

ALLERGEN IMMUNOTHERAPY IN HIV-INFECTED PATIENTS

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Currently, the most widely publicized infectious disease is that caused by the human immunodeficiency virus (HIV). Infection by this virus ultimately leads to a syndrome consisting of progressive destruction of the host immune system, with increasing susceptibility to opportunistic infections, certain malignancies, and ultimately death. The acquired immune deficiency syndrome (AIDS) is still virtually 100% fatal, although innovative new therapies hold promise for prolonged patient survival.⁷⁵ Strong efforts have been mounted for some time aimed at defining prognostic indicators that would allow clinicians to categorize risk of progression as well as early assessment of response to therapies.^{85, 93}

Although the progressive destruction of the immune system is the ultimate basis for host demise, many clinical conditions exist for the duration of HIV disease that are the result of inappropriate or excessive immune responses.¹⁰⁰ Such inappropriate responses can be clinically categorized as allergic, rheumatologic, and cutaneous. Although also found in HIV-negative patients, these conditions are a particular source of morbidity in the HIV-positive patient population.^{2, 92} Initially, little attention was paid to the specific therapies for these conditions per se because the primary immunodeficiency disease of HIV-infected subjects

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progressed rapidly, resulting in a high mortality rate in a relatively short period. Now, with the development of more effective antiviral therapies that can prolong survival of HIV-positive patients for well over a decade, conditions that affect quality of life rather than direct mortality are receiving increasing attention.³⁷ This is particularly true for allergic respiratory diseases that occur commonly in HIV-infected patients.

This article describes the immunopathophysiology of HIV infection that may account for the increased incidence or severity of immune-based diseases in these patients as well as allergic diseases in HIV-infected subjects, including clinical manifestations, therapeutic interventions, and rationale for therapy. Discussion then focuses on the potential role of allergen immunotherapy for allergic respiratory disease in HIV-positive patients, its efficacy, potential complications, comparison with vaccination against infectious agents, and possible use as a model for future HIV vaccine administration strategies.

IMMUNOPATHOPHYSIOLOGY OF HIV INFECTION

It is well appreciated that HIV, as it infects the host immune system, ultimately destroys elements of the immune response, leaving the host susceptible to overwhelming infection, or malignancy and death.⁶⁰ The demise of the host immune response cannot be fully explained as simply destruction of the elements by the virus, however. Indeed, at virtually any point in the course of the disease, less than 1% of CD4⁺ peripheral blood cells are found to contain viral cDNA and even fewer to have viral RNA.³² Thus, the mechanisms behind the destruction of the immune system are more complex.

In the normal host, presentation of antigen for a specific protective immune response elicits a complex series of events that results in a mixed cellular and humoral protective response, the intensity and nature of which depend on the specific inciting antigen.^{73, 99} Generally speaking, extracellular parasites (i.e., bacteria) incite primarily a humoral response, whereas intracellular parasites (i.e., virus, fungi, mycobacteria, etc.) elicit a cell-mediated response. Antiviral immunity is particularly complex because both arms are necessary for host resistance—cellular immunity to recover from a viral infection and humoral immunity to prevent reinfection. The host immune response has a variety of mechanisms to direct the immune response into the humoral versus cellular direction: nature of antigen-presenting cells,⁴⁹ major histocompatibility complex (MHC) restriction,¹⁸ and availability of specific T- and B-cell components.⁸² The central control of the cellular versus humoral response to an antigenic challenge appears to be by means of production of specific cytokine milieu, however.⁸⁷

A central source of these cytokines comes from CD4⁺ helper T-cell subpopulations, often referred to as *Th1* and *Th2* cells (Table 1).⁵⁴ Human *Th1* cells secrete a specific cytokine profile, including interferon gamma (IFN γ), and tumor necrosis factor beta (TNF β). These cytokines are

