High-activity antiretroviral therapy (HAART) has led to a dramatic improvement in the quality of life and life expectancy of HIV-positive patients. This improvement and the increase in the number of cases of HIV infection diagnosed in Spain since 20021 are 2 factors involved in the increased prevalence of this infection. For this reason, psoriasis in association with HIV is becoming increasingly frequent in dermatology clinics.

Epidemiology

The true frequency of patients with psoriasis and HIV infection varies depending on the series. A study of 2000 infected patients carried out in San Francisco showed a prevalence of 2.5%,2 a figure comparable to that for the general population. Another study of 700 infected patients...
in Berlin showed a prevalence of 5%, which was higher than that in the reference population. Data for the Spanish population show a prevalence of HIV infection in association with psoriasis of 4%. This figure, however, was obtained from a selected population with a predominance of intravenous drug abusers and patients with very low CD4 counts; it is therefore not comparable with the mean for Spain, which is estimated at 1.4%.

Furthermore, no relationship has been found in the different series studied between the mechanism of HIV transmission and the development of psoriasis lesions.

## Relationship With Immune Status

Initial studies suggested a link between increasing immunosuppression and the severity of the psoriasis, such as a Spanish study of 1161 patients with CD4 counts of less than 450/µL, of whom 81% presented psoriasis lesions. The tendency to develop more severe forms of psoriasis in patients with low CD4 counts was also observed in several later studies.

A recent study carried out in Singapore on 96 HIV-positive patients, of whom 24 presented psoriasis lesions, revealed that 70% developed lesions at the time of diagnosis or later; this suggests that HIV has a direct effect on the onset of psoriasis. Furthermore, patients who presented a higher degree of immunosuppression (CD4<200/µL) had a 9-fold higher risk of suffering from psoriasis lesions.

## Immunopathogenesis

Both psoriasis and HIV infection have been linked to overexpression of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ); this is known as the Th1 inflammatory response. High levels of these cytokines have also been found in synovial fluid and in the cutaneous lesions of patients with psoriasis.

Elevated levels of TNF-α occur at all stages of HIV infection. They have been linked with increased viral replication, depletion of CD4+ T lymphocytes and some clinical signs and symptoms such as fever, cachexia, aphthous ulcers, fatigue, and dementia. The direct effect on viral replication means that levels of TNF-α correlate directly with the viral load. It has also been shown that levels of TNF-α in HIV infection reach peak values with the onset of opportunistic infections such as tuberculosis.

The 2 nonselective inhibitors of TNF-α, thalidomide and pentoxifylline, have been shown to reduce viral load when administered to asymptomatic HIV-positive patients and to those with active infections due to *Mycobacterium tuberculosis*. Treatment with thalidomide lowered TNF-α levels, whereas treatment with pentoxifylline did not.

In terms of the link between HIV infection and TNF-α, several studies have attempted to evaluate the safety, tolerability, and efficacy of anti-TNF therapies in HIV-positive patients. A trial by Wallis et al enrolled 16 HIV-positive patients with CD4 levels of less than 200/µL, who had been diagnosed with active pulmonary tuberculosis. Those patients were treated with etanercept at a dosage of 25 mg twice a week for 4 weeks, and standard antituberculous therapy was instated. Despite the low statistical power of the study, a more favorable response was observed in the group that received etanercept than in the control group, when radiologic response, time to negative sputum culture, and constitutional symptoms were evaluated. Treatment with etanercept was shown to be safe in that phase 1 study. Analyses showed a 25% increase in CD4 counts at the end of the treatment period, with no effect on the viral load.

Mallon et al contributed new data on the pathogenic mechanisms of psoriasis when they studied the prevalence of HLA-C alleles in the specific context of psoriasis and HIV infection. In a sample of patients with psoriasis, they found significant differences in the prevalence of the Cw0602 allele between patients with and without HIV infection (79% and 25%, respectively). The immune disruption that takes place in HIV infection may act as a trigger for psoriasis in people with a genetic predisposition due to the Cw0602 allele. This allele has also been linked to cases of guttate psoriasis that appeared after pharyngotonsillitis or cases in which streptolysin titers were greater than 200 IU/mL when compared to the control population (100% compared to 20%).

