

Psoriasis in the Patient With Human Immunodeficiency Virus, Part 2: Review of Treatment

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GOAL

To understand psoriasis in patients with human immunodeficiency virus (HIV) infection to better manage patients with these conditions

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the need for topical therapy, phototherapy, systemic therapy, or antiretroviral therapy for patients with psoriasis and HIV.
2. Evaluate the adverse effects of some therapies for psoriasis in immunocompromised individuals.
3. Discuss how certain therapies manage the symptomatology of psoriasis.

CME Test on page 201.

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Psoriasis is a chronic, immune-mediated skin disease affecting approximately 1% to 3% of the human immunodeficiency virus (HIV)-infected

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population. Psoriasis appears in patients with HIV either as the first clinical manifestation of the disease or, less commonly, during the advanced stages of HIV when it has progressed to AIDS.

This 2-part series reviews the pathogenesis of HIV-associated psoriasis as well as the various therapeutic regimens that have effectively treated psoriasis in patients with HIV. These therapies address the profound immune dysregulation that defines psoriasis. The second part of the series focuses on the treatment of HIV-associated psoriasis.

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The stepwise approach to the treatment of psoriasis, from topical to systemic treatment depending upon the severity of the condition, applies to the management of immunocompetent patients with psoriasis. Treatment of psoriasis associated with human immunodeficiency virus (HIV) infection is challenging because most of the available modalities currently marketed for treatment involve immunosuppression; additionally, the symptomatology in patients with HIV often is more severe and refractory to conventional treatment.¹

The second part of this series serves to complement the review of the pathogenesis of psoriasis in patients with HIV² by delineating currently available therapeutic options while also reviewing landmark studies that have evaluated the efficacy and safety of these measures in immunocompromised patients with psoriasis (Table).

Topical Therapy

Treatment options for psoriasis in HIV-infected individuals include conventional topical therapies, such as corticosteroids, tar, calcipotriene, or anthralin, for mild localized disease.¹⁵ Calcipotriol, a topical vitamin D₃ analog, is a biologically active form of vitamin D capable of inhibiting cell proliferation in cultures of human keratinocytes and has been an effective local treatment of HIV-associated psoriasis.¹⁶ Gray et al³ reported the use of topical calcipotriol daily in conjunction with oral etretinate to markedly improve erythrodermic psoriasis that had been refractory to etretinate monotherapy, psoralen plus UVA (PUVA), and topical steroids in a patient with advanced HIV disease (CD4 lymphocyte count, 70×10⁶ cells/L).

Phototherapy

In more advanced cases in which psoriasis is refractory to topical therapy, UV radiation (either UVB or PUVA) can be utilized.¹⁷⁻²⁰ Increased risk for skin cancer and reduced resistance to infection are possible consequences of the immunomodulatory effects of these UV therapies.²¹ In an immunocompromised patient, such as one with HIV infection, even modest changes in the immune system can be clinically relevant.²² Concerns about the use of UV therapy in HIV-infected individuals arose from *in vivo* and transgenic animal experiments in which HIV markers were induced or up-regulated, and HIV transcription and replication were activated.²³⁻²⁵

The effects of UVB and PUVA treatment on the clinical course of HIV infection have shown increases in p24 antibodies and viral load after phototherapy; overall, UV radiation does not appear to have a deleterious effect on the CD4 lymphocyte count or clinical status in treated patients.²⁶ UV

radiation is generally considered to be a safe treatment modality in HIV-infected individuals, and Adams et al²⁷ have proposed clinical guidelines for its use as follows:

- “Is the skin disease UV responsive? If the answer is yes, consider phototherapy.
- Do alternative therapies offer less risk to the patient? If yes, it may be judicious to try alternative treatments first.
- Is anticipated improvement in morbidity after phototherapy enough to justify potential risks? If yes, proceed with phototherapy. If no, consider other treatments.
- Are there other contraindications to phototherapy (eg, medication that confers photosensitivity)? If yes, weigh the risk-benefit ratio.”

