NEW GUIDELINES RECOMMEND EARLIER TREATMENT

On December 1, the U.S. Department of Health and Human Services (DHHS) released the latest version of Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Based on a growing body of evidence, treatment is now recommended for people with 350–500 cells/mm³; half the expert panel favored treatment even for people with more than 500 cells/mm³, while the remainder deemed it “optional.”

The guidelines also recommend ART, regardless of CD4 count, for pregnant women, people with HIV-associated nephropathy (kidney disease), and hepatitis B virus (HBV) coinfection requiring treatment. In addition, the integrase inhibitor raltegravir (Isentress) was added to the list of “preferred” options for first-line therapy, while lopinavir/ritonavir (Kaletra) was changed to “alternative” due to side effects. The DHHS guidelines are available at www.aidsinfo.nih.gov/Guidelines.

The latest guidelines from the European AIDS Clinical Society, released in November, do not include a blanket recommendation for ART initiation under 500 cells/mm³, but do recommend treatment initiation within the 350–500 cells/mm³ range, or even higher, for pregnant women, people older than 50 years, individuals with high HIV viral load or rapidly declining CD4 count, and people with coexisting conditions, including hepatitis B or C, kidney disease, cancer, and elevated cardiovascular risk.

On the eve of World AIDS Day, the World Health Organization (WHO) issued updated global HIV treatment guidelines, which are widely used in low- and middle-income countries. The new WHO guidelines recommend ART initiation at 350 cells/mm³, up from 200 cells/mm³.

Based on recent studies, WHO also now recommends that HIV positive mothers and/or their infants should take antiretroviral drugs during breastfeeding, which the agency advises should continue throughout the first year of life. Finally, the guidelines recommend replacing more toxic drugs—such as d4T (stavudine; Zerit)—with more tolerable alternatives. The WHO guidelines are available at www.who.int/hiv/pub/arv/advice/en/index.html.

MARAVIROC APPROVED FOR FIRST-LINE THERAPY

In late November, the U.S. Food and Drug Administration (FDA) approved the first CCR5 antagonist, maraviroc (Selzentry), for treatment-naive individuals with exclusively CCR5-tropic virus (determined using the Trofile assay). Given the first-line approval of the first integrase inhibitor, raltegravir, this past July, people starting ART now have a wider array of effective and well-tolerated options.

The MERIT trial initially suggested that maraviroc did not work quite as well as efavirenz (Sustiva) for treatment-naive people with high viral load, but an analysis using the current, more sensitive Trofile assay found that the two drugs worked equally well after excluding participants originally misclassified as having only CCR5-tropic virus. Maraviroc is well-tolerated overall, and recent studies suggest that it may produce larger CD4 cell gains and reduce inflammation more than drugs from other classes (see “Inflammation, Immune Activation, and HIV,” page 12).

TELPREVIR UNDER STUDY FOR HIV/HCV COINFECTION

The investigational hepatitis C virus (HCV) protease inhibitor telaprevir—the furthest along of the new directly targeted antiviral agents—is now being tested in HIV/HCV coinfected individuals. The drug has demonstrated good antiviral activity in combination with pegylated interferon plus ribavirin in clinical trials of people with hepatitis C alone,
and developer Vertex Pharmaceuticals plans to request FDA approval in the second half of this year. For further information, see “Open Clinical Trials,” page 53.

GOOD RESULTS FOR NEW BOOSTER AND QUAD PILL

Gilead Sciences’ experimental Quad pill worked as well as Atripla (the tenofovir/emtricitabine/efavirenz coformulation) in a head-to-head trial of once-daily, all-in-one first-line regimens, researchers reported at CROI (abstract S8LB). The Quad is a combination pill containing the experimental integrase inhibitor elvitegravir, the novel boosting agent cobicistat (formerly GS 9350), tenofovir, and emtricitabine.

In a Phase II trial, 90% of participants in the Quad arm achieved a viral load below 50 copies/mL at 24 weeks, compared with 83% in the Atripla arm. The two coformulations produced equivalent CD4 cell gains, but the Quad was associated with fewer side effects, especially neuropsychological symptoms.