## Clinical Signs and Symptoms

The first reference to the link between psoriasis and HIV was published in 1985, when it was found that this infection could precipitate or exacerbate psoriasis or Reiter syndrome.

In their classic study, Obuch et al distinguished 2 groups among HIV-positive patients who presented psoriasis lesions, according to whether they had been diagnosed with psoriasis before (1/3) or after (2/3) contracting HIV infection. Another, more recent, study grouped patients based on whether or not they had a personal or family history of psoriasis.

The first group, consisting of patients in whom psoriasis appeared before HIV infection or who had a family history of psoriasis, presented psoriasis lesions similar to those in the general population, with psoriasis in plaques being the most frequent clinical form. A higher percentage of patients who developed psoriasis lesions after HIV infection, however, presented severe and extensive psoriasis. Thus, despite the fact that the most frequent presentation was also the plaque form, a statistically significant percentage of patients predominantly presented...
the inverted forms of psoriasis, with intense involvement of the scalp, armpits, and groin. Palmoplantar involvement and localized or generalized pustular forms were also more common. There were no intergroup differences in the erythrodermal forms.

Episodes of guttate psoriasis were diagnosed in both groups, sometimes in association with a prior streptococcal pharyngeal infection. The lesions of the patients in the first group improved after antibiotic therapy, whereas the lesions of the patients in the second group were refractory to antibiotic treatment. An increase was also observed in the frequency of secondary infections due to *Staphylococcus* or *Candida*, with some cases of cutaneous sepsis due to *Staphylococcus aureus*.

Thus, the sudden exacerbation of extensive and severe inflammatory psoriasis should indicate suspected HIV infection and requires a serological analysis. In patients already diagnosed with HIV, the considerable efficacy of the new antiretroviral drugs has meant that the classical clinical forms predominate due to the improved immune status of these patients.

HIV-positive patients present different types of spondyloarthropathy in which severe joint involvement is observed, with joint destruction; they also present nail involvement and associated palmoplantar lesions. Joint involvement in patients with psoriasis and HIV infection is aggressive and is more prevalent and clinically more florid than in HIV-negative patients.25 Unlike in Reiter disease, sacroiliac involvement is rare in these patients.

Table 1 provides a summary of the clinical characteristics of psoriasis in HIV-positive patients.

### Other Psoriasiform Dermatoses in HIV Infection

Certain skin diseases share some of the clinical manifestations of psoriasis and it is important to be able to differentiate them. This may be difficult in HIV-positive patients since, as mentioned above, psoriasis may have an atypical presentation in these patients.

### Reiter Disease

Reiter syndrome illustrates the difficulty of differential diagnosis in HIV-positive patients, due to the severe joint involvement and the varied morphology of the lesions that may develop in patients with psoriasis. Diagnosis of Reiter disease is indicated by the characteristic triad of polyarthritis, urethritis, and conjunctivitis, together with the typical skin lesions.

The disease is most frequent among young men and the association with HLA-B27 is a characteristic finding, which is present in between approximately 80% and 90% of patients. Patients with this association typically have more serious disease.

HIV infection and other intestinal and genitourinary infections have been implicated in the pathogenesis of the disease. The prevalence of Reiter disease is therefore higher in HIV-positive patients than in the general population.

Typical of the disease are episodes of vesicular-pustular lesions on the palms and soles; over the course of the episode, the lesions coalesce, progressing to scabs and hyperkeratosis. Also typical are genital involvement in the form of circinate balanitis, and involvement of the nails. The extensor surface of the limbs and the scalp may also be affected, though to a lesser extent. Due to the clinical similarity to psoriasis lesions, however, diagnosis requires the presence of more elements of the triad.

Treatment options for this disease are the same as those for psoriasis. Oral acitretin is considered the treatment of choice in HIV-positive patients.

### Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is a rare disease that is clinically characterized by the appearance of follicular hyperkeratotic papules on an erythematous base. The lesions show a marked tendency to coalesce, extending in a caudal direction and leaving islands of sparing. Involvement of the palms and soles also often occurs in the form of reddish-orange keratoderma with a waxy appearance. Development of varying degrees of erythroderma is characteristic of the disease.