Oracion et al²⁸ recommend HIV serology in patients who are candidates for phototherapy and monitoring of viral load and CD4 lymphocyte count before treatment, at monthly intervals during treatment, and 3 months after treatment. Despite the lack of definitive clinical evidence of deleterious effects of phototherapy in HIV-infected individuals, the risk-benefit ratio of phototherapy should be examined on a case-by-case basis, taking into account the patient's stage of HIV disease; the degree of discomfort, disfigurement, and disability caused by the dermatologic condition; and the availability of other possible treatment modalities.²⁶

The impact of the immunosuppression or HIV activation during phototherapy on the progression of HIV disease is poorly understood. Phototherapy has been reported to have no apparent adverse effects in studies measuring CD4 T-cell counts as an immunologic parameter.^{17,29-31} A prospective study conducted by Breuer-McHam et al⁴ followed patients with documented HIV infection referred by their dermatologists for phototherapy of psoriasis or pruritus by measuring T-cell subsets, levels of p24 antigen, and HIV RNA values. For comparison, HIV-positive individuals without skin disease, with quiescent psoriasis or pruritus or with Kaposi sarcoma, were studied as a control group. Human immunodeficiency virus–negative controls included those with psoriasis undergoing UVB or PUVA phototherapy. All patients were treated with UVB for 1 minute up to 3 times weekly, with the dosage increasing over time for 6 weeks. The light box emitted 1.01 mW/cm² or 1.01 mJ/s. The data showed that although phototherapy clinically benefits HIV-positive patients with skin disease, phototherapy can increase both p24 and viral load in patients who are not receiving suppressive antiviral therapy. When patients' viral load levels were suppressed at baseline by antivirals, they also were

protected from any increase in HIV RNA levels at the end of the 6-week phototherapy period. Dramatic changes occurred in the serum HIV RNA of black patients who were found to have greater increases at week 6 than white patients. Therefore, the skin pigmentation type (Fitzpatrick skin types IV and V) must be taken into account because, in general, more UV light is given to more darkly pigmented individuals with consequently greater increases in circulating virus. Low-dose UV light may be safely used to decrease HIV expression at appropriate doses in conjunction with suppressive antiviral therapy.⁴

The reliance of clinicians on phototherapy in HIV-infected individuals varies tremendously among treatment centers, and a survey revealed almost no agreement as to which type of UV therapy is optimal among these patients.²² One survey found that phototherapy is widely used for HIV-infected patients: 80% (249/311) received UVB, 9% (28/311) received PUVA, and the remaining 11% (34/311) received a variety of combinations.³² A case has been made that PUVA may be preferable to UVB therapy because of its increased efficacy, especially with thick plaques and palmoplantar involvement, as is frequently encountered in the setting of HIV-associated psoriasis.³³ However, it should be noted that psoralens are commonly associated with gastrointestinal side effects and concomitant use of medications that can photosensitize the skin, such as trimethoprim-sulfamethoxazole, may be a contraindication to phototherapy.^{34,35}

Systemic Therapy

In the past, dermatologists have opted for systemic immunosuppressive therapy in severe refractory cases in which neither topical nor UV therapy had yielded benefit to patients with HIV-associated psoriasis. Cyclosporine A (CyA) has been used to successfully treat intractable psoriasis in immunocompetent patients, often showing results after conventional therapy has failed.^{36,37} Cyclosporine A is known to inhibit T-cell activation, thereby reducing the number of CD4 cells while also inhibiting HIV replication by removing the host cell target.³⁸ A case study conducted by Allen,⁵ which involved an HIV-positive patient (CD4 lymphocyte count, 0.04×10^9 cells/L) with psoriasis who had failed to improve with multiple treatments including zidovudine, methotrexate sodium, and etretinate combined with topical steroids, disputed the theory that the added immunosuppression associated with CyA would only aggravate the already present immune dysfunction in patients with HIV infection. An immediate benefit was seen with the administration of CyA at 5 mg/kg, as shown by the rapid clearing of psoriatic lesions and a