Gilead is also testing cobicistat as a stand-alone drug, a potential competitor for ritonavir (Norvir), currently the sole approved boosting agent, or pharmacoenhancer. In a 24-week analysis, 84% of treatment-naive participants receiving the protease inhibitor atazanavir (Reyataz) boosted with 150 mg cobicistat achieved undetectable viral load, compared with 86% of those receiving atazanavir boosted with 100 mg ritonavir. CD4 cell increases and overall adverse event rates were also similar.

In both trials, however, people taking cobicistat had higher serum creatinine levels and lower estimated glomerular filtration rate (eGFR), two indicators of possible kidney dysfunction. Presenter Calvin Cohen explained that prior studies of healthy HIV negative volunteers suggested that cobicistat may inhibit kidney tubular secretion, leading to elevated creatinine, but it does not appear to cause serious kidney toxicity. Since creatinine is one factor used to calculate eGFR, he said, cobicistat alters estimated but not actual glomerular filtration rate.

Gilead has announced that Phase III studies of both the Quad pill and cobicistat alone are expected to start by the middle of 2010; the company plans to request approval of the two in parallel, along with an elvitegravir/cobicistat coformulation.

VICRIVIROC FACES FURTHER CHALLENGES

Merck’s investigational CCR5 antagonist vicriviroc did not demonstrate non-inferiority to optimized background therapy for treatment-experienced people in the VICTOR studies, researchers reported at CROI (abstract S4LB), leaving the drug’s fate uncertain.

VICTOR-E3 and VICTOR-E4 were identical Phase III trials conducted in different geographical regions. Participants were randomly assigned to receive either 30 mg once-daily vicriviroc or placebo in combination with an optimized background regimen.

Enrollees had documented resistance to at least two antiretroviral drug classes, but were required to have at least two active drugs (i.e., not compromised by resistance) in their background regimen; about 60% had three or more active drugs. Approximately 40% used raltegravir and darunavir (Prezista), newer agents less subject to resistance.

In a combined modified intent-to-treat analysis of 721 participants with exclusively CCR5-tropic HIV, 64% of participants in the vicriviroc arms achieved viral load below 50 copies/mL at 48 weeks compared with 62% in the placebo arms, not a significant difference; CD4 cell gains were also similar. Therefore, vicriviroc did not demonstrate non-inferiority to the optimized background regimen.

Vicriviroc did show an advantage, however, for participants with fewer active drugs in their background regimen. Among people with two or fewer active background drugs, 70% in the vicriviroc arms and 55% in the placebo arms achieved undetectable viral load, a difference that did reach statistical significance.

The VICTOR studies raise the issue of how new antiretroviral drugs are tested in the era of highly effective ART. Presenter Joseph Gathe explained that with modern drugs, even many heavily treatment-experienced patients can construct suppressive regimens; in contrast, drugs approved in the past faced less stiff competition. Vicriviroc failed to work better than a potent background regimen that was already working well, but it was superior to a less active background.

“While these results are disappointing, it is becoming increasingly difficult for an additional HIV medicine to demonstrate a significant incremental benefit as the fourth or fifth drug added to optimized background therapy,” said Merck’s Lisa Dunkle. Prior to CROI, Merck informed investors that it does not plan to seek FDA approval of vicriviroc for treatment-experienced patients, though it will continue to evaluate the drug as first-line therapy.

HIV RESERVOIR IN BONE MARROW

HIV can hide inside multipotent hematopoietic progenitor cells (HPCs) in the bone marrow, presenting a challenge for efforts at eradication, according to a study in the March 7, 2010, online edition of Nature Medicine. HPCs are a type of stem cell that gives rise to multiple types of blood cells.

Kathleen Collins and colleagues from the University of Michigan at Ann Arbor looked at CD34+ HPCs in bone marrow samples from 15 HIV positive individuals. They found HIV
genetic material in HPCs from all six participants with high plasma viral load, and from four of nine individuals who had undetectable plasma HIV RNA on ART for at least six months.

When the researchers added wild-type HIV to laboratory cultures of HPCs from HIV negative donors, the virus infected and killed most HPCs, but some containing the latent provirus, or viral genome, went dormant. When they used differentiation factors to force the HPCs to start developing into blood cells, the viral genome was activated and began producing new virus particles.

This research helps solve the mystery of where—besides latent CD4 T-cells—HIV is able to hide in the body for prolonged periods. “This finding is important because it helps explain why it’s hard to cure the disease,” said Collins. “Ultimately, to cure this disease, we’re going to have to develop specific strategies aimed at targeting these latently infected cells.”