Most cases of PRP are acquired, though occasional familial cases occur. Different environmental factors have been suggested as triggers, including infections—particularly HIV.

According to Griffiths,28 PRP is divided into 5 categories, depending on age, duration, and type of skin involvement. A sixth category has been proposed for the
form of PRP associated with HIV infection.29 Besides the typical lesions, clinical signs and symptoms in HIV-positive patients may include nodular and cystic acne conglobata and hidradenitis suppurativa, as well as elongated follicular spines. The disease tends to be resistant to conventional topical and oral treatment with acitretin, but may respond to HAART.

Amicrobial Pustulosis

Several diseases manifest with sterile polymorphonuclear pustules and are included in the differential diagnosis for pustular psoriasis. These diseases are classified in 2 groups, depending on whether the pustules are grouped in the palmoplantar area (localized forms) or occur all over the body (generalized forms). Following is a brief description of 3 examples of these diseases:

SAPHO Syndrome

Palmoplantar pustulosis may be associated with sterile inflammatory bone lesions. SAPHO syndrome is an entity that frequently manifests with localized pustules in the palmoplantar region and bone involvement, particularly affecting the anterior wall of the chest. The name is the acronym formed from the most prevalent manifestations: synovitis, acne, pustulosis, hyperostosis, and osteitis. Diagnosis is based on established clinical criteria, as the palmoplantar lesions alone are indistinguishable from palmoplantar pustular psoriasis.

Subcorneal Pustular Dermatitis or Sneddon-Wilkinson Disease

Subcorneal pustular dermatitis predominantly affects middle-aged women. The pustular lesions coalesce to form rounded or circinate plaques predominantly on the abdomen and in the intertriginous areas, such as the armpits and groin. Palmoplantar or mucous-membrane involvement is rare.

This disease has a cyclical course in which old pustules disappear, leading to surface desquamation and the formation of new pustules.

Unlike pustular psoriasis, this disease usually responds well to oral dapsone.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis is an acute, nonrecurring disorder that has traditionally been linked to numerous drugs and, more recently, to enterovirus infections, hypersensitivity to mercury, and spider bites. It affects all age groups and both sexes equally.

Onset of symptoms is acute with high fever for 2 or 3 days. The development of the lesions, in the form of small pustules in a skin-fold or on the face from where they spread rapidly, coincides with the onset of general malaise. Symptoms resolve within 1 or 2 weeks with generalized laminar desquamation.

Histopathology

From a histologic point of view, the psoriasis presented by HIV-positive patients is indistinguishable from that of noninfected patients. However, Munro microabscesses appear less frequently in patients infected with HIV, the acanthosis is more irregular, and there is a less marked thinning of the suprabasal layer.30 The presence of necrotic keratinocytes is also more common.

Plasma cells and histiocytes are also more frequently observed in the infiltrate in HIV-positive patients.

Whereas the ratio of CD4 cells to CD8 cells is estimated at 2.05 in HIV-negative patients, this ratio is inverted in HIV-positive patients and the mean CD4/CD8 ratio is between 0.5 and 0.8.31

Prognosis

Psoriasis is not considered a diagnostic disease of AIDS and it does not affect survival, but it does have a considerable effect on the quality of life of these patients.32 Furthermore, some of the drugs used to treat psoriasis may have serious repercussions due to both their immunosuppressive effect and their interactions with other drugs.

Treatment

Since the first studies linking psoriasis with HIV infection, emphasis has been placed on the resistance of these patients to conventional treatment. Furthermore, there are little data in the literature—typically isolated cases or small series.

Antiretroviral Treatment

Exacerbation of psoriasis lesions with increasing degrees of immunosuppression suggested antiretroviral treatment as a therapeutic strategy. With the introduction of the first drugs that acted specifically against HIV (with zidovudine [AZT] as the only such drug available), several cases were reported of partial improvement of psoriasis lesions that had previously been refractory to other treatments.33 The drug was shown to be useful and safe, though its mechanism of action against psoriasis was unknown. It probably acts
by reducing keratinocyte proliferation due to its mechanism of interference with DNA synthesis.

