

## Cutaneous manifestations of anti retroviral therapy used for post-exposure prophylaxis

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### ABSTRACT

Health care workers are at increased risk of needle stick injuries. Blood borne diseases that could be transmitted by such an injury include HIV, Hepatitis B, HCV and many others. Post exposure prophylaxis should be immediately started within 72 hours and should be continued for 28 days. Currently two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are given along with one NNRTI (Non-Nucleoside reverse Transcriptase Inhibitor) including Efavirenz or Nevirapine. Multiple adverse effects have been reported with all the Anti- Retroviral Therapies including various cutaneous manifestations. A 22-year-old intern doctor studying in tertiary hospital of Ahmedabad had a needle stick injury with a needle contaminated with blood of HIV positive patient. Post Exposure prophylaxis was started within 72 hours consisting of fixed dose regimen of Tenofovir disoproxil sulphate, Efavirenz and lamivudine. He was started with the drug within 2 hours and was prescribed one drug per day for next 27 days. On 22nd day he started having rash on his body which started on palms and soles. On 23rd day he saw severe facial edema along with edema on lips and rash spreading to other parts of the body. He was diagnosed with Hypersensitivity reaction and angioedema due to ART drug therapy. He was instructed to stop ART medications and was given antihistaminic for the symptoms. Patient's angioedema was relieved in 2-3 days and rash disappeared after 4-5 days. As he had already finished 23 days of therapy he was instructed to discontinue the drugs. No recurrence of rash or angioedema was noted. This case points out the severity of side effects in the normal healthy people taking ART as Post Exposure Prophylaxis. Apart from cutaneous manifestations, angioedema is a very grievous condition which doctors should always have lower threshold for diagnosis. Early diagnosis can prevent further complications. ART drugs have many complications and these patients should have intensive regular monitoring while on treatment. Also, proper education is required for needle cut injuries in health care workers.

**Keywords:** Anti- retroviral therapy, Angioedema, Needle-stick injuries, PEP, Rash

### INTRODUCTION

Health care workers are at increased risk of needle stick injuries. Blood borne diseases that could be transmitted by such an injury include HIV, Hepatitis B, HCV and many others.<sup>1</sup> Punctures by contaminated needles can inject hazardous drugs, but contact with infectious fluids, especially blood, is by far the greatest concern. Medical students are at increased risk of needle stick injuries and

blood borne infections during their clinical activities while performing procedures on patients. In one of the studies from United States, nurses accounted for 68%, interns for 35%, and resident doctors for 31% of BBF exposures.<sup>2</sup> Another study conducted in Mumbai, India, observed that the incidence of occupational exposure due to infected blood and body fluids were highest among resident doctors (76%), followed by nurses (11%), and interns (5%).<sup>3</sup>

Post exposure prophylaxis should be immediately started within 72 hours and should be continued for 28 days. Either 2 drug or 3 drug regimens are advised for the same. Currently two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are given along with one NNRTI (Non-Nucleoside reverse Transcriptase Inhibitor) including Efavirenz or Nevirapine.<sup>4</sup> Newer drug of Protease inhibitors (PI) are also given in PEP but most of the time it is reserved as second line therapy.

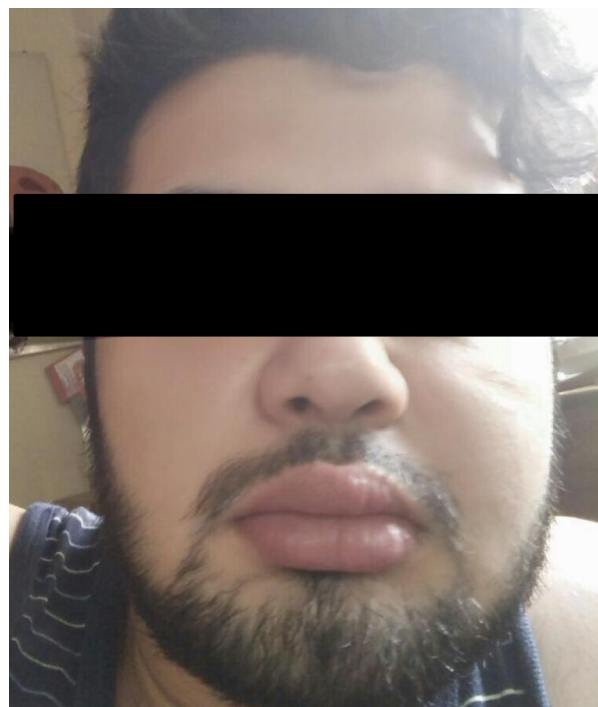
Multiple adverse drug reactions have been documented for different classes of Anti-Retroviral Therapy. Common cutaneous adverse drug reactions are maculopapular exanthema which are usually evident on the trunk and are characterised by severe pruritus. NRTIs can cause vasculitis, mucocutaneous pigmentation, hair and nail changes whereas NNRTIs are more commonly associated with hypersensitivity reactions, urticaria, morbilliform eruptions. Apart from these two classes, PI are also associated with various cutaneous side effects including lipodystrophy and hypersensitivity reactions.<sup>5</sup>

