at least 50% in size and/or there were 50% fewer lesions after therapy

But there were some participants who did not benefit from PLD, as follows:

- 13 (15%) patients had little or no improvement
- 7 participants died while receiving PLD
- 3 participants did not complete their PLD regimens, probably because they were not effective

Results—Relapse

Of the 75 participants who had a favourable response (either a complete recovery or only a partial regression of lesions) researchers were able to report the long-term results on 61. These 61 people were monitored for an average of four years after their chemotherapy was complete.

In total, eight participants had their KS lesions return. In five people, this happened within one year of stopping chemotherapy.

Participants who relapsed tended to have lower CD4+ counts when they initially began chemotherapy or had low CD4+ counts after they completed chemotherapy.

Concern over deaths

Death rates were relatively high in this study and the possible reasons for this are complex and discussed later. Here are the overall details concerning deaths:

About 30% (29 out of 98 participants) died over the course of the study, as follows:

- 8 patients died while being treated for KS
- 9 patients died within one year after stopping chemotherapy

- 12 patients died more than a year after the end of their chemotherapy

The researchers noted that only three participants died from complications related to worsening KS. However, eight people died from serious blood and viral infections.

What caused additional concern was that in the remaining 19 patients all but two died from tumour-related complications. However, none of the tumours were KS—they were different forms of lymphoma. Participants died from lymphoma-related complications at the rate of about 2% per year. Death rates in KS studies now that HAART is available are generally much lower.

All patients with lymphoma tested positive for HHV-8. The significance of this finding will be discussed later.

Explanations

In reviewing the Spanish study, other researchers have noted the unexpected and high death rate. One explanation may be that patients in the Caelyx study were quite ill, given their extent of KS. However, this does not account for the many new cases of lymphoma that occurred after treatment with Caelyx.

A diagnosis of KS can be followed by subsequent diagnoses of cancer several years later. Both KS and lymphoma are associated with HHV-8 infection. Given that the immune suppression from HIV infection persists, even in HAART users, it is possible that this particular group of patients was more susceptible to cancer-causing viruses. However, high rates of death and subsequent lymphoma have not been noticed in other KS studies.

Another possibility is that prolonged exposure to chemotherapy, in this case doxorubicin, may have increased the risk of lymphoma. A previous study in HIV negative people with cancer suggests the possibility that exposure to doxorubicin may have played a role in the subsequent development of a second cancer such as leukemia or lymphoma.

So what to do? Experts in AIDS-related KS writing an editorial in the journal *Clinical Infectious Diseases* have suggested that HAART be the treatment of choice for mild or limited KS (fewer than 10 lesions and no lesions in the mouth or throat and no KS-related water retention). Close monitoring should be done to ensure that no new lesions appear and that over the medium- and long-term, KS lesions regress. If a few new skin lesions do appear, doctors should consider local treatment for them, remembering that HAART can help the immune system fight KS but that this immune response "may be delayed by several months or years," according to the editorial.

In more serious cases, where KS is affecting an organ or is life-threatening, the experts recommend the following course of action:

"HAART should be associated with adjuvant therapy, such as taxanes [Taxol] or liposomal anthracyclins chemotherapies. Evaluation of the response to therapy should be performed regularly to prevent both early and late complications of chemotherapy and to avoid excessive dosages of chemotherapy in this population, which is at risk of developing lymphoproliferative disorders."

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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.

The Canadian AIDS Treatment Information Exchange (CATIE) in good faith provides information resources to help people living with HIV/AIDS who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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What CATIE Does

The Canadian AIDS Treatment Information Exchange (CATIE) is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

CATIE Publications

TreatmentUpdate
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available on-line or contact us at 1.800.263.1638 to receive a print subscription.

A Practical Guide to HAART
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Practical Guide series also includes:

- **A Practical Guide to Nutrition**
- **A Practical Guide to Complementary Therapies**
- **A Practical Guide to Herbal Therapies**

The Positive Side magazine
Holistic health information and views for PHAs.

Fact Sheets & Supplement Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

pre*fix
A harm reduction booklet for HIV+ drug users.

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