The introduction of combined therapies has made it very difficult to evaluate the effect of these drugs separately and there is thus nothing in the literature in this regard. As with earlier single-drug therapy, current combined therapies achieve clinical improvement of psoriasis lesions, even in recalcitrant cases resistant to other treatments. Anecdotally, some patients present severe exacerbations coinciding with initiation of HAART. The severity of the clinical picture correlates with an improvement in the CD4 cell count. This paradoxical response has been linked to immune reconstitution syndrome.

However, as well as the direct effect of reducing the frequency and severity of the psoriasis lesions, currently available antiretroviral therapy achieves a level of immune reconstitution that means patients can tolerate immunosuppressive psoriasis treatments that were not admissible in the pre-HAART era.

Topical Treatment

Any of the different commercially available topical treatments for psoriasis may be used in these patients. Nevertheless, these treatments are usually insufficient, as severe forms are frequent.

Phototherapy

Use of phototherapy is widely accepted for the treatment of psoriasis associated with HIV infection, and for other diseases presented by HIV-positive patients, such as pruritus, eczema, prurigo, and eosinophilic folliculitis. In fact, phototherapy and retinoids, alone or in combination, have traditionally been considered the treatment of choice for psoriasis in patients with HIV infection.

Regimens with both UVB and psoralens plus UVA (PUVA) may be used in HIV-positive patients. Some older studies, however, recommend PUVA therapy rather than UVB therapy.

Exposure to large accumulated doses of ultraviolet light can increase the viral load when patients do not receive antiretroviral treatment. However, exposure to short doses of phototherapy in patients on antiretroviral treatment does not worsen the pre-existing situation. This response is affected by the phototype; thus, patients with a greater degree of pigmentation who require higher doses of radiation are more susceptible to increased viral load.

Phototherapy worsens the outcome of Kaposi sarcoma, which is therefore a contraindication for this type of treatment.

Retinoids

Both acitretin and etretinate are effective, particularly in erythrodermic, pustular, and palmoplantar forms of psoriasis. This, together with the fact that they do not cause immunosuppression, makes retinoids first-line drugs. Usual dosages are between 0.5 and 1 mg/kg per day.

Furthermore, joint disease also responds to treatment in most patients.

Although they are generally well tolerated, a side effect that can limit the use of retinoids is their negative effect on the lipid profile. HIV-positive patients have altered lipoprotein levels, with increased triglycerides and free fatty acids. This profile deteriorates with the introduction of triple antiretroviral therapy. Very high triglyceride levels may become a contraindication or cause for suspension of treatment with retinoids.

Immunosuppressives: Cyclosporine and Methotrexate

The immunosuppression that characterizes HIV infection has traditionally been considered an absolute contraindication for treatment with methotrexate or cyclosporine in patients with moderate to severe psoriasis. The ability of cyclosporine to lower the CD4 cell count is well known. In fact, serious complications, such as fulminant Kaposi sarcoma and pneumonia due to Pneumocystis jiroveci (formerly, Pneumocystis carinii), have been detected due to the use of these drugs in severely immunosuppressed patients. Furthermore, the frequent association of HIV infection with abuse of alcohol or other drugs, or with chronic infections due to hepatotropic viruses, limits the use of these immunosuppressants.

Despite the reticence of dermatologists to treat immunosuppressed patients, such as HIV-positive patients, with therapies that might increase their level of immunosuppression, these drugs are used in specific cases to treat psoriatic arthritis or Reiter disease in HIV-positive patients.

Studies have been published on the use of cyclosporine in early stages of HIV infection, with encouraging results. A dosage of 2 mg/kg per day in patients with incipient HIV infection, with CD4 counts above 500/µL showed an increase in the viral load, with no variations in CD4 levels or increased risk of infections.

The introduction of HAART and the radical change in immunologic terms has meant that specialists feel more confident when prescribing these drugs. The most recent studies have tested the long-term use of methotrexate and shown it to...
be a safe drug. Nevertheless, infectious and neoplastic complications continue to appear with greater frequency than in the HIV-negative population.

Biologic Therapy

The introduction of biologic therapies in recent years has brought new hope to the treatment of patients with psoriasis and HIV infection. The experience of physicians from other specialties has contributed data on the safety and efficacy of these drugs in the treatment of other diseases in HIV-positive patients. This has led to new ways of thinking about how these patients can be treated.