GAINS IN LIFE EXPECTANCY

People with HIV who receive timely antiretroviral treatment before they experience serious immune deficiency may reach a lifespan comparable to that of the HIV negative general population, according to two European studies presented at CROI.

Dutch researchers reported findings from ATHENA (abstract 526), a long-term national observational study in the Netherlands. This analysis included 4,612 participants enrolled between 1998 and 2007 who had not yet started ART at 24 weeks after HIV diagnosis; about 75% had a CD4 cell count above 350 cells/mm³ at baseline, and planned to start therapy when it fell below this level.

For an asymptomatic HIV positive person at age 25, the expected median remaining duration of life was 52.7 years, versus 53.1 years for the general population, a difference of just five months; by age 55, the difference had increased to 1.3 years for men and 1.5 years for women. However, men and women who did not start ART until after they developed CDC stage B disease—indicating symptomatic HIV disease but no AIDS-defining conditions—lost 6.0 and 7.5 years of life, respectively, by age 55.

In the second study (abstract 527), investigators compared age- and sex-specific death rates in the general population and among 80,642 HIV positive participants in COHERE, a collaboration of 25 European observational cohorts who started combination ART for the first time after 1997; here, the median CD4 count was lower, at 225 cells/mm³.

Individuals who started ART with fewer than 200 cells/mm³ had a 13-fold higher risk of death compared with the general population, falling to a three-fold risk if starting with 200–349 cells/mm³, and about twice the risk with 350–499 cells/mm³. Men with a CD4 count of 500 cells/mm³ or higher had a risk of death statistically equivalent to that of age-matched HIV negative men after three years on ART; women, however, remained at about double the risk of HIV negative women even after five years of treatment.

SMOKING CESSATION LOWERS CARDIOVASCULAR RISK

Cigarette smoking is associated with a significantly elevated rate of cardiovascular disease among people with HIV, but the risk begins to drop after quitting and continues to decline over time, according to findings from the large D:A:D (Data Collection on Adverse events of Anti-HIV Drugs) study presented at CROI (abstract 124).

D:A:D includes more than 33,000 HIV positive participants in the U.S., Europe, and Australia with generally well-controlled HIV disease (most on ART, more than 60% with viral load below 50 copies/mL, median CD4 count about 450 cells/mm³). More than one-third were current smokers and 19% were former smokers; about 8,200 said they quit after entering the cohort.

Current smokers had more than three times the risk for myocardial infarction (MI; heart attack) and ex-smokers approached twice the risk compared with people who never smoked. Among people who quit smoking during follow-up, excess MI risk decreased from 3.73-fold higher during the first non-smoking year, to 3.00-fold after 1–2 years, and finally to 2.07-fold after more than three years—still about twice the risk of life-long nonsmokers.

Looking at a broader endpoint of cardiovascular disease, current smokers had 2.19-fold higher risk and former smokers had a 1.38-fold higher risk relative to nonsmokers. Again, excess risk declined steadily among people who quit during the study, falling from 2.32-fold higher during the first year to 1.49-fold after more than three years. But the risk of mortality due to all causes did not decrease in a similar pattern, suggesting that risk of death remains elevated after quitting. “Smoking cessation efforts should be a priority in the management of HIV-positive patients,” the researchers recommended.

VITAMIN D DEFICIENCY

Low levels of vitamin D are common among HIV positive people around the world, according to a set of studies presented at CROI. Vitamin D deficiency promotes bone loss—a concern for people with HIV, who are already at higher risk than the general population—and has been linked to cardiovascular disease, cancer, and other conditions.

In an analysis of 672 participants (about 75% men) in the CDC’s SUN Study (abstract 750), which includes individuals with generally well-controlled HIV disease at clinics in four U.S. cities, 72% were found to have insufficient
blood levels of 25-hydroxyvitamin D (< 30 ng/mL); none were receiving vitamin D supplements.

Looking at U.S. women (abstract 754), a cross-sectional analysis of 609 participants (79% HIV positive, 21% HIV negative) in the Women’s Interagency Health Study found that 60% had vitamin D deficiency (< 20 ng/mL) and 24% had insufficiency (< 30 ng/mL). Worsening deficiency was strongly linked to higher risk for bacterial vaginosis (disruption of the normal balance of microorganisms in the vagina).

