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Dermatological Management of Human Immunodeficiency Virus (HIV)

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ABSTRACT

Atypical presentations of typical dermatological conditions are common in human immunodeficiency virus (HIV). This article will focus on three specific topics: eosinophilic folliculitis, psoriasis, and cutaneous mycoses. Their unique presentations in HIV and treatments are discussed.

Key Words: HIV, eosinophilic folliculitis, psoriasis, cutaneous mycoses

Despite attempts at increasing awareness of HIV and its transmission, this infection continues to spread and remains a significant cause of morbidity and mortality worldwide. As of 2003, there were an estimated 1 million people living in the US with HIV infection, and nearly 40,000 cases were diagnosed in 2005.[1] HIV infection affects nearly every organ system in the body, including the skin. HIV-infected patients can pose diagnostic challenges, as their altered immune status may lead to atypical presentations of common cutaneous diseases, as well as the occurrence of uncommon or opportunistic skin disorders. Management of cutaneous disease in sero-positive patients can also be challenging, as the dermatological manifestations may be more severe, may recur with greater frequency, and may be refractory to standard treatment. The addition of highly active antiretroviral therapy (HAART) further complicates the picture as other dermatologic manifestations may arise as part of the immune reconstitution phenomenon. The scope of issues encountered in HIV-positive patients is too broad to discuss in its entirety. This article will focus on three diseases and their management: eosinophilic folliculitis, psoriasis, and cutaneous mycoses.

Eosinophilic Folliculitis

Eosinophilic folliculitis (EF) is seen commonly in HIV with CD4 cell counts of <250-300/mm^3.[2,3] It presents as recurrent, pruritic, erythematous papules and pustules that are usually distributed on the face, shoulders, upper back, and upper extremities.[3] The pruritus associated with EF can be severe and debilitating. Its etiology is not well elucidated, but some theories propose an infectious derivation. EF is an example of a dermatosis that is associated with immune-reconstitution.[3] It is described as a phenomenon wherein HAART triggers a generalized immune activation as viral loads decrease and CD4 lymphocytes increase.[4,5] Studies have shown that EF typically flares shortly after starting antiretroviral therapy, but will resolve from 3 weeks to several months later.[3] Clinicians should warn patients with EF that after starting HAART, their skin will likely worsen initially, then improve. EF can be difficult to manage, as response to treatment is variable and it tends to recur once treatment is discontinued. Various treatments have been employed,

including: isotretinoin, UVB phototherapy, itraconazole, and metronidazole, among others, with contrasting results.[2] The treatment of EF with potent topical corticosteroids is reportedly effective, but is accompanied by skin atrophy and hypopigmentation. This can be a problem given the distribution of EF on the face, and can be especially challenging in dark-skinned individuals.[6] A relatively recent case study showed promising results with topical tacrolimus. Subjects who applied daily topical tacrolimus 0.1% to the face had an average lesion clearance time of 2.6 months with an absence of residual scarring. The average remission of 12.3 months was seen in subjects with well controlled viremia on HAART. The associated pruritus subsided within days.[2] Given these promising results and the relative safety of topical tacrolimus, clinicians may want to consider this as an alternative to corticosteroids, which can cause hypopigmentation and scarring in dark-skinned patients, resulting in potential disfigurement.

Psoriasis

The prevalence of psoriasis in HIV-infected individuals is the same or slightly higher than that seen in noninfected individuals, but its clinical presentation can be more severe.[7,8] The severity of presentation often correlates with the degree of immunosuppression. HIV-positive patients with pre-existing psoriasis may see a flare of lesions as their CD4 count decreases and their viral load increases. A higher frequency of guttate and inverse psoriasis, as well as cases of generalized erythrodermic type psoriasis, has been reported in HIV-positive patients.[9] Psoriasis has been the presenting manifestation of HIV in some individuals, thus HIV testing should be considered in patients that present with *de novo* psoriasis.[8]

Treatment of psoriasis in HIV-positive patients can be challenging, as it is often refractory to standard psoriasis treatments.[7] When started on HAART, patients' psoriasis tends to improve as the immune system is reconstituted.[10] Case reports have shown a dramatic and rapid improvement of psoriasis in HIV-positive patients who have been either started or restarted on HAART.[7,10] Consequently, these reports emphasize the importance of strict adherence to antiretroviral regimens. This response is paradoxical, as drugs effective at treating psoriasis are targeted at T-lymphocytes, yet a low CD4 cell count causes worsening of the psoriasis. Although still unclear, the development of psoriasis is postulated to be an expression of the disease, which depends on the ratio of CD4 to CD8 cells. This ratio decreases in advanced HIV.[11] It is also thought that TNF-α, an inflammatory cytokine associated with both psoriasis and HIV replication, may play a role.[10] Subjects on HAART should have lower viral replication and therefore, reduced levels of TNF-α. The regulatory T-cell subpopulation may also play a role, as this dedicated population is deficient in psoriasis, but expanded in the peripheral blood of HIV patients on HAART.[10] 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.