Table 1. CYTOKINE PROFILES OF T-HELPER SUBPOPULATIONS

Th1	Th2	Both (Th0)
IFN γ	IL-4	IL-2
IL-12	IL-5	IL-3
TNF β	IL-6	GM-CSF
	IL-10	
	IL-13	

important helper factors in the generation of cellular immune responses, including antigen-specific cytotoxic T lymphocytes (CTL) and natural killer (NK) cells.^{70, 90} Additionally, IFN γ in particular has an antagonistic activity against Th2 cytokines.⁶¹ In contrast, Th2 cells secrete IL-4, IL-5, IL-10, and IL-13, which are involved in isotype switching of B cells as well as proliferation and differentiation into antibody-secreting plasma cells.⁴⁰ In particular, IL-4 and IL-13 are involved in the isotype switch from IgM to IgE, the antibody responsible for classic allergic disease. IL-4 and IL-10 are also regulatory cytokines, antagonizing the activities of Th1 cytokines.⁴¹ In humans, helper T cells can have a third cytokine secretory pattern. Th0 cells²³ are capable of secreting all of the above mentioned cytokines and are often thought of as precursors. Whether this represents a differentiation pathway for Th cells remains to be determined. Thus it can be said that the nature, intensity, and duration of a specific immune response depend on the often delicate balance between Th1 and Th2 numbers or activities.⁷¹

A developing consensus among those who care for patients and do research related to progression of HIV disease is that disease progression is linked to increases in HIV expression as well as sustained decreases in peripheral CD4 + cell counts.⁴² With more sensitive measures of HIV viral load through branch DNA analysis and RT-PCR technology, it is now understood that replicating HIV is present throughout the course of disease.²² In the asymptomatic person, the HIV is reasonably well contained in regional lymphoid tissue by a complex HIV-specific immune response as well as nonspecific follicular dendritic cells (FDC).^{30, 59} As long as the FDC function properly, HIV is relatively contained. HIV-specific CTL can be found in relative abundance early in infection and persist well into advanced disease.⁸ As CTL wane, viral load increases.⁹⁶ Because CTL depend on cytokines such as IFN γ and IL-12 for activity,⁷⁰ Th1 activity in HIV-infected persons appears to be particularly important. Shearer and colleagues⁸¹ have hypothesized that a Th1/Th2 cytokine imbalance is responsible for the rapid progression of HIV infection into AIDS in some infected subjects. Clinical evidence to support this notion comes primarily from the observations that HIV-positive patients who are anergic to recall antigens have a more advanced disease progression than do those who retain positive delayed-type hypersensitivity (DTH) profiles.^{7, 26} DTH reactions depend on cytokines from antigen-specific Th1 cells for macrophage activation and subsequent skin

erythema and induration.¹² Furthermore, HIV patients tend to have elevated serum IgE (a result of Th2 activity) compared with HIV-negative controls⁹⁸ and may have a higher incidence of atopy. A recent study followed a group of HIV-patients with middle disease categorized by either normal or elevated serum IgE levels. In the normal IgE group, only 12% progressed to AIDS with the 24-month observation period. In contrast, all of the patients with high IgE levels had progressed to AIDS within 24 months.³⁴ Either the decrease of Th1 cytokines or increased influence of regulatory Th2 cytokines (i.e., IL-4 and IL-10) may result in decreased cellular immunity against HIV, and thus disease progression.

This concept remains controversial. Several groups have advanced the hypothesis that, if a Th1/Th2 imbalance is important in HIV progression, patients in later disease should have more Th2 than Th1 activity; however, cloning efforts have produced mostly Th0 or Th1 clones regardless of the stage of disease.^{28, 46} Although these data are provocative, it is well appreciated that cells other than CD4+ Th cells can produce all of the aforementioned cytokines and that it is the total effector and regulatory *milieu* that ultimately dictates a specific cellular versus humoral immune response.^{5, 65} Few argue the importance of an intact cellular immune response in host resistance to HIV progression. Thus it may be more appropriate to think of a type 1 versus type 2 cytokine imbalance as being responsible for the decreased cellular immunity seen in certain subjects early in their course of HIV-induced disease.⁸³

IMMUNE-BASED DISEASES IN HIV-POSITIVE PATIENTS

Clinically, this translates to the observation that disease progression, peripheral CD4 counts, and HIV load are inextricably linked.⁴² As a result, situations that result in sustained decreases in CD4 counts and evidence of increased viral load (i.e., HIV RNA expression), because of concomitant diseases, lifestyles, or therapeutic interventions, are viewed with considerable concern. Searches for life situations that could promote this ominous combination have included those maladies in which immune hypersensitivity is known to occur such as autoimmune, rheumatologic, cutaneous, and allergic diseases.^{4, 10} Autoimmune mechanisms are implicated in a variety of clinical complications seen in HIV-positive patients, including cardiomyopathies,³¹ skeletal myopathies,¹¹ neuropathies,⁵⁵ and various hematologic abnormalities, including leukopenias and thrombocytopenias.^{3, 15} Again, the rationale is based upon the relative increase in Th2 activity results in the increased production of auto-antibodies as well as possible loss of immunoregulatory control mechanisms.