Turning to Europe, in a retrospective analysis of 211 participants (75% men) in the Swiss HIV Cohort (abstract 752), vitamin D deficiency rates before starting ART were not so high (14% if tested during the fall and 42% if tested during the spring); percentages were similar one year after starting ART. In an analysis of 856 HIV positive participants in the Italian ICONA cohort (70% on ART, 30% prior to ART initiation), 54% had vitamin D insufficiency and 7% had deficiency (abstract 751).

Finally, in a study looking at the link between vitamin D levels and health outcomes among women in Tanzania (abstract 753), women with low levels (< 32 ng/mL) had a 192% higher risk of vaginal candidiasis (thrush), a 45% higher likelihood of wasting, and a 28% higher risk of upper respiratory infections.

Vitamin D is produced by the body when the body is exposed to sunlight, and is available in foods such as cold-water fish and fortified dairy products. While deficiency risk factors varied somewhat across these studies, researchers consistently found greater insufficiency during seasons with less sunny weather and in climates where people received less sun exposure, and among people with darker skin; people who used NNRTIs also were more likely to be deficient that those using protease inhibitors.

While these vitamin D insufficiency rates are alarming, they may not be much higher than those of the HIV negative general population; in the U.S. for example, it is estimated that as many as three-quarters of the population may not get enough. Researchers are increasingly aware that vitamin D deficiency is more common than previously assumed, and many experts believe current recommended levels should be increased.

THAI VACCINE TRIAL SHOWS MINIMAL BENEFIT

The ALVAC/AIDSVAX prime-boost combination HIV vaccine demonstrated a small and only marginally significant protective effect in the Phase III RV144 clinical trial in Thailand. While detailed data did not live up to the initial hype, some researchers hailed the findings as proof-of-concept that a preventive HIV vaccine can work.

In September, the U.S. Military HIV Research Program (MHRP) announced that in an analysis of more than 16,000 study participants, those who received ALVAC/AIDSVAX had a 31% lower risk of HIV infection compared with placebo recipients. However, a closer look at the complete data, presented at the AIDS Vaccine 2009 conference in Paris and simultaneously published in the October 20, 2009, online edition of the New England Journal of Medicine, revealed less impressive results.

Overall, 56 vaccine recipients and 76 placebo recipients were newly infected with HIV during follow-up. In an intent-to-treat analysis, there was a trend toward a significant protective effect, with an efficacy of 26.4%; however, the P value (a standard statistical measure) of 0.08 did not reach the usual 0.05 cut-off for significance and the confidence interval was very wide, indicating considerable uncertainty about whether the results were due to chance alone.

In a modified intent-to-treat analysis that excluded seven people who were belatedly determined to have been already HIV-infected at study entry, vaccine efficacy was 31.2%—the figure reported in September—and this just reached the cut-off for statistical significance, with a P value of 0.04. But in a per-protocol or as-treated analysis of participants who received all vaccine doses as scheduled, efficacy fell to 26.2% and was no longer close to borderline significance (P = 0.16). Vaccination did not affect viral load levels or CD4 cell counts in participants who did become infected.

“Although the results show only a modest benefit, they offer insight for future research,” the RV144 investigators concluded. For example, they plan to explore why ALVAC/AIDSVAX provided the greatest protective effect during the first year (about a 60% risk reduction), and why heterosexual participants at low or medium risk for HIV infection appeared to derive more benefit than high-risk participants such as gay men or injection drug users.

The Thai trial results were “the first signal of [HIV vaccine] efficacy, extremely modest though it might be,” National Institute of Allergy and Infectious Diseases director Anthony Fauci said at a CROI plenary. In particular, the findings may offer insights about the correlates of protection, or what needs to happen for a vaccine to work.

PRO 2000 MICROBICIDE PROVES INEFFECTIVE

The experimental vaginal microbicide PRO 2000, which appeared promising in earlier studies, did not protect women from becoming infected with HIV in a large Phase III clinical trial in Africa, investigators announced in December.

PRO 2000 is a 0.5% microbicidal gel inserted into the vagina prior to sexual intercourse. An earlier study of more than 3,000 African women (HPTN 035) was the first to suggest that a microbicide might help prevent male-to-female sexual transmission of HIV, with a 30% protective effect.
that fell just short of statistical significance.