Cutaneous Mycoses

Cutaneous dermatophytosis is generally more varied, extensive, and atypical in HIV than in immunocompetent hosts. As with psoriasis, the frequency of cutaneous dermatophytosis in the HIV population is not significantly greater than in noninfected individuals. Involvement of the nails is seen as proximal, subungual onychomycosis. Often the majority of the toenails are involved, which is a classic sign in HIV-infected patients.[12] Extensive lesions refractory to treatment are typical.[13] Pruritus and pain are not always present in this population despite the potential for extensive involvement.[12]

The most common etiologic organism of cutaneous fungal infection is *Trichophyton rubrum*, which generally inhabits the cornified layer of the dermis. Deeper penetration into the stratum corneum occurs after the dermatophyte releases enzymes, such as keratinase.[14] The skin has a number of defense mechanisms in place to prevent penetration below the epidermis, including a cell-mediated response.[15] In the immunocompromised population, however, invasive fungal infections can be identified, although they are rare. It is important to recognize and treat cutaneous fungal infections early, as delay of treatment allows for the infection to become more deeply invasive. Deep or locally invasive dermatophyte infection will typically present as nodular eruptions near the initial site of infection. Abscesses, mycetomas, and atypical lesions may also occur.[14]

Treatments used for various mycoses in immunocompetent individuals may not be sufficient to treat the same infections in the immunocompromised. For example, systemic therapy may be necessary even for superficial infections, whereas topicals alone would likely be adequate to treat the same infection in immunocompetent patients.[12] Resistance to oral antifungals, such as fluconazole, is a problem when it is used long-term as prophylaxis or for frequent short-term exposures. These drugs are used to treat candidal infections. In addition, immunosuppressed patients are more likely to be infected with atypical fungi.[12] Oral antifungals such as ketoconazole, fluconazole, and griseofulvin are usually effective in treating superficial and deep dermatophyte infections in this population.[14] However, when systemic therapy fails to be curative, surgery may be required. Failure to eradicate the infection has led to death in patients due to septicemia and systemic dissemination.[16,17] In order to make a proper diagnosis and prescribe an appropriate treatment regimen, it is important that, in addition to potassium hydroxide (KOH) mounts, cultures be performed on Sabouraud's agar to allow for specific species identification.[14]

In some cases, antiretroviral therapy alone is sufficient

to clear dermatophyte infections in immunosuppressed patients. However, it is important to consider possible interactions between antiretrovirals and antifungals, particularly ketoconazole. Although not contraindicated, it is advisable to use the medications concomitantly with close observation, as both ketoconazole and certain antiretrovirals have an effect on cytochrome P-450, leading to increases or decreases in either ketoconazole levels and/or antiretroviral levels.[18] Other antifungals such as griseofulvin and terbinafine have not been shown to interact with HIV medications, and no specific warnings exist.[14] Amphotericin B, a potent broad spectrum antifungal agent is still used in certain cases. However, this drug has substantial toxicity and must be used with caution. The development of an entirely different class of antifungals, echinocandins, has had a significant impact on the therapeutic approach to fungal infections. Drugs in this class, such as caspofungin, have few side-effects and few drug interactions. However, this drug does not have an oral preparation and has a relatively narrow spectrum of activity when compared with amphotericin B.[12] The choice of an antifungal agent will depend on the patient, the organism being treated, and the severity of the infection.

Conclusion

HIV infection can lead to a myriad of dermatoses with complicated clinical presentations. The altered immune status of HIV-infected individuals leads to diagnostic and therapeutic challenges. As dermatologists, it is important to be aware of the varied dermatoses associated with HIV, as well as their management. Knowledge of HIV-associated dermatologic manifestations may be useful in helping to make the diagnosis of HIV. Additionally, recognition of the need for more intensive therapy in these patients can provide improved care, and ultimately, improved patient outcomes.

