

## Highly Active Antiretroviral Therapy Induced Cutaneous Adverse Drug Reactions in Patients with Human Immunodeficiency Virus Infection

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### Summary

Worldwide, over 40 million people are infected with the Human Immunodeficiency Virus (HIV). The High Activity Antiretroviral Therapy (HAART) combines at least three antiretroviral (ARV) drugs and, for over a decade, has been used to extend the lifespan of the HIV-infected patients. HIV-infected patients have a higher risk of developing cutaneous reactions than the general population, which has a significant impact on patients' current and future care options. The severity of dermatologic and cutaneous adverse reactions varies greatly, and some may be difficult to manage. HIV-infected patients just at the beginning of High Activity Antiretroviral Therapy can frequently show a wide variety of adverse drug effects such as erythema multiforme, urticarial reaction, hyperpigmentation, drug rashes, toxic epidermal necrolysis or Stevens–Johnson syndrome. The early detection and treatment of cutaneous adverse drug reactions, identification of the causative agent, are essential to prevent the progression of the reaction. This review gives an overview of the most common features of a highly active antiretroviral therapy induced dermatological and cutaneous adverse reactions from Nucleoside Reverse Transcriptase Inhibitors (NtRTIs), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Entry Inhibitors, Integrase Inhibitors, Maturation inhibitors. Paying special attention to the newest drugs approved for the treatment of HIV infection, such as rilpivavine, maraviroc, vicriviroc, raltegravir, elvitegravir and bevirimat.

**Keywords:** Highly active antiretroviral therapy; cutaneous adverse drug reactions; human immunodeficiency virus

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### Introduction

Worldwide, over 40 million people are infected with the Human Immunodeficiency Virus (HIV)<sup>1</sup>. The High Activity Antiretroviral Therapy (HAART) introduced in 1996 combines at least three antiretroviral (ARV) drugs<sup>2,3</sup> and, for over a decade, has been used to increase their lifespan and quality of life of the HIV-infected patients. These antiretroviral drugs fall into eight categories [nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), co-receptor inhibitors (CRIs) and integrase inhibitors (INIs). Maturation inhibitors (i.e. bevirimat) represent the most recent advance in the search for effective and selective anti-HIV agents. Combination of several anti-HIV drugs [often referred to as highly active antiretroviral therapy (HAART)] has drastically altered AIDS from an almost uniformly fatal disease to a chronic manageable one. In fact, within the first year of treatment, adverse drug reactions, and not treatment failure, are the most common reasons for the discontinuation of HAART among HIV-infected patients. Patients infected with HIV are highly susceptible to adverse dermatological reactions to specific medications. Up to 80% of HIV-infected patients experience adverse drug reactions at some point during their therapy, presumably as a result of immune dysregulation, altered drug metabolism and/or polypharmacy.<sup>4</sup> HIV-infected patients have a higher risk of developing cutaneous reactions than the general population, which has a significant impact on patients' current and future care options. The severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage. HIV-infected patients at the beginning of the antiretroviral treatment can frequently show a wide variety of adverse drug effects such as erythema multiforme, hypersensitivity reactions typically manifests as an erythematous, maculopapular, pruritic, hair loss, drug rashes, urticarial reaction, injection site reaction, hyper pigmentation, Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) Cutaneous adverse drug reactions have been reported with all antiretroviral medications. The early detection and treatment of cutaneous adverse drug reactions to highly activity antiretroviral Therapy plus identification of the causative agent, are essential to prevent the progression of the reaction, preventing additional exposures and ensuring the appropriate use of medications for the current clinical conditions of the HIV-infected patients. This review gives an overview of the most common features of a highly active antiretroviral therapy induced dermatological and adverse cutaneous reactions.

#### ***Nucleoside Reverse Transcriptase Inhibitors (NtRTIs):***

Reverse transcriptase inhibitors include the nucleoside analogues zidovudine, stavudine, lamivudine emtricitabine, tenofovir, abacavir, didanosine, zalcitabine. These were the first class of drugs that were licensed for the treatment of HIV infection. They are indicated for this use as part of combination regimens. It should be stressed that none of these drugs should be used as monotherapy for HIV infection. The reverse transcriptase inhibitors block the HIV replication cycle at the point of RNA-dependent DNA synthesis, the reverse transcription step.

#### **Zidovudine (ZDV)**

Pigmentation of fingernails and toenails has been reported in patient receiving zidovudine. A dark, bluish discoloration at the base of the finger nails was evident 2 to 6 weeks after initiation of zidovudine therapy. The cause of this nail pigmentation is unknown but may result from injury to the nail bed, matrix, and/or plate; increased stimulation of matrix melanocytes by zidovudine may be involved. Cutaneous leukocytoclastic vasculitis, characterized by distinctive

dermal perivascular inflammation without visceral involvement has been reported in at least 2 patients receiving zidovudine. The vasculitis was associated with fever and appeared to be a hypersensitivity reaction. Hypersensitivity reactions have been reported rarely in patients receiving zidovudine. Anaphylaxis, angioedema, Stevens-Johnson syndrome, and Toxic epidermal necrolysis have been reported. Excessive eyelash growth was reported in a human immunodeficiency virus (HIV) patient receiving zidovudine 200 milligrams every four hours. The selective growth of eyelashes and lack of effect on other body hair remain unexplained in this case. The elongation of the patient's eyelashes was temporally (less than two weeks) related to the initiation of zidovudine therapy<sup>5</sup>. Other adverse dermatologic effects, including acne, changes in skin pigmentation, pruritus, and urticaria, have been reported in patients receiving zidovudine, but a causal relationship has not been established.