dramatic improvement in overall well-being, though the CD4 lymphocyte count remained low. No clear signs of acute deterioration or opportunistic infections were reported, except for a brief episode of oral thrush that responded to treatment with nystatin.⁵ While it is theorized that CyA, by inhibiting T cells and other antigen-presenting cells, could slow the overall course of HIV infection, further clinical trials are required to identify HIV-positive patients who will reap the overall benefits of treatment with CyA.⁶ Methotrexate sodium has been reported to cause profound leukopenia and death in some psoriatic patients with HIV infection and is therefore used with great trepidation.³⁹ Additionally, because of the known interaction with trimethoprim-sulfamethoxazole, methotrexate sodium is contraindicated in patients being treated prophylactically for *Pneumocystis carinii* pneumonia.³⁵

Tumor Necrosis Factor Blockers

The pathogenesis of psoriatic HIV infection revolves around cytokines that are involved in chronic inflammation. Tumor necrosis factor α (TNF- α) represents one such cytokine that is important in mediating immune responses in healthy patients; however, in patients with HIV infection, TNF- α has been shown to stimulate viral replication in vitro and also may contribute to the development of aphthous ulcers, fatigue, lipodystrophy, fever, and dementia.⁴⁰⁻⁴⁴ In patients with psoriasis, TNF- α , along with other mediators, induces keratinocytes to produce chemotactic factors for T cells and neutrophils and is strongly up-regulated in the psoriatic epidermis.⁴⁵ Some biologic agents are known to inhibit the effects of TNF- α in skin and attenuate its destructive process on bone and joints.⁴⁶ These biologic agents (ie, adalimumab, alefacept, efalizumab, etanercept, infliximab) have been employed as treatment of psoriasis.⁴⁷⁻⁵⁰

Various controlled trials have been conducted on the efficacy and safety of TNF blockers in psoriasis. This therapy has been proven to be a valuable option for controlling psoriasis versus placebo because it has a more rapid time to response, gives a better clearing rate of plaques, and most importantly, is well-tolerated by all study participants.^{51,52} While TNF blockers have been demonstrated to be effective and safe in clinical trials of healthy patients treated for inflammatory conditions, its use in patients with HIV infection has not yet been examined in detail because it is thought that cytokine-suppressive medications may increase the risk of opportunistic infections, sepsis, and progression to AIDS.⁴⁶

Aboulafia et al⁷ described the use of etanercept in an HIV-positive patient (CD4 lymphocyte count, $<0.05 \times 10^9$ cells/L; HIV RNA viral load,