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Dermal Fillers: Ever-Expanding Options For Esthetic Use

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ABSTRACT

Aesthetic volume rejuvenation with dermal fillers continues to be a very popular procedure that is sought by a growing number of patients who seek the rounder softer contours attributable to a more youthful appearance, including fuller curves of the cheeks, lips, and temples. Not only are fillers easier to use, but the outcomes that equal or exceed more invasive surgical options make volume restoration an increasingly popular procedure. Continued patient demand has fueled the introduction of a wider variety of injectable fillers, which include dermal and subdermal fillers with varying degrees of viscosity and duration of benefit. There are also several dermal implants that have stood the test of time or offer innovative technologies and approaches. This article will focus on the most popular, time-tested, and innovative fillers available today.

Key Words: Dermal fillers, facial rejuvenation, lip augmentation

The advances in medical care and improvements in patients' quality of life have resulted in an increasing movement from practicing medicine for disease detection and treatment, to the prevention and alleviation of the inevitable signs of ageing. The youthful fullness and curves of the face are altered and reduced as we age. One of the features of the ageing face is the loss and redistribution of facial fat and collagen. These changes, in combination with static and dynamic facial rhytids, are largely responsible for the emergence and expansion of corrective surgery. There is a trend toward less invasive approaches. Different modalities are used to address each aspect of facial ageing. In most cases, these techniques work synergistically to deliver the desired results, and in that regard, facial volume augmentation can be considered as one of the most important components of a comprehensive facial rejuvenation program.

Recent advances in soft tissue augmentation materials, techniques, and approaches have greatly increased the therapeutic options available to our patients. With proper techniques and skills, these products can restore the facial youthfulness with relative ease and little or no downtime for patient recovery. The following discussion will focus on the most popular dermal and subdermal fillers that have stood the test of time, as well as those that offer innovative advances and approaches.

Autologous Fat

Autologous fat continues to be one of the more popular dermal fillers because it is fully biocompatible, allowing for transferability from one area of the body to another in the same patient. It is also biodegradable and plentiful. The degree of permanency of autologous fat in the recipient site varies depending on the technique used by the physician, as well as patient factors. Influencing factors such as smoking habits and anticoagulation (both exert a negative effect on fat graft survival), as well as physician care, and meticulous attention to detail (both can enhance the effect on fat graft survival) are important predictors of procedural and outcome success. With the abundance of supply, larger volumes can be injected/ transferred without significantly adding cost to the patient. The objective of the procedure is to produce a high rate of fat graft uptake by optimizing conditions for survivability of cells at recipient sites, such as the cheeks, lips, temples, as well as the back of the hands.

Recently, the technique for harvesting, processing/ preparation, and delivery of fat has been refined, and long-term corrective results have been documented.[1] Having said that, it is important to note that the predictability of this procedure depends on many factors, making it challenging for novice practitioners to successfully achieve desired outcomes.

Collagen

Collagen is one of the most important components of the dermis, and so, quite naturally, was developed for cosmetic applications. Injectable bovine collagen was the first dermal filler to be granted US FDA clearance more than 25 years ago. There are several sources of injectable collagen available. (See Table 1)

Although skin testing is required for some of the earlier established bovine-derived products, the newer injectable collagens do not require skin allergy testing. The recently introduced porcine-derived Evolence™, with an innovative cross-linking technology, has been shown to produce longer lasting results than Zyplast® for the correction of nasolabial folds.[2] Collagen-based products enjoy an impressive long-term safety profile

and, as such, will remain one of the more popular choices for dermal augmentation.

Collagen Sources	Type	Trade Names (Manufacturer)
Human	Autologous	Isolagen™ Therapy* (Isolagen)
	Allogenic	Cymetra® (LifeCell)
		Cosmoderm® (Inamed)
		Cosmoplast® (Inamed)
		Alloderm® (LifeCell)
Bovine		Zyderm® (Inamed)
		Zyplast® (Inamed)
Porcine		Evolence® (ColBar LifeScience)

Table 1: Sources of injectable collagen.
*Not approved by the US FDA

Hyaluronic Acid

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide that is a component of all connective tissues. Because of its uniform structure throughout all living species, adverse immune reactions are rare. HA has hydrophilic properties, allowing it to attract and attach to water molecules. There are several families of popular HA injectables. (See Table 2)

Manufacturer	Trade Name	Derivation
Q-Med	Restylane®	NAD
	Restylane® Fine Lines	
	Restylane® SubQ	
	Perlane®	
Inamed	Hylaform® Fine Line	AD
	Hylaform® Plus	
	Juvederm™ Ultra	NAD
	Juvederm™ Ultra Plus	
Teoxane	Teosyal® Kiss	NAD
	Teosyal® Ultra Deep	
Galderma/ Anika	Elevess™	NAD

Table 2: Families of popular HA injectables. NAD = non-animal derived; AD = animal derived.