But the MDP 301 trial—the largest microbicide study to date, with more than 9,000 participants—found no evidence that PRO 2000 reduced women’s risk of infection. Over 12–24 months of follow-up, the HIV incidence rate was 4.5 per 100 person-years in the PRO 2000 arm versus 4.3 per 100 person-years in the placebo arm.

Speaking at CROI, Fauci said that studies of non-antiretroviral microbicides like PRO 2000 have produced “failure after failure,” and the time has come to move on to next-generation products containing antiretroviral agents such as tenofovir or maraviroc.

**ART LOWERS HETEROSEXUAL TRANSMISSION RISK**

Findings from the Partners in Prevention study, presented at CROI (abstract 136) and published in the May 27, 2010, advance issue of The Lancet, indicate that starting combination ART early can reduce the risk of HIV transmission between partners in heterosexual couples. The trial (which was designed to assess whether treating genital herpes could reduce HIV transmission) included more than 3,000 serodiscordant (one positive, one negative) couples in seven sub-Saharan countries.

At study entry, participants had CD4 cell counts above 250 cells/mm² and were not on ART. During two years of follow-up, 349 HIV positive participants (10%) started ART, half with a CD4 count below 200 cells/mm², one-third with 200–349 cells/mm², and 15% with 350 cells/mm² or higher (including pregnant women receiving antiretroviral drugs to prevent perinatal HIV transmission).

A total of 151 new infections occurred, of which 103 were verified as transmissions within a couple with known ART status, not including perinatal prevention. Of these transmission cases, 102 were from HIV positive participants not taking ART (an incidence rate of 2.24 per 100 person-years). In the absence of treatment, the likelihood of transmission increased as the positive partner’s CD4 count decreased (from 8.79 per 100 person-years below 200 cells/mm² to 1.82 per 100 person-years above 500 cells/mm²).

One transmission, however, was from a person receiving therapy (0.37 per 100 person-years). While ART reduced the risk of transmission by 92%, this single infection demonstrates that treatment does not completely eliminate risk.

**COMMUNITY BENEFITS OF “TEST AND TREAT”**

Effective ART dramatically reduces the risk of HIV transmission, and mathematical models have suggested that universal voluntary testing and widespread treatment could essentially halt the spread of the epidemic. Two studies presented at CROI offered early indications that expanded testing and treatment may be helping to lower HIV incidence in “real-world” settings in high-income, low-prevalence countries.

Moupali Das-Douglas from the San Francisco Department of Public Health (abstract 33) reported that between 2004 and 2008, a 40% decrease in “community viral load”—or viral load across an entire population group—was associated with a 50% reduction in new HIV diagnoses (including both recent infections and new diagnoses of existing infections).

By 2008, an estimated 80% of newly diagnosed individuals were linked to care; about 90% of these were on ART, and about 75% of treated people achieved undetectable viral load. The investigators concluded that these findings “support the hypothesis that wide-scale early ART can have a preventive effect at a population level.”

Julio Montaner and colleagues from the British Columbia Centre for Excellence in HIV/AIDS (abstract 88LB), a group that has pioneered mathematical modeling of the effects of treatment, explored associations between expanded HIV testing, ART coverage, community viral load, and decreased HIV transmission in British Columbia, largely driven by injection drug users (IDUs) in the Downtown Eastside district of Vancouver.

The number of HIV tests performed annually in British Columbia rose from 153,635 in 2004 to 182,151 in 2008, and the number of people receiving ART doubled from about 2,500 in 2000 to about 5,000 in 2009. Average community viral load declined over the past five years, and the proportion of people with HIV RNA levels below 500 copies/mL increased from about 40% in 2004 to about 75% in 2009. During the same period, total new HIV diagnoses decreased, including a steep decline among IDUs (from 150 cases in 2004 to 80 in 2009).

The researchers said these findings “demonstrate an association between expanded [ART] coverage, decreased provincial plasma viral load, and decreased new HIV diagnoses,” which followed initiation of a treatment outreach effort targeting IDUs. Montaner suggested the decrease was likely due to expanded ART rather than behavior change, since needle exchange and other harm reduction efforts were widely implemented well before the decline began.