ALLERGIC DISEASES IN HIV-POSITIVE PATIENTS

Atopy is a classic Th2 condition.¹⁶ In genetically susceptible subjects, exposure to allergens generates antigen-specific IgE that binds to mast

cells and, on subsequent allergen exposure, crosslinks to activate the mast cell to release preformed mediators and synthesize new ones responsible for the characteristic signs and symptoms, depending upon the end organ(s) affected.⁷⁸ IL-4 (and perhaps IL-13) is an obligate cytokine necessary for isotype switch from μ to ϵ heavy chain.^{17, 94} IL-4, as well as other Th2 cytokines (i.e., IL-5, IL-10), are growth or activation factors for mast cells¹³ as well as eosinophils,²⁰ a primary inflammatory cell in allergic reactions.

Atopic disease occurs in HIV-positive patients with reportedly similar or even increased frequency compared with HIV-negative controls.^{9, 19} A central question is reactivation versus new-onset atopic disease. The spectrum of disease is similar, from allergic rhinitis to asthma to cutaneous disease; however, in contrast with the HIV-negative population, IgE-mediated drug allergy occurs more frequently in the HIV-positive population.⁴⁴ A detailed discussion of allergic manifestations in HIV-infected patients is found elsewhere in this issue.

The clinical course of atopic diseases in HIV-infected patients is similar to that of the HIV-negative population. The inciting agents are most often classic environmental allergens such as pollens, dust, molds, and danders.⁷⁶ In contrast to HIV-negative atopic subjects, however, HIV-positive patients exhibit evidence of IgE specific for various microbes,⁶⁴ including bacteria,⁶³ fungi,⁴⁵ viruses,⁹⁷ and even HIV itself.⁶² The role of these antigens in the clinical manifestations of allergic disease has been implicated but never firmly established. With allergic nasal disease, atopic HIV-positive patients are at risk for secondary infectious rhinosinusitis.⁸⁹ Although the most common etiologic agents are virus, *Pneumococcus*, *Hemophilus*, and *Moraxella*,⁹¹ HIV-positive patients are at increased risk of infection with atypical organisms, such as various fungi.⁵⁰ Additionally, because of their often chronic use of antimicrobial agents or development of adverse drug reactions and drug allergies, sinusitis in HIV-positive patients often requires prolonged therapy with more potent antibiotics, further altering the patient's microbial milieu⁷⁴ and increasing risk of sensitization to the newer antimicrobial agents.²⁹ Thus, simple hay fever (particularly that accompanied by chronic nasal congestion) merits early and aggressive therapy in these patients.

Therapeutic interventions for allergic diseases in HIV-positive patients are usually no different from any other patient population. Use of antihistamines, decongestants, cromolyn, and even topical steroids can be pursued without any special precautions.⁴³ Although there has been some concern about the possibility of mucosal immunosuppression with resulting opportunistic infections when topical steroids are used in rhinitis and asthma, no widespread incidence has been reported by those allergists who care for HIV-positive patients. Our experience with atopic HIV-positive patients supports this notion. The use of systemic steroids in HIV-positive patients bears special mention because, especially in asthmatic subjects, steroids are often avoided because of concern for further immunosuppression, although such concerns remain controversial.⁴⁷ Although monitoring for evidence of increased opportunistic infec-

tions is appropriate, there is little evidence to suggest that judicious use of systemic steroids in asthmatic patients, when clinically indicated, should be avoided. It would be preferable to reduce the need for systemic steroids with other medications, avoidance, or possible alteration of sensitivity where possible, however. It is for such patients that allergen immunotherapy is most likely to be considered as a therapeutic option.