The duration of benefit following therapy with different HA fillers has not been rigorously studied. Although all products contain essentially the same HA molecule, the differences between the formulations relate to the quantity/ concentration of HA, the degree of cross-linking, and the amount of proteins incorporated, which affect flow characteristics and the target placement within the dermal-subcutaneous continuum.[3,4] Recently, a new HA product has been approved by the US FDA for soft tissue augmentation, Elevess™ (Anika Therapeutics). This novel formulation includes a high concentration of HA combined with lidocaine, which can provide patients with a more comfortable procedural experience.

The versatility of HA products expands the physician's options when selecting an implant for each unique application (dermal, subdermal, subcutaneous or supra-periosteal injections). This versatility, combined with the low risk of immune reactions, makes HA products the cornerstone of injectable fillers.

Calcium Hydroxylapatite

Calcium hydroxylapatite (CaHA), the major mineral constituent of bone, has been used for more than a decade in dentistry and reconstructive surgery. Its safety record in these disciplines is well established. Recently, a product containing microscopic CaHA particles suspended in a polysaccharide gel (Radiesse®, BioForm Medical) has been successfully used for aesthetic soft tissue augmentation.[5] When injected, the small particles of CaHA act as a scaffold for collagen to grow. Because there are no animal-based ingredients contained in the product, skin testing is not required. Over time, CaHA particles are slowly dissolved into calcium and phosphate ions through normal metabolic processes. Current studies indicate that some degree of correction persists for up to 18 months.[6] It is important to note that CaHA is radio opaque and can be visible on regular X-Rays.

Poly-L-Lactic Acid

Poly-L-lactic acid (PLLA) (Sculptra™, Sanofi-Aventis) is not a classic filler, but rather, a stimulator. PLLA has been safely used for over 4 decades as suture material. It is a nontoxic, immunologically inactive, synthetic biodegradable lactic acid polymer. Unlike other products discussed in this review, Sculptra™ is reconstituted with sterile water prior to injection. The mixture is injected into the deep dermis or subcutaneous space with the tunneling or threading technique. It is important to distribute the product evenly to minimize the possibility of granuloma formations. Patients usually require three monthly treatments to achieve the desired results. With each treatment, there is stimulation of neocollagenesis secondary to small PLLA particles. It is important to note that the initial studies demonstrate an increase in skin thickness as early as 6 weeks after injection.[7] The

duration of the desired effects can last up to 96 weeks, making Sculptra™ a unique option to consider, as well as providing extended results for the patient.

Silicone

Silicone oil, derived from silica and composed of purified polydimethylsiloxane, has been used for facial augmentation and scar revision for decades. The recent introduction of Silikon® 1000 (Alcon Laboratories) has revived the use of this controversial filler. A microdroplet technique is used to inject silicone into the dermal-subcutaneous junction. Overcorrection is avoided and repeat treatments at intervals of 4–6 weeks are advisable. Complications in the past, such as granulomas, were primarily due to large volume injections or adulteration of the silicone used. Because injected silicone provides permanency, it does not require skin testing and will not support bacterial growth. Its cost, relative to other available dermal fillers on the market, make it an attractive option, however, more research is needed to fully establish its place in the aesthetic arena.

Polymethylmethacrylate

Polymethylmethacrylate (PMMA) microspheres (Artecoll®, Artefill®, Artesense™, Artes Medical) is a permanent filler and stimulator of neo collagenesis, where the PMMA particles are suspended in a collagen vehicle. Following the injection, the collagen is quickly degraded, leaving the PMMA beads indefinitely; the subsequent collagen reaction around the particles creates volume. Unlike temporary fillers, the immediate filling effect disappears rather quickly and, over time, gradual, but long-lasting correction is established. Although granulomas have been reported, with the use of proper technique (injection at the dermal subcutaneous junction using threading or tunneling methods) and applying a series of injections at appropriate sites, PMMA fillers can provide excellent long-term correction.[8]

Adverse Effects

Complications arising from soft tissue augmentation can be attributed to several factors: the patient, the physician, and product characteristics.[9] Patient suitability and appropriate product selection are paramount in obtaining the desired results. However, even if these criteria are satisfied, complications can arise.

The most common early side-effects include bleeding (bruising and hematomas), pain, swelling, and erythema. To reduce the incidence and the severity of these complications, any substance that can impede blood clotting (e.g., acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and excessive alcohol consumption) should be discontinued for an appropriate length of time prior to receiving treatment unless otherwise recommended by a physician. In addition, appropriate topical, as well as local/ regional anesthesia, and cold compresses can be used to relieve mild symptoms. Rare complications, such as skin necrosis and blindness, require rapid diagnosis and immediate intervention.