**Stavudine (D4T)**

Stavudine is very well tolerated, and hypersensitivity reactions have been described only in multidrug therapy clinical trials. Rash has been reported in 40% of patients receiving stavudine alone and in 18 to 30% of those receiving stavudine in conjunction with other antiretroviral agents (indinavir and either didanosine or lamivudine) in clinical studies. Of several trials<sup>6,7,8</sup> including stavudine with lamivudine, efavirenz, nevirapine, and abacavir, rashes, hypersensitivity reactions, and SJS have been reported. Allergic reactions have been reported in patients receiving stavudine during postmarketing surveillance.

**Lamivudine (3TC)**

In studies A3001, A3002, B3001, and B3002 in HIV-infected adults receiving lamivudine in conjunction with zidovudine, rash was reported in 9% of patient. Rash also was reported in 5% of adults who received lamivudine for the treatment of chronic HBV infection in clinical studies. A case of contact dermatitis was reported in a health care worker taking lamivudine for post exposure prophylaxis after occupational exposure to HIV. Patch testing confirmed the diagnosis. A recent evaluation of long-term safety and tolerability of the lamivudine / abacavir combination as components of highly active antiretroviral therapy (HAART) found that 1585 of 2279 (70%) patients experienced at least 1 drug-related adverse event, and of these, 175 patients (8%) experienced a drug hypersensitivity reaction, compared with 10 patients of 325 (3%) in the control group receiving a lamivudine, zidovudine, and efavirenz combination<sup>9</sup>. Anaphylaxis, urticaria, alopecia, rash, pruritus, erythema multiform, and Stevens–Johnson syndrome have been reported in patient who received lamivudine or the fixed combination of lamivudine and zidovudine during postmarketing surveillance.

**Emtricitabine (FTC)**

Emtricitabine is a once-daily nucleoside reverse transcriptase inhibitor that is used in combination with other antiviral agents. It is generally very well tolerated with most adverse events being mild to moderate in severity<sup>10</sup>. Patients treated with emtricitabine may experience discoloration of their skin, nails, or tongue, which manifests as a mild increased pigmentation of the skin. Of 814 patients enrolled in phase 3 clinical trials of emtricitabine, 29 (4%) of participants developed the skin discoloration, and higher rates were reported in black patients. There were no severe effects from this discoloration, and it did not result in any treatment discontinuation. The pathogenesis of this skin reaction is unknown.<sup>11</sup> A smaller (n 5 294) randomized study of lamivudine versus emtricitabine with stavudine or zidovudine and a PI or nonnucleoside reverse transcriptase inhibitor revealed a rash event rate of 17% for emtricitabine

versus 14% for lamivudine. Eruption events included pruritus, maculopapular eruptions, urticaria, and vesiculobullous or pustular and allergic reactions.<sup>12</sup> A second randomized, double-blind trial with either emtricitabine or lamivudine with didanosine and efavirenz (n5286) revealed a rash event rate of 30% and a 3% skin discoloration rate.<sup>13</sup> A case of hypersensitivity to emtricitabine/ tenofovir was reported with similar clinical symptoms to abacavir (ABC) hypersensitivity reactions<sup>14</sup>.

### **Tenofovir (TDF)**

Tenofovir disoproxil fumarate is a nucleotide analogue similar to adefovir and cidofovir. Rash, including pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash, has been reported in 5% to 7% of the patients treated with tenofovir. In a double-blind study, in HIV treatment-naive patients, rash occurred in 18% of the patients who received treatment with tenofovir.<sup>15</sup> A case of lichenoid eruption with eosinophilia associated with tenofovir therapy was described.<sup>16</sup> A tenofovir hypersensitivity syndrome, consisting mainly of a maculopapular rash on the face, extremities and trunk, has been reported in nine HIV-infected patients.<sup>17</sup>

### **Abacavir (ABC)**

The major adverse effects associated with abacavir therapy are potentially life threatening hypersensitivity reactions. There is evidence that abacavir hypersensitivity is an immunologic reaction influenced by certain genetic factors. Manifestations of hypersensitivity usually are apparent within the first 6 weeks of abacavir therapy. It has been reported to occur in patients, ranging from 2.3% to 9%.<sup>18</sup> Abacavir hypersensitivity is a reversible, life-threatening, immune-mediated systemic reaction that generally occurs within the first 6 weeks of exposure to the drug.<sup>19</sup> Symptoms most commonly associated with a hypersensitivity reaction are fever (80%), rash (70%), gastrointestinal effects (50%), lethargy or malaise (40% to 60%) and upper or lower respiratory effects (18% to 30%). The clinical classification of abacavir hypersensitivity includes at least two of the following symptoms: fever, rash, nausea, vomiting, headache, respiratory and gastrointestinal symptoms, lethargy, myalgia or arthralgia occurring, 6 weeks after exposure and resolving within 72 h of withdrawal of the drug.<sup>20</sup> Overall, 98% of the cases included either fever or rash or both. Rash was described as maculopapular or urticarial rash and generally was mild or moderate in severity. A hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B\*5701 allele. Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported during postmarketing surveillance in patients receiving abacavir concomitantly with other drugs known to be associated with these severe adverse effects. Stevens–Johnson syndrome also has been reported in patients receiving the fixed-combination preparation of abacavir, lamivudine, and zidovudine. In such cases, abacavir should be discontinued and should not be reinitiated because of the possibility that the patient may have multiple drug sensitivities and because of the clinical signs and symptoms of Stevens–Johnson syndrome and toxic epidermal necrolysis are similar to those of abacavir hypersensitivity. erythema multiform has been reported with use of abacavir or the fixed combination preparation containing abacavir, lamivudine, and zidovudine.