ALLERGEN IMMUNOTHERAPY IN HIV PATIENTS

The controversy surrounding allergen immunotherapy (AIT) in HIV-infected patients comes from two major sources: (1) concerns about decreased efficacy, and (2) causing progression of underlying HIV disease. To address these concerns appropriately, this author first considers the use of AIT in HIV-negative atopic patients.

AIT involves the repeated parenteral administration of allergen extracts to an atopic subject over time.⁷⁷ The aim is to decrease and, in some instances, eliminate the clinical sensitivity to the specific allergen. The dose is initially small and gradually increased for safety reasons. The major risks associated with AIT include temporary worsening of symptoms and the possibility of a major systemic mast cell-mediated reaction that is rarely life-threatening.⁸⁷ Generally, significant improvement is noted within the first year of AIT, and a defined course of therapy (3–7 years) is typically offered. Clinical improvement is noted by decreases in seasonal (or provocative) symptoms, improved efficacy of control medications, or decrease in amount of medications necessary for symptom control. When appropriately tested (skin or RAST) and results correlated with clinical symptomatology, up to 95% of allergic rhinitis patients treated with AIT will demonstrate clinical improvement.⁵⁸ Use of AIT is the final modality of therapy in atopic patients who do not respond adequately to allergen avoidance, environmental control, or medications.²⁷

For some time, the mechanisms to explain the efficacy of AIT have remained somewhat obscure. The proven clinical efficacy of AIT dates back over 50 years.³⁶ Early studies suggested that AIT could produce “blocking” IgG antibodies that would prevent mast cell-bound IgE from being crosslinked by allergen.⁵³ Recent studies have demonstrated that AIT can decrease allergen-induced IL-4⁷⁹ or increase IFN γ production *in vitro*.^{1, 21} This could have the effect of downregulating specific IgE production as well as decreasing mast cell or eosinophil activity. The result is an alteration of antigen-specific host immune responses from atopic to nonatopic. Such manipulation typically is safe and longlasting in otherwise normal atopic patients. But what of those with underlying immune-based disease?

There have been very few studies examining the efficacy of AIT in patients with rheumatologic, cutaneous, or malignant diseases; however, most allergists avoid AIT in any of these patient populations. Patients

that have various autoimmune diseases accompanied by atopic disease often are receiving significant immunosuppressive therapies for their rheumatologic conditions that partially or totally control their atopic symptoms. Additionally, significant concern exists over the possible exacerbation of the underlying rheumatologic process by AIT. To date, however, no studies have documented this concern.

A similar mindset has occurred for HIV-positive patients who are atopic. Initially, life expectancy after diagnosis was so short that AIT was not even considered owing to the prolonged duration of therapy. Then, as HIV-positive patients have survived for significantly longer periods, AIT still has been avoided because of concerns over potential worsening of underlying HIV disease by repeated parenteral antigen exposures.³⁵ Such concerns were based initially on *in vitro* and later *in vivo* studies using various vaccine antigens.

VACCINE THERAPY IN HIV-POSITIVE PATIENTS

There are two major types of vaccination programs in HIV-positive patients: (1) prophylactic vaccines against communicable infectious diseases,⁶⁹ and (2) therapeutic vaccines against HIV itself.⁶⁸ In the former, the initial concept was to expose the remaining Th cells to antigens to generate memory T (and B) cells for defense against future infectious exposures. Early concern was developed when it was observed that antigen- or mitogen-activated CD4+ T cells were more easily infected with HIV *in vitro* than were resting cells.²⁵ Logically, because vaccine antigen exposure activates T cells, the concern is that such clones will become HIV infected and possibly eliminated, resulting in decreased host response to the natural antigen, or, more ominously, increase in HIV disease progression.⁷² Indeed, recent studies using standard tetanus vaccination in an asymptomatic HIV-positive population sample resulted in a transient decrease in absolute circulating CD4+ cells as well as increased blood HIV RNA expression.⁸⁶ The authors acknowledged that the clinical meaning of transient changes in these parameters, all of which resolved in this patient sample, was unclear. Furthermore the natural infection that such vaccines seek to prevent would almost surely have as much if not more effect on both the CD4 count and blood HIV expression.