Although the use of anti-TNF drugs was contraindicated by clinical guidelines until relatively recently, the most recent literature would seem to indicate that their use does not significantly increase rates of morbidity and mortality in these patients; nor does it appear that inhibiting TNF-α has a negative effect on the CD4 count or viral load.

However, as the risk of using these drugs in HIV-positive patients has not been evaluated in controlled studies, during therapy it is essential to carry out optimal antiretroviral treatment, the recommended prophylaxis against infections, and a strict clinical and analytical follow-up.

Infliximab

The increased susceptibility to intracellular pathogens caused by drugs that act by blocking TNF-α is well known. There is a higher risk of reactivating latent tuberculosis with infliximab than with the other anti-TNF drugs. This is thought to be due to its combined effect as a TNF-α and IFN-γ blocker.

Different studies, however, have used infliximab to treat psoriasis or other rheumatologic diseases in HIV-positive patients, with good results.

Bartke et al treated a 46-year-old patient who presented an episode of psoriasis with severe skin and joint involvement after beginning HAART with didanosine, lamivudine, and zidovudine. The episode was not controlled with a combination of methotrexate and corticosteroids. Before beginning treatment with infliximab, the patient was receiving quadruple antiretroviral therapy and presented a CD4 count of 770/µL and a viral load of less than 500 copies/mL. Treatment with infliximab was instated, methotrexate was maintained, and corticosteroids were progressively reduced until they were suspended. After 2 months, the cutaneous symptoms had resolved, the joint complaints were controlled, and the laboratory markers of activity were normal. Clinical improvement was maintained after 6 months of treatment and the CD4 count was 814/µL, with a viral load of less than 400 copies/mL. Infliximab was well tolerated during 18 months of treatment and no side effects were observed.

Nevertheless, caution should be the rule, as an HIV-negative patient treated with infliximab and cyclophosphamide for rheumatoid arthritis presented a reduction in the CD4 count during treatment.
Efalizumab

To date, the literature contains no references to the use of efalizumab in HIV-positive patients. However, 4 clinical trials carried out on patients negative for HIV and hepatitis C virus (HCV) showed that the incidence of infections did not increase in patients who received efalizumab compared to the placebo group.60

Etanercept

A recent review of the use of etanercept in psoriasis and psoriatic arthritis concluded that it is an effective and safe treatment for patients infected with HIV or HCV.61 In HCV patients, etanercept did not alter the viral load, affect liver function, or increase the risk of infections.62 In fact, based on its anti-TNF function, it has been tested as additional therapy with ribavirin and interferon for treating chronic HCV infection.63

Nevertheless, an HIV-positive patient who presented a CD4 count of less than 50/µL and a viral load of 4200 copies/mL despite antiretroviral therapy, developed extensive plaque psoriasis with severe joint involvement that did not respond to different disease-modifying treatments, including corticosteroids, hydroxychloroquine, and minocycline. In view of the disease progression, it was decided to instate treatment with etanercept. After 3 weeks, at a dose of 25 mg twice a week, the skin lesions improved drastically and the arthritis stabilized. The lymphocyte count and viral load remained stable for 4 months but the patient suffered from recurrent polymicrobial infections due to germs such as Stenotrophomonas maltophilia and Pseudomonas aeruginosa; it was therefore decided to suspend treatment.64

The first case of a patient coinfected with HIV and HCV who was treated with etanercept was published recently.65 The patient suffered from severe psoriatic arthritis associated with psoriatic skin lesions that did not respond to a combination of methotrexate and cyclosporine. Doses of 25 mg of etanercept twice a week achieved remission of the skin and joint symptoms.

The available experience with etanercept for the treatment of diseases other than psoriasis in HIV-positive patients also supports its safety, as in the case of an HIV-positive patient with severe rheumatoid arthritis that was resistant to conventional treatment but responded to etanercept; the patient’s viral load was maintained under control using antiretroviral therapy.66

Risk of Drug Interactions in Psoriasis Treatment

HIV-positive patients commonly receive several drugs, both for treatment of the virus and for prophylaxis against associated opportunistic infections. This requires increased caution when prescribing other drugs.