### CASE REPORT

A 22-year-old intern doctor studying in tertiary hospital of Ahmedabad had a needle stick injury with a needle contaminated with blood of HIV positive patient. According to guidelines of NACO (National AIDS Control Organisation, India), fixed drug combination dose of anti-retroviral therapy was started. It consists of tenofovir disoproxil fumarate (300mg) lamivudine (300mg) and efavirenz (600mg) and it was started within next two hours. He was given the first dose immediately within 2 hours and then one tablet each day for next 27 days (total 28 day course). He had the first dose side effects including nausea, dizziness and headache. He was well compliant with medication. He complained of having early morning side effects of dizziness, nausea/vomiting accompanied by fatigue for his entire therapy duration. On 22<sup>nd</sup> day he started having rash on his body starting from palms and sole. On 23<sup>rd</sup> day he saw severe facial edema along with edema on lips as shown in fig.1 and rash spreading to other parts of the body. Rash was erythematous macular in quality and accompanied by pruritus. The skin was tender to touch which he complained as difficulty in walking as his soles were tender due to diffuse rash on his both the soles. Due to presence of significant facial edema, patient presented to the hospital for evaluation. He was diagnosed with Hypersensitivity reaction and angioedema due to ART drug therapy. He had never had any allergic drug reaction in past.

Patient was instructed to stop the combined ART therapy and was started on Anti-histaminic drugs (bd) to decrease the rash and the edema. Patient's angioedema was relieved in 2-3 days and rash disappeared after 4-5 days. As he had already finished 23 days of therapy he was instructed to discontinue the drugs and carry out the HIV viral titre which returned negative after 1 and then even after 3

months. No recurrence of rash was recorded in subsequent follow-up.



**Figure 1: Facial edema with lip swellings.**

### DISCUSSION

Needle stick injuries are one of a big hazards to health care workers. Many studies have been conducted regarding the prevalence and awareness of the needle-stick injuries in the health care workers especially doctors and medical students.<sup>6</sup> Most of studies have shown that medical students are at increased risk of injuries due to lack of proper training and therefore they tend to have these injuries in their initial exposure to the ward procedures, phlebotomy and emergency rooms. Education about standard precautions must be enforced to reduce this incidence and prevalence.<sup>7</sup> Along with that HBV vaccination also plays an important role as HBV transmission is more common as compared to HIV through such injuries.<sup>8</sup>

Our intern doctor was on his first emergency medicine rotation at one of the busiest emergency trauma centre in the city. Patient got a superficial cut from the needle used for phlebotomy for a 25-year-old patient who was admitted for multiple concerns including jaundice, weakness, vomiting and abdominal pain in the emergency room. The patient's blood came positive for both HIV (high viral load) as well as Hepatitis B and the patient died due to multiple organ involvement in the next four days. The intern doctor immediately reported to the ART centre in this hospital. He had already completed the booster dose of Hep-B vaccine and his titres were >1000 IU so Hep-B vaccination or IVIG were not indicated here.

Lamivudine is a synthetic nucleoside analogue that is widely used in multidrug and in fixed dose combination therapies for treatment of HIV. Various erythematous eruptions as well as paronychia have been reported with it.<sup>9</sup> Apart from that, allergic contact dermatitis, alopecia, anaphylactoid reactions and angioedema have also been reported with Lamivudine.<sup>10</sup> In one of the studies by MA Kainer et al, they have reported a case with temporal relation of angioedema and urticaria to Lamivudine. Although our case presentation is almost similar to their case, our patient had started with a fixed dose combination whereas in this study the patient was started with only Lamivudine and so it was possible for this causality relation for them.<sup>11</sup>

Tenofovir is also belonging to NRTI drug class and cases of maculopapular rash and other drug reactions have also been reported. In a study by Lockhart et al, they have reported 9 cases of hypersensitivity consisting mainly of maculopapular rash on face, extremities and trunk who were treated with Tenofovir in their clinic.<sup>12</sup>

Efavirenz is one of NNRTI used commonly in multidrug combination therapies. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) directly inhibit the HIV-1 reverse transcriptase (RT) by binding in a reversible and non-competitive manner to the enzyme. Nevirapine and Efavirenz are two most commonly used NNRTI in the fixed drug dose combinations. Rash is one of the most common side effects of both the drugs along with early CNS side effects like dizziness with Efavirenz. Many literature and research studies have shown that rash is more frequent with NNRTIs as compared to NRTIs. Also, early morning dizziness and nausea/vomiting symptoms that our patient had can be attributed to Efavirenz but other effects due to other drugs cannot be ruled out.<sup>13</sup>

In this case, patient had started the drug regimen for PEP and no other drugs were being taken by him along with it. Also, it was started only 22 days before the reaction although most cases report cutaneous symptoms as early as 8-10 days, period of 22 days can still be considered as a shorter duration. Also, he has not had any similar cutaneous allergic reactions to any other drugs in past. Amongst the three drugs of the combination regimen, as discussed above, all three drugs have some associations with various cutaneous manifestations. So, authors cannot attribute this reaction to any single drug but it can be either adverse reaction due to a single drug or due to a combined effect of all the three drugs. Also, immediate stopping of the drug helped reverse the symptoms rapidly within a week. Drug causality, symptoms onset within the time frame of starting the drug and symptoms getting relieved on stopping the drug all contribute that he had these reactions due to the PEP treatment started.

## CONCLUSION

Although many cases have been reported for cutaneous side effects of different drugs of ART, most of the cases

are in HIV infected patients. Our case points out the severity of side effects in the normal healthy people taking ART as Post Exposure Prophylaxis. Also, angioedema is a grievous condition associated with these drugs which doctors should be precautious about and have little threshold for its diagnosis. Newer drugs combinations including Protease inhibitors are considered safer compared to the NNRTI regimens which can be considered in such patients. Also, more awareness needs to be created regarding needle stick injuries to prevent any kind of infection transmission and also any kind of drug reaction due to the prophylactic drugs.

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