4200 copies/mL) on highly active antiretroviral therapy (HAART) who had developed extensive psoriatic plaques, onychodystrophy, and psoriatic arthropathy with severe periarticular bone demineralization that was previously unresponsive to corticosteroids, hydroxychloroquine sulfate, and minocycline hydrochloride. Etanercept, a soluble TNF-receptor fusion protein, was prescribed at a dosage of 25 mg subcutaneously twice weekly. After 3 weeks, skin lesions had improved dramatically and joint inflammation stabilized, allowing the patient to regain ambulation. While the patient's CD4 lymphocyte count and HIV RNA viral load remained stable as his psoriatic plaques and joint inflammation improved, the clinical course was complicated by frequent polymicrobial infections including enterococcal cellulitis, cystitis, bacteremia, and *Pseudomonas aeruginosa* infection of the knee joint and lungs, which led to the eventual discontinuation of the TNF blocker.⁷ A recent case report by Linardaki et al⁸ focused on a patient with psoriatic lesions of the elbows, knees, scalp, and trunk, as well as concomitant hepatitis C virus and HIV infection (CD4 lymphocyte count, 340 cells/mm³; HIV RNA, <10,000 copies/mL). The exanthema was considered to be HIV related and was moderately improved with HAART, but the eventual presentation of debilitating polyarthritis refractory to methotrexate sodium and CyA yielded therapy with etanercept 25 mg twice weekly. Marked improvement in all inflammatory manifestations as well as remission of the psoriatic exanthema occurred promptly after initiation of etanercept.⁸ Sellam et al⁹ reported cases of psoriasis and psoriatic arthritis in 2 HIV-infected patients, one with AIDS. Both patients experienced severe skin and joint manifestations despite therapy with methotrexate sodium, prompting the add-on of infliximab, a monoclonal antibody to TNF- α , to the therapeutic regimen. Infliximab was found to rapidly and dramatically clear skin lesions and alleviate joint disease. The therapeutic effect lasted throughout follow-up, which was 2 years in one patient and 4 years in the other. Control of the HIV infection was satisfactory, with no reported opportunistic infections.⁹ Bartke et al¹⁰ also reported successful treatment of widespread psoriatic lesions and arthritis of the knee and ankle joints with infliximab in a patient with HIV infection (CD4 lymphocyte count, 68 cells/mm³; HIV-1 RNA, 1040 copies/mL¹). Multiple anti-inflammatory therapeutic measures were unsuccessful, including acitretin; methotrexate sodium; prednisolone; UVB therapy; and multiple topical therapies such as calcitriol cream, triamcinolone acetonide cream 0.5%, and tazarotene gel 0.025%. The patient was placed

on infliximab 3 mg/kg and within 2 days displayed a decrease in swelling of the joints and dramatic improvement of psoriatic plaques, with only minor side effects being reported such as lumbosacral bone pain.¹⁰

It is now recommended that in the setting of HIV infection, TNF- α antagonists should be reserved for highly selected patients who have refractory chronic inflammatory psoriatic disease, including debilitating joint pain. Antagonists of TNF- α may promote the recurrence of opportunistic infections or add to the risk of viral-induced lymphoproliferative malignancies associated with HIV-related immunosuppression; therefore, it is mandatory that optimal antiretroviral therapy and close monitoring of clinical and laboratory parameters be conducted. Additionally, prophylaxis of *Pneumocystis jiroveci* is recommended in patients with low CD4 lymphocyte counts.⁹

Antiretroviral Therapy

The demonstration of HIV transcripts using in situ hybridization in dermal dendritic cells in psoriatic lesions but not on nonlesional skin suggests that HIV infection might play a direct role in the initiation of psoriatic inflammation.⁵³ The hypothesis is supported by the observations of an improvement of psoriasis in HIV-infected individuals after antiretroviral therapy with zidovudine (also known as azidothymidine [AZT]).⁵⁴ The apparent clearing of psoriasis with AZT was first reported in 2 HIV-positive patients by Duvic et al¹¹ in 1987 and has been followed by numerous anecdotal confirmations.^{14,55-58} In an open-label study of 19 assessable HIV-positive patients with psoriasis, 90% (17/19) had either a partial or complete improvement during therapy with AZT at dosages of 1200 mg daily.⁵⁴ However, lower dosages may not produce a substantial effect.¹⁷ A study conducted by Townsend et al⁵⁹ evaluated HIV-negative patients who each received 200 mg of AZT every 4 hours during waking hours for a total of 1000 mg daily for 8 weeks. If a response was evident, treatment was continued for an additional 8 weeks. Clinical response was correlated with histologic changes in skin lesions at baseline and week 4. Four of 12 HIV-negative patients with long-standing, extensive psoriasis improved up to 80% after 16 weeks of therapy, and after 4 weeks of therapy with AZT, 50% of the biopsies displayed improved epidermal differentiation as characterized by the reappearance or the increased prominence of the granular layer and decreased parakeratosis. While 11 of 12 patients experienced macrocytosis within weeks of treatment, anemia did not develop in any patients. Four patients had a slight decrease in white blood cell count and absolute neutrophil count, but neither leukopenia nor neutropenia developed in any patients.⁵⁹ Overall, the drug was well-tolerated in