COMPARISON OF VACCINATION AND AIT IN HIV-POSITIVE PATIENTS

Perhaps by association, the concerns raised by vaccine therapy in HIV-positive patients have been extended to AIT. The concerns regarding increased susceptibility of allergen-specific Th cells to infection by HIV during AIT is understandable; however, there are several fundamental differences to consider. First, standard vaccine therapy has classi-

cally had its efficacy judged (from a laboratory standpoint) by examining pre- and postvaccine antibody titers³⁸—a Th2-based phenomenon.⁶ Activation of clones outside of the spectrum of the specific antigen exposure by cytokines (called an *innocent bystander effect*) has been well described.⁴⁸ It is possible that vaccines may transiently accomplish such a switch, which could account for the altered CD4/HIV load balance. It is still unclear whether the natural infection with agents that stimulate Th2 responses (i.e., bacterial) might do likewise on a more pronounced or prolonged basis.

In contrast, successful AIT appears to alter an allergen-specific Th2 to a Th1 expression.^{1, 21, 79} Although no evidence to demonstrate any differences in susceptibility to HIV infectivity between Th1 and Th2 exist *in vitro*, an innocent bystander effect of AIT could be expected to result in the maintenance of generalized and possibly HIV-specific cellular immunity *in situ*. Again, an unchecked allergic response with prolonged Th2 activity could also have adverse clinical effects on HIV progression in the susceptible patient. Such a hypothesis is based on observations of the adverse relationships among high IgE, atopic disease, and HIV disease progression.^{24, 95} This author recently has completed a case study of one HIV patient with severe allergic rhinitis unresponsive to medical management who underwent 1 year of AIT for dust mite, grass, tree, and weed sensitivity (Marshall GD: Submitted for publication, 1997). His absolute CD4 counts as well as HIV load (measured by branch DNA analysis) were monitored at regular intervals. His CD4 numbers remained stable, there was no evidence of increased viral expression in serum, his underlying HIV disease showed no evidence of progression, and his atopic symptoms improved dramatically. Although by no means definitive, these results provide the impetus for conducting a larger trial of AIT in atopic patients.

CONTROLLED TRIAL OF AIT IN ATOPIC HIV-POSITIVE PATIENTS

There remains a great deal of social pressure on HIV-positive patients.⁸⁰ Job security, insurability, and many social interactions can be adversely affected. As a result, many persons at risk for becoming HIV positive avoid testing, and those who know that they are positive choose not to divulge that information, even to their physicians. With the incidence of allergic rhinitis approaching 17 million in the United States alone, there are almost certainly HIV-positive people (both known and unknown to their allergists) who are currently receiving AIT. Additionally, for the reasons discussed above, there are HIV-positive atopic patients who would clearly be candidates for AIT except for their underlying disease. How should allergists and immunologists handle these patients? Should an arbitrary decision be made to deny all HIV-positive atopic subjects access to AIT? Are there any special precautions that should be taken, including special monitoring techniques? Should an

Table 2. SUGGESTED INCLUSION CRITERIA FOR AIT TRIAL IN HIV-POSITIVE PATIENTS

Early/middle HIV disease
No AIDS-defining illness
CD4 $\geq$ 400/mm ³
Allergic rhinitis only
Unresponsive to environmental control/pharmacotherapy
Otherwise eligible for AIT
Careful clinical and laboratory monitoring available
Regular reassessment of safety and efficacy

atopic patient with any CD4 count be treated? What about patients who have progressed to AIDS?

Clinical trials with adequate numbers of participants to answer these questions in a statistically sound fashion will require several years and much money to accomplish. In the interim, there may be patients who will meet the above-described criteria for AIT previously described and whose atopic condition is severe enough to warrant immunologic intervention. If an allergist immunologist is considering treating an HIV-positive atopic patient with AIT, several safety guidelines should likely be followed (Table 2). First, initial trials should be limited to those patients with allergic rhinitis only. For all its promise, the efficacy of AIT is clearly established for allergic rhinitis only.³⁹ Trials in other atopic conditions (e.g., asthma) should await the establishment of safety of AIT in HIV-positive rhinitis patients. This caution is based on the questions regarding AIT efficacy for asthmatic subjects¹⁴ and the lack of any reported efficacy for other atopic conditions. Additionally, AIT should be limited to pollens and dust mites and should not be used for dander-sensitive subjects, who can limit their allergen exposures. Next, patients should be ones who would otherwise qualify for AIT except for his or her HIV status; that is, classic nasal symptoms with confirmatory positive allergy test results (preferably in vivo) unrelieved by standard medical therapy or environmental control, who can be monitored carefully and repeatedly for a specified time for both safety and efficacy. The subject should have early-to-middle HIV disease (i.e., peripheral CD4 count $\geq$ 400/mm³) with no history of opportunistic infection or AIDS-defining illness and no evidence of plasma HIV viremia. Viral load in the blood must be monitored with sensitive techniques such as branch DNA or RT-PCR. Serum measurements of p24 antigen are too insensitive to detect evidence of early virus activation.⁵² CD4 populations also should be monitored. As a minimum, DR and CD25 should also be studied for signs of cell activation that could signal increased susceptibility to infection and thus disease progression.^{66, 67} Monitoring should be obtained before a given weekly injection to minimize spurious changes that could occur shortly after allergen injection but have no specific clinical importance. The patient should be monitored monthly for at