### **Didanosine (DDI)**

Rash and pruritis have been reported in patients receiving didanosine. Transient morbilliform rash, as well as mild erythematous macular eruptions, have been reported. In early clinical studies evaluating didanosine, rash or pruritis was reported in 7 to 9% of patients receiving didanosine monotherapy. In more recent clinical studies rash was reported in 13 to 30% in patients receiving didanosine in conjunction with stavudine and either nelfinavir or indinavir<sup>21</sup>. Alopecia also has been reported with didanosine. An Anaphylactoid reaction has been reported rarely in patient receiving didanosine. Stevens-Johnson syndrome was reported in a 35-year-old male being treated with didanosine for HIV infection. The symptoms developed 21 days after didanosine was initiated and resolved rapidly after it was discontinued.

### **Zalcitabine (DDC)**

A transient symptom complex of cutaneous eruptions (maculovesicular in nature), fever, malaise, and aphthous ulcers have been a relatively frequent complication of zalcitabine therapy in AIDS patients, and generally occur during the first 4 to 6 weeks of therapy. This complex primarily occurs in patients receiving higher doses of zalcitabine, and is rare with lower doses of the drug (0.005 mg/kg every 4 hours or 0.01 mg/kg every 8 hours). Cutaneous lesions resolve after withdrawal of zalcitabine, and even with higher doses this symptom complex generally subsides with continued administration of the drug after 1 to 3 weeks. Other dermatologic effects that have been reported include pruritus, night sweats, urticaria, and lip blisters with sensory neuropathy occurring in at least 1% of patients. A hypersensitivity syndrome has been described in 2 patients who were treated with the combination of zidovudine and zalcitabine. Both patients had CD4<sup>+</sup> T counts less than 10/mL and developed rashes 5 and 12 days after beginning zalcitabine. The reaction in the first patient was described as an exfoliative dermatitis<sup>22</sup> with fever, eosinophilia (3100 cells/mL), and lymphadenopathy. Skin biopsy revealed a perivascular CD8<sup>+</sup> T lymphocytic infiltrate. Improvement occurred within a few days of discontinuation of therapy.

### ***Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs):***

NNRTI drugs were first introduced in 1998<sup>23</sup>. These classes of drugs have two advantages: they increase the adherence to the HAART and delay the use of PIs. Cutaneous problems (rash) and hepatotoxicity are the main side effects induced by NNRTI. An important factor in an NNRTI rash is previous history of adverse cutaneous reactions. The mechanism of action involves the non competitive binding of the drug to the reverse transcriptase enzyme. According to the guidelines, HAART usually includes at least one NNRTI as a first-choice drug<sup>24-26</sup>. Nonnucleoside Reverse Transcriptase Inhibitors include nevirapine, efavirenz, delavirdine, etravirine, rilpivirine. In clinical practice, general cutaneous reactions appear to be less common with efavirenz than with delavirdine or nevirapine.

### **Nevirapine (NVP)**

The most frequently reported adverse reaction to nevirapine therapy is rash. Rash reported usually is mild to moderate, consists of maculopapular erythematous cutaneous eruptions (with or without pruritus), and is located on the trunk, face and extremities. The most common drug-related adverse event secondary to nevirapine is nonurticarial eruption. It occurs most frequently within the first 6 weeks of therapy. In controlled studies, 13.3 or 5.8% of patients receiving



nevirapine or placebo, respectively, experienced a mild to moderate rash (grade 1 or 2) during the first 6 weeks of therapy and 1.5 or 0.1% of patient receiving nevirapine or placebo, respectively, experienced a serious rash (grade 3 or 4). Women appear to be at higher risk of nevirapine associated rash than men. Severe and life-threatening skin reactions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have been reported. Anaphylaxis, angioedema, bullous eruptions and urticaria have been reported during postmarketing surveillance. Risk factors for the development of rash associated with nevirapine include higher pretreatment CD4<sup>+</sup> T-cell count (>250 cells/mm<sup>3</sup> for women and >400 cells/mm<sup>3</sup> for men), lower HIV-1 RNA level, Chinese ethnicity, and female sex.<sup>27, 28</sup> Therefore, a black box warning recommends intensive monitoring during the first 18 weeks of therapy, especially in women with CD4<sup>+</sup> T-cell counts greater than 250 cells/mm<sup>3</sup>.<sup>29</sup> concomitant use of prednisone or antihistamines during the first 14 days of therapy in an attempt to prevent nevirapine-associated rash has not been effective and is not recommended. There have been reports that concomitant use of prednisone increased the incidence and severity of rash during the first 6 week of nevirapine therapy. Management of patient who develop rash while receiving nevirapine should be based on the type and severity of symptoms. Serum transaminase concentrations should be immediately evaluated in any patient experiencing rash, especially during the first 18 weeks of therapy. Delay in discontinuing nevirapine after onset of rash may result in a more severe reaction. If nevirapine is discontinued because of severe skin rash, skin rash combined with increased serum transaminase concentration or other symptoms, or hypersensitivity reaction, the drug should be permanently discontinued and not reinitiated. While nevirapine therapy generally can be continued in patients with mild or moderate rash (e.g., erythema, pruritus, diffuse erythematous macular or maculopapular rash), dosage should not be increased until the rash has resolved. Mild to moderate rash resolves within 2 weeks in about 50% of patient and within 1 month in about 75% of patient; these patient may be treated symptomatically with antihistamines, antipyretics, and/or non steroidal anti-inflammatory agents.