Studies Evaluating Therapies for Immunocompromised Patients With Psoriasis

Study (Year)	No. of Patients	Indication	Regimen	Results
Topical Therapy				
Gray et al ³ (1992)	1	Recalcitrant plaque psoriasis	Topical calcipotriol + oral etretinate	Marked improvement in psoriasis within days without alteration in serum calcium
Phototherapy				
Breuer-McHam et al ⁴ (1999)	32	Referred by dermatologist for phototherapy of psoriasis or pruritus	UVB for 1 min up to 3× weekly for 6 wk at 1.01 mW/cm ²	<ol style="list-style-type: none"> 1. More UVL is given to individuals with Fitzpatrick skin types IV and V, allowing greater increases in HIV RNA levels 2. Low-dose UVL may be safely used to decrease HIV expression at appropriate doses in conjunction with suppressive antiviral therapy
Systemic Therapy				
Allen ⁵ (1992)	1	Recalcitrant plaque psoriasis	Cyclosporine A	<ol style="list-style-type: none"> 1. Rapid clearing of psoriatic lesions, though the CD4 lymphocyte count remained low 2. Brief episode of oral thrush that responded to nystatin
Tourne et al ⁶ (1997)	1	Acute generalized pustular psoriasis and rapidly progressive, deforming arthropathy leading to fusiform swelling of fingers and toes	Cyclosporine A	<ol style="list-style-type: none"> 1. Marked improvement of psoriasis and arthropathy within 1 week 2. Condition remained stable and no opportunistic infections in 2 y follow-up period
TNF Blockers				
Aboulatia et al ⁷ (2000)	1	Recalcitrant psoriatic plaques, onychodystrophy, and psoriatic arthropathy	Etanercept	<ol style="list-style-type: none"> 1. After 3 wk, skin lesions improved and joint inflammation stabilized, allowing the patient to regain ambulation 2. Clinical course was complicated by frequent polymicrobial infections

Study (Year)	No. of Patients	Indication	Regimen	Results
TNF Blockers (continued)				
Linardaki et al ⁸ (2007)	1	Psoriatic lesions of the elbows, knees, scalp, and trunk, with severe psoriatic arthritis and concomitant HCV and HIV infection	Etanercept	Improvement of inflammation and remission of psoriatic exanthema
Sellam et al ⁹ (2007)	2	Recalcitrant psoriasis and psoriatic arthritis	Infliximab	<ol style="list-style-type: none"> 1. Rapidly and dramatically improved skin lesions while alleviating arthropathy, lasting through 4 y of follow-up 2. Control of HIV infection was satisfactory, with no reported opportunistic infections
Bartke et al ¹⁰ (2004)	1	Recalcitrant psoriatic lesions and arthritis of the knee and ankle joints	Infliximab	Decreased swelling of joints and dramatic improvement of psoriatic plaques, with only minor side effects such as lumbosacral bone pain
Antiretroviral Therapy				
Duvic et al ¹¹ (1987)	2	Opportunistic infections and psoriasis	Zidovudine	Allowed for remission of psoriasis in 2 HIV-positive patients
Berthelot et al ¹² (1997)	1	Recalcitrant psoriatic plaques	Zalcitabine + ritonavir	Decrease of psoriatic symptoms
Vittorio Luigi De Socio et al ¹³ (2006)	1	Advanced HIV infection with psoriasis and concomitant HCV-related cirrhosis	Stavudine + tenofovir disoproxil fumarate + enfuvirtide	Complete resolution of psoriasis by wk 8
Mamkin et al ¹⁴ (2007)	1	Advanced HIV infection with severe psoriasis	Efavirenz + lamivudine-zidovudine	<ol style="list-style-type: none"> 1. Psoriasis markedly improved over the course of 5 d 2. During the next year, patient had 2 admissions with similar symptoms and was given the same treatment with excellent results