least the first 3 months and no less than quarterly for the duration of treatment.

Clinical monitoring, consisting of repeated assessment of symptom scores and medication diaries, should be maintained to document efficacy (or lack thereof) in a particular treated patient. Repeated assessments for adverse events, including local and systemic shot reactions (both immediate and delayed), as well as disease activity should be documented. In advance, proposed duration of AIT should be agreed on. Typically, if no demonstrable efficacy has occurred in a patient receiving AIT within 1 year of starting, that patient is considered a treatment failure and further intervention is stopped.²¹ Finally, AIT should be undertaken with the knowledge and support of the HIV-positive patient's primary care physician, who may be more able to detect subtle changes in the course of the underlying HIV disease. Written informed consent, which includes acknowledgment of potential risks and benefits, should be obtained.

CLINICAL TRIALS OF AIT IN HIV-POSITIVE PATIENTS: IMPLICATIONS FOR FUTURE HIV THERAPIES

The safety and efficacy of allergen immunotherapy in HIV-positive atopic patients should be established in a formal trial that would include careful clinical and laboratory monitoring. Optimal conditions for response and safety should be pursued in initial studies. Once safety is established, questions such as treatment at different stages of HIV disease (or peripheral CD4 levels), duration of therapy, treatment of other atopic diseases, and use of standardized allergens versus T-cell peptides can be addressed. Epidemiologic studies that establish the correlation between atopic disease and status of HIV disease should also be conducted on an international scale. Addressing the mechanism of activity of AIT in the HIV-positive compared with HIV-negative population to determine whether an allergen-specific Th2 to Th1 switch can occur in HIV-positive patients as well is also important.

The ability to generate antigen-specific Th1 responses could have particular importance to the development of therapeutic HIV vaccines. Until recently, assessment of vaccine efficacy has been accomplished by measuring antibody responses to the candidate vaccine correlated with any effects on HIV disease progression.^{33, 57} The importance of promoting increased cellular immune responses with HIV vaccine administration has been increasingly appreciated.^{51, 84} Unfortunately, measuring HIV-specific CTL activity before and after vaccine administration is extremely difficult from a technical standpoint and can be done by relatively few research laboratories. What is needed is a monitoring technique that can determine whether HIV vaccines can cause increased antigen-specific Th1 activity, preferably measured *in vivo*. Monitoring changes in DTH responsiveness with vaccine antigens during and after therapy is a potential approach to this problem.⁵⁶

If AIT proves to be both safe and efficacious in HIV-positive patients, positive effects on containing underlying HIV disease may also occur. Innocent bystander effects on HIV-specific clones may promote Th1 activity and thus preserve effective anti-HIV cellular immune responses. Additionally, future efforts for HIV vaccines could be patterned after AIT. This might include repeated injections of antigen at shortened (i.e., weekly) intervals, as well as altering the dose and/or composition of vaccines. Such exciting approaches should offer renewed optimism for the role of active immunomodulation in the treatment of HIV disease.

CONCLUSION

Patients with HIV disease have increased susceptibility to and often severity of atopic diseases, including allergic rhinitis. Allergen immunotherapy (AIT) has largely been denied these patients because of safety and efficacy concerns. Although concerns over HIV activation by standard vaccines continue to exist, there are theoretical reasons to believe that AIT is safe in HIV patients and, if efficacy can be established, might also have an indirect effect on controlling underlying HIV disease.

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