First and foremost, drugs that may trigger episodes of psoriasis (Table 2) should be avoided.

Drugs Used for Treatment or Prophylaxis of Opportunistic Diseases

The use of trimethoprim–sulfamethoxazole (cotrimoxazole) for the treatment of or primary or secondary prophylaxis against P. jiroveci in patients undergoing treatment with methotrexate increases methotrexate-induced inhibition of the metabolic pathway for folate, while also reducing its excretion in the kidneys, with the resulting risk of liver toxicity. The association of cyclosporine and cotrimoxazole has shown a reversible deterioration in renal function in patients who have undergone kidney transplant.65 Reduced cyclosporine activity has also been observed when it is administered in association with a sulfamide.

Ganciclovir, a drug used for the treatment of and secondary prophylaxis against infection by cytomegalovirus (CMV), is myelotoxic and nephrotoxic.66 The myelotoxicity is reversible but the risk increases when the drug is administered simultaneously with other myelotoxic drugs such as methotrexate. The nephrotoxicity may limit the use of cyclosporine in patients who are being treated with ganciclovir.

Sulfadiazine is a drug used for treatment of and prophylaxis against Toxoplasma gondii, through its induction of cytochrome 3A4, it causes a reduction in plasma levels of cyclosporine, thus reducing its efficacy as an immunosuppressive agent.67 The use of sulfadiazine in association with methotrexate has shown an increase in hematologic side effects due to reduced protein binding of the methotrexate.

Pyrimethamine is used in combination with sulfadiazine in the treatment of and prophylaxis against T. gondii as its mechanism of action inhibits folate metabolism. Thus, in patients receiving methotrexate, it may potentiate hematologic toxicity. This combination has caused convulsions in pediatric patients with leukemia involving the central nervous system.

The administration of fluconazole (a drug used for secondary prophylaxis against Cryptococcus neoformans) to patients undergoing treatment with cyclosporine may increase plasma concentrations of the latter drug.

Amphotericin B is the treatment of choice for C. neoformans and may potentiate the nephrotoxic effect of cyclosporine when both drugs are administered together.68

Rifampicin is used to treat tuberculosis and may reduce the effect of cyclosporine.

The association of other drugs used for prophylaxis against or treatment of tuberculosis (isoniazid, rifampicin, and...
pyrazinamide) and *Mycobacterium avium intracellulare* (clarithromycin) has not shown any interactions of note with the different drugs used to treat psoriasis. These interactions are summarized in Table 3.

**Table 3. Pharmacologic Interactions Between Drugs Used to Treat Psoriasis and Opportunistic Infections**

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<th>Drugs Used to Treat Human Immunodeficiency Virus</th>
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**Table 2. Drugs That Trigger Episodes of Psoriasis**

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<tr>
<th>Antimalarial drugs</th>
<th>β-Blockers</th>
<th>Angiotensin-converting enzyme inhibitors</th>
<th>Interferon-a</th>
<th>Lithium salts</th>
<th>Gold salts</th>
<th>Systemic corticosteroids</th>
<th>Nonsteroidal anti-inflammatory drugs (indomethacin)</th>
<th>Potassium iodide</th>
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<td>Cyclosporin</td>
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**Conclusions**

Observant dermatologists may suspect previously unknown HIV infection by observing the psoriasis skin lesions in patients with asymptomatic and early-stage HIV infection. In these patients, psoriasis reveals the presence of a systemic disease and is the key to early diagnosis.

Experience in the treatment of psoriasis in HIV-positive patients receiving immunosuppressive therapy is limited. Biological therapies probably constitute another weapon to be considered in the treatment of psoriasis in HIV-positive patients. Nevertheless, caution requires that this therapy be reserved for patients in the initial stages of infection or patients undergoing antiretroviral treatment, especially patients with normal (359–1519/µL) or slightly low CD4 counts. The risk-benefit relationship may be more favorable in these patients.

It should also be remembered that patients may be receiving other treatments for their underlying disease and it is therefore essential to take into consideration the possible interactions.
interactions between the different drugs when instating a particular treatment.

Declaration of Conflicts of Interest

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