Delayed complications include chronic inflammation, late allergic reactions, nodules, granulomas, discoloration, migration, and hypertrophic scarring. Although some of these adverse reactions cannot be predicted, early detection and initiation of appropriate therapy can help to minimize patient discomfort, severity of side-effects, and prevent the onset of sequelae.

Conclusion

The ever-expanding array of products for soft tissue augmentation is of real benefit for patients and physicians. From the patients' perspective, expectation of results, safety, and product durability are of primary concern. Physicians, on the other hand, can combine their knowledge of the anatomy and the ageing process to assess patient suitability, and determine the choice of product that will ultimately provide the results that each individual patient expects and deserves. As always, safety is of paramount importance, especially when physicians are dealing with the vulnerabilities of their patients.

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Thank You to Our Dermatologic Surgery Editors

After 5 years as the Editors of *Skin Therapy Letter's* Advances in Dermatologic Surgery section, Drs. Jeffrey Dover and Murad Alam have decided to step down. The editorial team at *STL* feels extremely privileged to have worked under the direction of these two leaders in their field. Because of their insightful approach, Drs. Dover and Alam have been instrumental in keeping *STL* readers abreast of the latest advances in dermatologic surgery. They have made significant contributions and we are very grateful for all of their hard work and foresight in selecting topics that have provided practical and relevant information to clinicians in this expanding area of specialty.

Stuart Maddin, MD
Editor-in-Chief

Class	Name/Company	Approval Dates and Comments
Antimicrobial Agent	**Nanocrystalline Silver Cream** *NPI32101* NUCRYST Pharmaceuticals	The US FDA approved this prescription topical cream in July 2007. NPI32101 is a patent protected nanocrystalline silver compound that acts as a broad spectrum antimicrobial barrier to organisms including strains resistant to MRSA, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
Antibacterial Agent	**Daptomycin for Injection** *CUBICIN®* Cubist Pharmaceuticals	The EMEA approved this IV antibiotic at 6mg/kg in September 2007 for the additional indications of right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*, and *Staphylococcus aureus* bacteremia, when associated with RIE or with complicated skin and soft-tissue infections.
Hand Eczema	**Oral Alitretinoin** *BAL4079* Basilea Pharmaceutica	The EMEA received a Marketing Authorization Application in September 2007 for this investigational drug for the treatment of severe refractory chronic hand eczema.
Vaccine	**Smallpox Vaccine** *ACAM2000* Acambis PLC	The US FDA licensed a new vaccine in August 2007 to protect against smallpox. This vaccine is intended for the inoculation of people at high risk of exposure to smallpox and could be used to protect individuals and populations during a bioterrorist attack. It will be included in the Center for Disease Control and Prevention's Strategic National Stockpile of medical supplies.

Drug News

Oncologic Agents	According to a study published in a recent issue of *Clinical Cancer Research*, the appearance of a rash in cancer patients treated with erlotinib (Tarceva®, Genentech) is strongly associated with longer survival. For patients taking this drug who developed a moderate-to-severe rash, survival without progression of disease was 245% longer than in patients who had a mild rash or none at all. These rashes can be controlled with mild steroids or antibiotics, and in most cases, they will improve with treatment. *Wacker B, et al. *Clin Cancer Res* 13(13):3913-21 (2007 Jul).
US FDA Regulations	In August 2007, the US FDA proposed a new regulation that sets standards for formulating, testing and labeling over-the-counter sunscreen products. This proposed regulation creates a consumer-friendly rating system designed to easily identify both levels of UVB and UVA protection offered by a product. Additional recommendations include the amended definition of SPF from "sun protection factor" to "sunburn protection factor", which is intended to contain consumer notions of adequate sun protection. A new expanded ratings system for UVA sunscreen products will use a scale of one to four stars. One star = low UVA protection, two stars = medium protection, three stars = high protection, and four stars = the highest protection available. If a sunscreen does not provide at least a low level of protection, the FDA is proposing that it must bear a "no UVA protection" mark on the front label near the SPF value. Ratings would be derived from two tests proposed to assess the effectiveness of sunscreens: the first measures a product's ability to reduce the amount of UVA radiation that passes through it; the second measures its ability to prevent tanning. When finalized, this regulation would amend the existing OTC sunscreen rule published in 1999. Additionally, the proposed rule would revise the existing SPF testing procedures and allow for new combinations of active ingredients. The FDA is asking for public comments on this initiative, and is accepting comments until November 26, 2007. To submit comments go to: www.fda.gov/dockets/ecomments.

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