### **Efavirenz (EFV)**

Efavirenz skin rashes are generally a mild-to-moderate diffuse maculopapular skin eruption or pruritic erythema. New onset rash was reported in 26% of the efavirenz-treated patients compared with 17% of the patients in control groups. The onset of rash was generally 11 days after starting treatment in adults with a median duration of 16 days<sup>30</sup>. Although treatment emergent rash generally manifests as mild to moderate maculopapular skin eruptions (NCI grade 1 and 2 reactions). Rash associated with blistering, moist desquamation, or ulceration (NCI grade 3 reaction) has been reported in about 1% of adults receiving efavirenz in clinical studies. The incidence of grade 4 rash (e.g., erythema multiforme, steven-Johnson syndrome) has been reported to be 0.1%. Occasionally, it could develop as vesicles, moist desquamations and/or mouth ulcerations. It has also been shown that efavirenz could induce photosensitive drug eruptions. In all cases, the photosensitivity developed 2 months after starting administration of efavirenz and the rash appeared only in the sun-exposed areas<sup>31-33</sup>. More over treatment-emergent rash generally occurs within the first 2 weeks of efavirenz therapy; median time of onset of rash in clinical studies in adults or children was 11 or 8 days, respectively. The incidence and/or severity of rash does not appear to be dose related. While efavirenz therapy should be discontinued in patients who experienced serious rash (i.e., rash associated with blistering, desquamation, mucosal involvement, or fever), mild to moderate rash resolves in most patients within 1 month with continued efavirenz therapy. The median duration of rash in adults

is 16 days. Moreover, there are some papers reporting cases of cutaneous leucocytoclastic vasculitis associated with efavirenz treatment<sup>34</sup>. Efavirenz has been implicated in SJS, although only with an incidence of 0.14% in all studies and expanded access.<sup>35</sup> Efavirenz treatment related to immune hypersensitivity reaction is rare. Behrens et al.<sup>36</sup> reported severe pulmonary hypersensitivity, maculopapular pruritic rash, myalgia and fever for 10 days after the initiation of efavirenz treatment. Rashes associated with nevirapine or efavirenz administration were significantly associated with the HLA-DRB101 allele. The results of this study suggest that the HLA-DRB101 allele plays an important role in the susceptibility to cutaneous reactions associated with nevirapine and efavirenz in HIV-infected patients<sup>37</sup>. Pruritus has been reported in up to 9% and increased sweating has been reported in up to 2% of patients receiving efavirenz in clinical studies. Other adverse dermatologic and sensitivity reactions reported during post marketing surveillance include allergic reaction, erythema multiform, nail disorder, skin discoloration, and Steven-Johnson syndrome.

### **Delavirdine (DLV)**

Rash is the most frequently reported adverse effects of delavirdine. In 2 clinical studies (study 21 part II and study 13C), rash was reported in 32-35% of adults who received the usual dosage of delavirdine in conjunction with NRTIs compared with 16-21% of adults who received the NRTIs alone. In these studies, grade 1 rash (erythema, pruritus), grade 2 rash (diffuse maculopapular rash, dry desquamation, or grade 3 rash (vesiculation, moist desquamation, ulceration) occurred in about 17, 14, and 4%, respectively, of patients receiving delavirdine in conjunction with NRTIs compared with 12, 6, and 0%, respectively, of patient receiving the NRTIs alone. There were no cases of grade 4 rash (erythema multiform, Steven-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis) in either patient group. Delavirdine-associated rash occurs mainly on the upper body and proximal arms with decreasing intensity of the lesions on the neck and face and progressively less on the rest of the trunk and limbs. Rash usually is evident within the first few weeks following initiation of delavirdine therapy; occurrence of rash after 1 month of therapy is uncommon. Because there is no evidence that the incidence of rash is decreased by initiating delavirdine therapy using a low dose and then titrating dosage, dosage titration is not recommended. Management of rash with delavirdine should be based on the type and severity of manifestations<sup>38</sup>. Patient with mild or moderate rash may be treated symptomatically with diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or topical corticosteroids. Dermatologic and sensitivity reactions reported in less than 5% of patients receiving delavirdine in conjunction with NRTIs in clinical studies 21 part II and 13C include allergic reaction, angioedema, cyst (epidermal or sebaceous), dermal leukocytoclastic vasculitis, dermatitis, desquamation, diaphoresis, discolored skin, dry skin, erythema, erythema multiform, folliculitis, fungal dermatitis, hair loss, nail disorder, petechiae, pruritus, seborrhea, skin hypertrophy, skin disorder, skin nodule, Steven-Johnson syndrome, urticaria, vesiculobullous rash, and wart.

### **Etravirine (ETV)**

Severe and potentially life-threatening skin reactions, including Steven-Johnson syndrome, hypersensitivity reactions, and erythema multiforme, have been reported in less than 0.1% of patients receiving etravirine. The drug should be discontinued and appropriate therapy initiated if severe rash occurs. In treatment experienced patients with NNRTI resistance, treatment with etravirine achieved better virological suppression at week 24 than placebo. Most rashes were

described as erythematous or maculopapular and were of mild or moderate severity. They tended to occur within the first few weeks of treatment (median onset 11-14 days) and resolved with continued treatment (median duration 12-16 days). In the etravirine group, women have been reported to be more prone to develop rash than men. If severe rash occurs, etravirine therapy should be discontinued and appropriate treatment initiated<sup>39</sup>. In phase 3 studies, 2% of etravirine-treated patients discontinued therapy because of rash<sup>40,41</sup>.