Abbreviations: UVL, UV light; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

this population, suggesting that immunocompetent patients who take AZT are less likely to have hematologic toxic effects than those with AIDS.⁶⁰ These remarkable results in the immunocompetent population suggest that AZT may directly decrease the rate of epidermal proliferation.⁶¹

Zidovudine is known to have a corticosteroidlike effect on immune function, which may suppress the lymphocyte-driven process associated with psoriatic lesions and lead to the clearance of plaques.⁶² This immunosuppressive phenomena was challenged, however, in a study conducted by Suchniak et al,⁶³ which analyzed the peripheral blood cell counts of 12 HIV-negative patients before and after treatment with zidovudine. Results showed no statistically relevant differences in the total leukocyte count, lymphocyte count, or neutrophil count after 4 weeks of antiretroviral therapy. Analysis of biopsies taken from the 12 enrolled patients showed only 2 specimens with decreases in the T-cell populations at 4 weeks of therapy.⁶³

The use of HAART also has proven beneficial in HIV-associated psoriasis. Berthelot et al¹² reported a decrease of psoriatic symptoms in an HIV-positive patient taking antiretroviral therapy with zalcitabine and zalcitabine and zalcitabine. Vittorio Luigi De Socio et al¹³ reported a case of a male affected with advanced HIV infection and hepatitis C virus-related cirrhosis who showed rapid improvement of clinical manifestations of psoriasis within 4 weeks of initiation of stavudine, tenofovir disoproxil fumarate, and enfuvirtide, and complete resolution by week 8. At 2-months post-onset of therapy, plasma HIV RNA was undetectable and the CD4:CD8 ratio was 0.8.¹³ It is postulated that improvement of psoriasis with HAART is a consequence of the restoration of the host immune response associated with the correction of the immune imbalances central to the pathogenesis of HIV infection.¹² Additionally, enfuvirtide has been shown to block HIV infection of dendritic cells that take part in psoriatic inflammation.⁶⁴ It also is thought that TNF- α , an inflammatory cytokine associated with both psoriasis and HIV replication, may be directly decreased by antiretrovirals, as patients on HAART have lower viral replication and, therefore, reduced levels of TNF- α . The regulatory T-cell subpopulation also may play a role, as this dedicated population is deficient in psoriasis but expanded in the peripheral blood of HIV-infected patients on HAART. Additional research will need to be conducted to further elucidate this phenomenon. Regardless, strict adherence to an antiretroviral treatment regimen is an important point to remember and to relay to patients.

Comment

Currently, more evidence has led us to believe that psoriasis in patients with HIV infection results from an environment of dysregulation formulated by viral particles manhandling the immune system. A possible culprit is the memory CD8 T-cell population that secretes products such as interferon- γ , which cause abnormal activation of keratinocytes and trigger psoriatic lesions. The ability of these now-independent keratinocytes to respond to bacterial superantigens allows for exacerbations of psoriasis to occur with increased frequency in immunocompromised patients, even as T-cell counts dwindle. Furthermore, these keratinocytes are able to maintain this vicious cycle of skin inflammation via proinflammatory cytokine secretions, such as TNF- α .

Elucidation of the behavior of psoriasis in patients with HIV infection has allowed the development of therapeutic measures to manage the symptomatology of the condition by attacking the numerous mediators involved in the inflammation at various angles. Whether using TNF- α antagonists to inhibit proinflammatory signals or employing UV therapy to inhibit cell proliferation, the treatment options available to patients with psoriasis and HIV infection are now plentiful. The paradox of how psoriasis can develop in patients with HIV infection has already begun to unravel and continued research will only clarify how this unlikely autoimmune condition is able to take hold of an already altered immune system.

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