While the correlations observed in these studies do not prove causation, the findings suggest that increased testing, more widespread treatment, and reduced community viral load can provide community-wide benefits by lowering the risk of HIV infection.

**NO DECREASE IN RISK PER SEX ACT?**

While studies like those above indicate that prompt treatment significantly reduces the likelihood of HIV transmission, an
Australian study published in the February 4, 2010, advance online edition of *AIDS* yielded the unexpected finding that the risk of transmission per act of sex between men—in particular uncircumcised men—appears not to have fallen since the advent of effective ART in the mid-1990s.

Fengyi Jin and colleagues estimated the per-contact probability of HIV transmission due to unprotected anal intercourse among 1,427 initially HIV negative homosexual men (the researchers’ classification) recruited in Sydney between 2001 and 2004. The researchers noted that about 70% of HIV positive men in Australia are on ART and 75% of treated individuals have undetectable viral load.

Follow-up continued until June 2007, at which point a total of 53 men had seroconverted. The estimated per-contact probability of transmission for unprotected receptive anal intercourse (i.e., the “bottom” becoming infected) was 1.43% if ejaculation occurred inside the rectum versus 0.65% if the insertive partner withdrew.

The per-contact probability of transmission for insertive anal sex (i.e., the “top” becoming infected) was 0.11% if the insertive partner was circumcised versus 0.62% if he was uncircumcised.

Taken together, these transmission rates are similar to the 0.82% risk per act of unprotected anal intercourse seen in a U.S. study from the early 1990s. The Australian study, however, sheds more light on specific risk factors.

Unprotected receptive anal sex with ejaculation was about twice as risky as either receptive intercourse with withdrawal or insertive intercourse for uncircumcised men, but ten times as risky as insertive intercourse for circumcised men. While 12 men were infected after having unprotected anal intercourse fewer than ten times, six others did not become infected despite reporting “extremely large numbers” of unprotected sex acts with known HIV positive partners.

Circumcision has been shown to reduce the risk of HIV transmission by as much as 60% among heterosexual men in low-income, high-prevalence settings such as Kenya and South Africa, but most studies looking at men who have sex with men in high-income, low-prevalence countries have not seen a similar protective effect. The Australian team, however, previously reported that circumcision may have some benefit for gay/bisexual tops.

**U.S. Lifts HIV Positive Visitor Restrictions**

On January 4, the U.S. formally ended its long-standing restrictions on HIV positive people traveling or immigrating to the country. The ban has been in effect since the late 1980s, when Congress declared HIV to be a “communicable disease of public health significance.” In 2008, legislation reauthorizing the President’s Emergency Plan for AIDS Relief (PEPFAR) removed the statutory ban and returned authority for determining excludable diseases to the Secretary of Health and Human Services.

The government issued a proposed policy change in June 2009, and in October, while signing legislation reauthorizing the Ryan White CARE Act, President Barack Obama announced that the ban would be lifted after a 60-day waiting period. Now that the restrictions have been rescinded, the International AIDS Society has announced that it will hold its 2012 International AIDS Conference in Washington, DC—the first in the U.S. since 1990.

South Korea also ended its ban on HIV positive visitors effective January 1, as did China in April; more than 50 countries, however, still have some sort of entry or residence restrictions based on HIV status. The policy changes are “a victory for human rights on two sides of the globe,” said UNAIDS executive director Michel Sidibé. “Let no country obstruct someone because of their HIV status,” he added. “Such discrimination has no place in today’s highly mobile world.”

**Congress Rescinds Needle Exchange Funding Ban**

In December, Congress took another step long demanded by AIDS activists, lifting the ban on federal funding for needle exchange programs. Instituted by a clause in appropriations legislation, this policy was in place for two decades despite a considerable body of evidence showing that needle exchange reduces transmission of blood-borne diseases such as HIV and hepatitis B and C, without promoting injection drug use.

This past July, Democrats in the House of Representatives removed the relevant clause from the proposed Labor and Health and Human Services appropriations bill for fiscal year 2010. Republicans attempted to add an amendment severely restricting where needle exchange programs could operate, but this effort was defeated. The U.S. House of Representatives and Senate passed a joint omnibus spending bill without the needle exchange funding prohibition and President Obama signed the legislation in December, putting an end to the ban.

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