### **Rilpivarin (RPV)**

A limited number of new drugs are either in, or are about to start, phase 3 clinical trials. TMC-278 or rilpivarin (RPV) is a new NNRTI that has been examined in a head to head trial with efavirenz<sup>42,43</sup>. Serious AEs were similar in the RPV and Efavirenz (EFV) groups (12.2% versus 14.6%), as were rates of grade 3 or 4 toxicities (27.2% versus 21.3%) and grade 3 or 4 lab abnormalities (26.5% versus 23.6%). Rash was seen less often in the RPV group, (9% versus 21%,  $P < 0.01$ ), as were dizziness and sleepiness (31% versus 48%,  $P < 0.01$ ), and abnormal dreams or nightmares (3% versus 11%,  $P < 0.05$ ). In the RPV group, triglycerides decreased by a mean of 9.9 mg/dL while increasing in the EFV group by a mean of 29.2 mg/dL. Qtc prolongation was seen in both groups; for RPV it was least in the 25 mg dose.

### **Protease Inhibitors (PIs):**

Protease inhibitor drugs are one of the pillars of the cocktail therapy. PIs have a potent activity against HIV, and treatment with these agents has been shown to reduce the incidence of mortality in HIV-infected patients. However, side effects associated with this drug often limit its long-term tolerability. The rate of rash in patients treated with a PI has been recently estimated as around 5%.<sup>44</sup> PIs include indinavir, saquinavir, nelfinavir, ritonavir, tipranavir, lopinavir, darunavir, amprenavir, fosamprenavir, atazanavir.

### **Indinavir (IDV)**

Anaphylactoid reaction has been reported with indinavir. In study 028 in treatment-naïve HIV-infected adults, pruritus occurred in 4.2 or 2.4% and rash occurred in 1.2 or 0.6% of patients receiving indinavir or indinavir in conjunction with zidovudine, respectively. Erythema multiform, Steven-Johnson syndrome, hyperpigmentation, alopecia, urticaria, ingrown toenails, paronychia, and vasculitis have been reported during postmarketing surveillance. Hypersensitivity reactions to indinavir are rarely reported. Ten years ago, a possible case of indinavir associated rash occurred in a 24-week open-label, phase I-II study evaluating the agent's safety,<sup>45</sup> but more recently, other cases have been described. An observational study in Italy observed 84 patients who had not responded to previous therapies with 2 nucleoside reverse transcriptase inhibitors or were naïve: 34 (40.5%) developed diffuse cutaneous dryness and pruritus and 48 patients (57.1%) experienced other cutaneous effects such as cheilitis, asteatotic dermatitis, scalp defluvium, and alopecia with indinavir therapy.<sup>46</sup> A review of hypersensitivity reactions in 132 subjects on indinavir, 6 (4.5%) developed symptoms. Five were cases of maculopapular rash, and 1 was urticarial.



**Saquinavir (SQV)**

Rash or pruritus occurred in 3.4% and dry lips/skin or eczema occurred in 2% of adults receiving ritonavir-boosted saquinavir (1 g of saquinavir and 100 mg of ritonavir twice daily). Rash, eczema, pruritus, or verruca has occurred in at least 2% of patients receiving saquinavir alone or in conjunction with other antiretroviral agents. Acne, allergic reaction, alopecia, chalazion, dermatitis (including seborrheic dermatitis), erythema, eczema, folliculitis, furunculosis, hair changes, hot flushes, increased sweating, maculopapular rash, nail disorder, papillomatosis, photosensitivity reaction, skin disorder, nodule, pigment changes, ulceration, urticaria, and xeroderma have occurred in less than 2% of patient receiving saquinavir. Drug fever, Steven-Johnson syndrome, bullous skin eruptions and polyarthritis, and severe cutaneous reactions associated with abnormal liver function test results occurred rarely in patients receiving the drug alone or in conjunction with other antiretroviral agents; these effects were considered to be at least possibly related to the study drug. There are only 3 case reports of possible hypersensitivity reactions to saquinavir. A 50-year-old woman developed fever and a swollen knee 10 days after starting ritonavir. She then experienced fever and a skin rash after 7 days of a HAART regimen including indinavir. The rash was a red-bluish erythematous purpuric rash. Then, 8 days after beginning saquinavir, she developed a vasculitic rash with neutrophil infiltration and many eosinophils in the superficial dermis on biopsy. Immuno fluorescence showed IgA deposition suggesting an antibody-mediated hypersensitivity reaction<sup>47</sup>.

**Nelfinavir (NFV)**

Rash has been reported in 1-3% of adults receiving nelfinavir in the recommended dosage in phase 2 and 3 clinical studies. Allergic reactions, dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria have been occurred in less than 2% of adults receiving nelfinavir in clinical studies. Hypersensitivity reactions, including bronchospasm, moderate to severe rash, fever, and edema, possibly related to nelfinavir have been reported during postmarketing surveillance. The incidence of rash with nelfinavir is reported to be low at <5%. Hypersensitivity manifested by rash has been reported in detail in some case reports. Most of the rashes have been maculopapular with some vesicular or bullous features,<sup>48</sup> but 3 cases have been urticarial,<sup>49</sup> indicating a probable type I hypersensitivity mechanism. The onset of the rash ranges from 5 days to 2 weeks.

**Ritonavir (RTV)**

Ritonavir is an antiretroviral agent that is used principally to boost the blood levels of other antiretroviral agents by competitive use of the P450enzyme clearance system in tissues (eg, hepatic cytochrome CYP3A). In clinical studies, rash occurred in 0.7-3.5% of patient receiving ritonavir in conjunction with other antiretroviral agents. Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema, have been reported in patient receiving ritonavir. Anaphylaxis and Steven-Johnson syndrome have been reported rarely. Other dermatological effects that have reported in less than 2% of patient receiving ritonavir alone or with other antiretroviral agents include acne, contact dermatitis, dry skin, eczema, erythema multiform, exfoliative dermatitis, folliculitis, fungal dermatitis, furunculosis, maculopapular rash, molluscum contagiosum, onychomycosis, photosensitivity reaction<sup>50</sup>, pruritus, psoriasis, seborrhea, skin disorder, skin melanoma, urticaria, and vesiculobullous or pustular rash.

**Lopinavir (LPV)**

Acute generalized exanthematous pustulosis was reported in a health care worker receiving post exposure prophylaxis with zidovudine, lopinavir, and lopinavir-ritonavir. Pustular rash and fever began 24 hours after the first dose of antiretroviral combination prophylaxis and resolved 48 hours after discontinuation of lopinavir-ritonavir.<sup>51</sup>

**Tipranavir (TPV)**

Rash, including maculopapular rash, urticarial rash, and possible photosensitivity reaction, has been reported in patients receiving ritonavir-boosted tipranavir. Rash occurred in 10% of women, 8% of men, and 21% of children receiving ritonavir-boosted tipranavir in clinical studies. The median time to onset of rash was 53 days and the median duration of rash was 22 days in adults. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus also has been reported. Discontinue tipranavir if severe rash develops. Females administered ethinyl estradiol followed by tipranavir-ritonavir had 33% incidence of rash<sup>50</sup>.

**Darunavir (TMC114)**

Severe skin reaction including erythema multiforme and Steven-Johnson syndrome, have occurred in patients receiving darunavir; fever and increased in serum transaminase concentration have occurred in some of these patients<sup>52</sup>. Rash (usually maculopapular and of mild to moderate intensity) has occurred in 7% of patients receiving ritonavir-boosted darunavir. Darunavir should be discontinued if severe rash occurs.

**Amprenavir (APV) / Fosamprenavir (FPV)**

Maculopapular rashes are reported in clinical trials with amprenavir or the phosphate ester prodrug of amprenavir, fosamprenavir, in as many as 3% of patients. Rash<sup>53</sup> (usually maculopapular and of mild or moderate intensity, with or without pruritus) has been reported in about 19% of adults receiving fosamprenavir in clinical studies; manifestations occurred approximately 11 days after initiation of fosamprenavir and persisted for a median of 13 days. Severe or life-threatening skin reactions including Steven-Johnson syndrome, were reported in less than 1% of patient receiving fosamprenavir in clinical studies. Some patients with mild or moderate rash have been able to continue fosamprenavir without interruption; reinitiation of fosamprenavir therapy following temporary interruption generally has not resulted in rash recurrence. Discontinue fosamprenavir if severe or life threatening rash or moderate rash accompanied by systemic manifestation occurs.

**Atazanavir (ATV)**

Rash (mild to moderate maculopapular eruptions) occurred in 21% of patients receiving atazanavir in clinical studies<sup>54</sup>. The median time to onset of rash was 8 week following initiation of atazanavir therapy and the median duration of rash was 1.3 weeks. Atazanavir generally was continued without interruption in these patients. If severe rash develops, atazanavir should be discontinued. Steven-Johnson syndrome and erythema multiform have been reported in patient receiving atazanavir.

**Entry Inhibitors:**

Infection of target cells by HIV is a complex, multi-stage process involving attachment to host cells and CD4 binding, co receptor binding, and membrane fusion. Drugs that block HIV entry are collectively known as entry inhibitors, but comprise a complex group of drugs with multiple mechanisms of action depending on the stage of the entry process at which they act. Two entry inhibitors, maraviroc and enfuvirtide, have been approved for the treatment of HIV-1 infection. Currently, most regimens are combinations of inhibitors of two viral enzymes—reverse transcriptase and protease. Nevertheless, several steps in the HIV replication cycle are potential targets for intervention. These steps can be divided into entry steps, in which viral envelope glycoproteins and their receptors are involved, and post entry steps, involving viral accessory gene products and the cellular proteins with which they interact. New treatment options target viral entry into the cell. These treatments include the HIV fusion inhibitor enfuvirtide, and new HIV coreceptor antagonists. Entry inhibitors include enfuvirtide, maraviroc, vicriviroc.

**Enfuvirtide (T-20)**

Hypersensitivity reactions, including rash, folliculitis, hematomas, contusion, injection site infection, injection site reactions (ISRs) associated with grades 3 and 4 induration (39% and 18%, respectively), erythema (22% and 10%, respectively), nodules and cysts (23% and 0.2%, respectively), and ecchymosis (5% and 2%, respectively) and grade 3 pain and discomfort (11%) and pruritus (3%) have been reported in phase 3 clinical trials of patients treated with enfuvirtide. but they are reported to occur in less than 1% of patients. In some biopsies of these reactions, multinucleated giant cells have also been noted. Neither enfuvirtide clinical trials nor postmarketing analysis has documented any immediate hypersensitivity reactions. Two hypersensitivity reactions attributed to enfuvirtide in clinical trials of multidrug-resistant patients, the occurrence of the rash was days to weeks after drug initiation<sup>55</sup>.

**Maraviroc**

Maraviroc is a specific, slowly reversible, non-competitive, small-molecule antagonist of the CCR5 chemokine receptor. It is the first CCR5 co-receptor antagonist approved. Several others are currently in preclinical and clinical development, including vicriviroc which recently entered phase III clinical trials. Both maraviroc and vicriviroc are small molecules that bind CCR5, preventing its interaction with gp120. By specifically targeting CCR5 they do not inhibit X4- or R5X4-tropic viral isolates<sup>56, 57</sup>. Hence, FDA approval of maraviroc stipulates that it is used as therapy for treatment-experienced adult patients in which only R5-tropic HIV-1 is detectable. Dermatologic adverse effects includes rash (11%), pruritus (4%), folliculitis (3%) skin neoplasms (benign; 3%), erythema (2%) have been reported. Cutaneous adverse events like Pruritic rash may precede the development of hepatotoxicity; therefore, patients with signs or symptoms of an allergic reaction (rash, eosinophilia and elevated IgE) should be evaluated to evidence hepatotoxicity.

**Vicriviroc**

Vicriviroc specifically binds to CCR5 and blocks cell migration that depends on CCL3, CCL4, and CCL5, and CCR5-dependent intracellular signalling at nanomolar concentrations. This drug does not substantially inhibit cytochrome P450 enzymes, but it is a substrate of CYP3A4. vicriviroc shows broad antiviral activity against genotypically diverse R5-tropic HIV-1 isolates in the nano molar range<sup>58</sup>. Vicriviroc is at different stages of Phase III clinical trials.

***Integrase Inhibitors:***

Major successes have been achieved in the development and clinical use of drugs that inhibit the HIV-1 RT and PR enzymes. HIV-1 encodes a third enzyme, integrase (IN), which is currently the focus of an intense research effort to develop new anti-HIV-1 drugs [53–57]. This research effort was validated in 2007 by the FDA approval of the first IN inhibitor for clinical use, MK-0518 (raltegravir). A second compound, GS-9137 (JTK-303, elvitegravir), is also performing well in clinical trials<sup>59</sup>.

**Raltegravir (RAL)**

Raltegravir (MK-0518) is an HIV-1 integrase strand transfer inhibitor (INSTI) that has been shown to be active against multidrug-resistant HIV-1 and both chemokine C-C motif receptor CCR5 trophic and chemokine C-X-C motif receptor CXCR4 trophic HIV-1 in vitro. A phase II dose-ranging study to assess the safety and efficacy of raltegravir compared with placebo in treatment-experienced patients with multidrug-resistant HIV-1 revealed that raltegravir at all doses had a safety profile similar to placebo and no dose-related toxicities<sup>60</sup>. All injection site reactions were related to enfuvirtide. Pruritus occurred in 4% to 9% of patients, but no rashes or hypersensitivity reactions were reported<sup>60</sup>.

**Elvitegravir (EVG)**

Elvitegravir is another integrase strand transfer inhibitor currently undergoing clinical development. Development of EVG/r is now continuing and is currently undergoing a phase 3 program in which it is being directly compared to RAL. An ongoing phase Study GS-US-183-0145 (Study 0145) will enroll 700 HIV-1 infected ARV treatment-experienced individuals and directly compare EVG/r (dosed QD) versus RAL 400mg (dosed BID)<sup>61</sup>.

***Maturation inhibitors:***

**Bevirimat (PA-457, DSB)**

Bevirimat is currently undergoing phase II clinical testing<sup>62</sup>. Initial studies, which were conducted over a ten-day period of dosing in a small number of HIV-1-infected volunteers given single daily oral doses of bevirimat, showed reductions in viral loads of 1 log at the highest doses of the compound. Viral genotyping was performed before initiation of therapy and several weeks after the completion of the study. No mutations associated with resistance in vitro<sup>62</sup> were observed in the patient-derived sequences<sup>63</sup>. No significant adverse effects of the compound have been observed thus far. Ongoing follow-up trials will involve higher doses of bevirimat, administered for longer periods of time.

**Table 1.** Most common dermatologic, adverse cutaneous reactions associated with Highly Active Antiretroviral Therapy in the management of HIV infection.

<b>Class of drugs</b>	<b>Dermatologic and Cutaneous adverse reactions</b>
<b>Nucleoside Reverse Transcriptase Inhibitors (NtRTIs)</b>	
Zidovudine (ZDV)	<ul style="list-style-type: none"> <li>• Pruritus, rash, skin/nail pigmentation changes,</li> <li>• Steven-Johnson syndrome (SJS)</li> <li>• Toxic epidermal necrolysis (TEN), urticaria</li> </ul>
Stavudine (D4T)	• >10%: Rash (18% to 30%)
Lamivudine (3TC)	• 1% to 10%: Rash (5% to 9%)
Emtricitabine (FTC)	<ul style="list-style-type: none"> <li>• &gt;10%: Hyperpigmentation (children 32%; adults 2% to 4%; primarily of palms and/or soles but may include tongue, arms, lip and nail; generally mild and nonprogressive without associated local reactions as pruritus or rash)</li> <li>• Rash (17% to 30%; includes Pruritus, maculopapular rash, vesiculobullos rash, pustular rash, and allergic reaction)</li> </ul>
Tenofovir (TDF)	• 1% to 10%: Rash event (Maculopapular, pustular, or vesiculobullos rash, pruritus or urticaria 5% to 7%; treatment native 18%)
Abacavir (ABC)	<ul style="list-style-type: none"> <li>• 1% to 10%: Rash (5% to 6%, children 7%), hypersensitivity reaction</li> <li>• &lt;1%: Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis.</li> </ul>
Didanosine (DDI)	• 1% to 10%: Rash/pruritus (7% to 9%)
Zalcitabine (DDC)	• Aphthous ulcers, pruritus, urticaria, and lip blisters
<b>Non nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>	
Nevirapine (NVP)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (grade 1/2: 13%; grade 3/4: 1.5%) is the most common toxicity; occurs most frequently within the first 6 weeks of therapy; women may be at higher risk than men.</li> <li>• Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis.</li> </ul>
Efavirenz (EFV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (5% to 26%, grade 3/4: &lt;1%; children up to 46%, grade 3/4: 2% to 4%)</li> <li>• 1% to 10%: Pruritus (up to 9%)</li> <li>• &lt;1%: Erythema multiforme, nail disorder, skin discoloration, Steven-Johnson syndrome (SJS)</li> </ul>
Delavirdine (DLV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (16% to 32%)</li> <li>• 1% to 10%: Steven-Johnson syndrome (SJS)</li> </ul>
Etravirine (ETV)	• Skin rash
Rilpivirine (RPV)	• Skin rash
<b>Protease Inhibitors (PIs)</b>	
Indinavir (IDV)	<ul style="list-style-type: none"> <li>• &gt;10%: Pruritus (4%), rash (1%)</li> <li>• &lt;1%: Steven-Johnson syndrome (SJS), urticaria, vasculitis.</li> </ul>
Saquinavir (SQV)	• 1% to 10%: Pruritus (3%), rash (3%), dry lip/skin (2%), eczema (2%), verruca
Nelfinavir (NFV)	<ul style="list-style-type: none"> <li>• 2% to 10%: Rash (1% to 3%)</li> <li>• &lt; 2%: urticaria</li> </ul>
Ritonavir (RTV)	• 2% to 10%: Rash (up to 4%)

	<ul style="list-style-type: none"> <li>• &lt; 2%: urticaria, Steven-Johnson syndrome (SJS), skin melanoma</li> </ul>
Lopinavir (LPV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (children 12%; adults up to 5%)</li> <li>• &lt; 2%: Maculopapular rash, Steven-Johnson syndrome, skin ulcer.</li> </ul>
Tipranavir (TPV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (children 21%; adults 3% to 10%)</li> <li>• &lt; 2%: hypersensitivity, pruritus</li> </ul>
Darunavir (TMC114)	<ul style="list-style-type: none"> <li>• 2% to 10%: Rash (2% to 10%)</li> <li>• &lt; 2%: Steven-Johnson syndrome (SJS), toxic skin eruption, skin inflammation</li> </ul>
Amprenavir (APV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (20% to 27%)</li> </ul>
Fosamprenavir (FPV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (up to 19%; onset ~11 days; duration ~13 days)</li> <li>• 1% to 10%: Pruritus (7% to 8%)</li> <li>• &lt; 1%: Steven-Johnson syndrome (SJS)</li> </ul>
Atazanavir (ATV)	<ul style="list-style-type: none"> <li>• &gt;10%: Rash (5% to 21%; median onset 8 weeks)</li> <li>• &lt; 2%: Steven-Johnson syndrome (SJS), macropapular rash</li> </ul>
<b>Entry Inhibitors</b>	
Enfuvirtide (T-20)	<ul style="list-style-type: none"> <li>• &gt;10%: Injection site reaction (98%; may include, erythema, induration, pruritus, ecchymosis, nodule or cyst formation)</li> <li>• 1% to 10%: Folliculitis (2%)</li> </ul>
Maraviroc	<ul style="list-style-type: none"> <li>• 2% to 10%: Rash (11%), pruritus (4%), folliculitis (3%), skin neoplasms (benign; 3%), erythema (2%)</li> </ul>
<b>Integrase Inhibitors</b>	
Raltegravir (RAL)	<ul style="list-style-type: none"> <li>• 2% to 10%: Rash (<math>\leq</math> 5%), pruritus (3% to 4%), folliculitis (<math>\leq</math> 2%)</li> <li>• Anogenital warts (<math>\leq</math> 2%), Steven-Johnson syndrome (SJS)</li> </ul>
Elvitegravir (EVG)	Ongoing clinical trials
<b>Maturation inhibitors</b>	
Bevirimat (PA-457, DSB)	Ongoing clinical trials

### Conclusions

Highly Active Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The medical management of patients with HIV infection is challenging to physicians and other healthcare professionals who are not familiar with the use of antiretroviral agents. The adverse effects of Highly Active Antiretroviral Therapy may cause symptoms affecting a variety of organ systems. It is important to recognize the safety profile of these new treatments. Skin toxicities are common complications of HIV infection, and this is a significant risk factor for adverse drug reactions. In HIV-infected patients, there is a high prevalence of severe skin reaction including erythema multiforme and Steven-Johnson syndrome induced by antiretroviral therapy. Furthermore, HIV-infected patients may have recurrent cutaneous reactions from other medications such as antibiotics, non-steroidal anti-inflammatory drugs and antituberculosis agents. Withdrawal of the suspected drug is essential for prognosis. It is also important to perform a causality assessment of the suspected drug reaction in order to determine whether drug discontinuation is mandatory, as well as to put emphasis on patient education in order to avoid the development of skin toxicities in the future. As efforts continue in the development of newer HAART, treating physicians and Pharmacists must remain aware of new and developing syndromes associated with Highly Active antiretroviral usage.



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