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Up to 70% of HIV-positive individuals report experiencing symptoms related to atopy

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HIV-infected individuals (HIV+) have been reported to have a higher rate of type 1 hyperactivity (HR1), commonly referred to as allergies though more appropriately termed atopy.¹⁻⁴ Despite 30 years of research, it is still not clearly understood how HIV, an immune-suppressive infection, can cause an increased occurrence of symptoms that are the result of an amplified immune response. For the most part, atopy does not result in significantly increased morbidity in the HIV+ population. However, utilization data has found that any individual with even mild atopy symptoms average three additional office visits, nine more prescriptions, and \$1500 in additional health care costs per year than those without symptoms.⁵ This burden may be amplified within the HIV+ populations of which up to 70% report some degree of atopy symptoms.⁶

Atopy is caused by HR1 immune reaction to a substance (allergen) that is normally harmless or does not cause an

immune reaction in all humans. The body's response to an allergen (allergic response) is caused when an allergen activates immunoglobulin E antibodies (IgE) that have been produced by B lymphocytes. IgE bonds to mast cells, basophils, and eosinophils of the immune system and, when activated, cause these cells to release numerous mediators including histamine, proteases, chemotactic factors, and synthesis of other mediators such as prostaglandins, leukotrienes, platelet-activating factor, and cytokines.² These mediators act on surrounding tissues resulting in vasodilation, smooth-muscle contraction, and further immune system response—symptoms associated with atopy.¹ More specifically, these symptoms include airway constriction, skin and mucus membrane inflammation, and increased mucus secretion and are frequently exhibited as eczema (atopic dermatitis), allergic rhinitis (hay fever), allergic conjunctivitis, or allergic asthma.

Although the pathology that increases the occurrences of atopy in the HIV+ is

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TEST EARLY, TREAT EARLY:

In search of a common approach to HIV treatment

Sylvana Niciteretse, MPH

As soon as the human immunodeficiency virus enters the human body, it typically starts replicating and the CD4 cell counts progressively decrease if the HIV-infected individual is not tested and not on antiretroviral therapy. The progression time toward acquired immunodeficiency syndrome is estimated to be an average of about ten years, a period that varies from one individual to another. Since 1996, antiretroviral therapy (ART) has changed the course

of HIV from a deadly to a chronic disease. At the same time, many studies have been done to identify the life cycle of the virus, the disease progression, and the efficacy of ART. However, with these therapeutic successes, the research community is still searching for an HIV cure and vaccine. The HIV healthcare providers and supportive care team, on their end, are testing new therapeutic approaches, among them "Test early, treat early" in order to achieve these two

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Poorly controlled atopy interferes with quality of life

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not fully understood, it is known that HIV+ individuals have higher levels of IgE, especially as CD4 T lymphocyte (CD4) cells decrease in advanced disease.^{3,7,8} Even with low CD4 levels, HIV+ individuals have dramatic increases in IgE activation when exposed to allergens, resulting in increased prevalence of atopy.^{4,9-11} This elevated IgE is likely secondary to a deregulation of the immune system stemming from altered CD4 function that increases in later stages of HIV disease.^{3,7,9,12,13} In a “normal” immune system, CD4 stimulates both T lymphocyte-helper 1 (TH1) (resulting in the cellular immune response via IgG *et al*) and lymphocyte-helper 2 (TH2) (resulting in the humoral immune response via IgE *et al*). With HIV infection, this balance is disrupted and TH1 function is diminished as TH2 function increases, resulting in increased IgE levels.⁹⁻¹¹ With the increase in TH2 function comes the increase in production of interleukin (IL)-4 (the cytokine responsible for IgE class switching) and IL-10 (the cytokine responsible for down-regulation of TH1).^{3,14,15} In addition to promoting IgE production, the increase in TH2 activity inhibits the ability of TH1 cells to synthesize IL-2, IL-12, and interferon (IFN)-gamma, as well as antiviral cytotoxic T lymphocyte activity which plays a critical role in the progression of HIV infection.³ Though most of HIV research has focused on the decreased function of the TH1 and cellular immunity, as medical advances have successfully managed this dysfunction, the “increased” activity of TH2 and

humeral immunity have become a more prominent health issue in the HIV+ population

Even without a complete understanding of the pathology, it is well known that atopy is frequently seen in HIV-positive patients.^{3,15,16} Atopy can range from mild itching, rhinitis, or sinus congestion to systemic immune response involving the gastrointestinal system, mucus membrane inflammation, or bronchial spasm, including asthma.¹ From a generalized HIV+ outpatient population of 203 patients, 66% reported symptoms of atopy.¹⁷ More recently, studies have reported prevalence of atopy-associated rhinitis as high as 70% and sinus congestion as high as 68% in HIV+.⁶ At the University of Pittsburgh, 20% of the adult HIV clinic population had a diagnosis of asthma, twice as high as the general population.¹⁸ Other studies have reported higher prevalence of positive allergy skin tests (objective measure of HR-1) in HIV+ populations compared to non-HIV-infected.^{19,20} Sinus and nasal symptoms are among the most common atopy complaints in the HIV+, most specifically rhinorrhea.²¹ HIV+ individuals exhibited atopy to many of the same allergens as the non-HIV-infected (HIV-), including pollens, dust, molds, and dander.²² But as mentioned, the HIV+ may have increased IgE activity and atopy due to exposure to various pathogens including bacteria, fungi, viruses, and even HIV itself.¹

A diagnosis of atopy requires a thorough allergic history, personal and family medical history, and identification of allergic triggers to assist in treatment planning.²³ Patients may complain of coughing with minimal clear secretions that may be worse at night. A sore

throat, worse in the morning, or general hoarseness are common complaints and associated with chronic postnasal discharge that irritates the pharynx, especially during sleep. Classic physical findings include allergic shiners (dark, puffy, lower eyelids) and a transverse crease on the lower third of the nose from chronic nose rubbing. Conjunctival erythema, bluish mucosal turbinates, clear rhinorrhea, and posterior pharynx cobblestoning from follicular hypertrophy are also common atopy findings. Red flaky itchy skin patches, urticaria, angioedema, dermatitis, and cracked skin on joints and hands with lichenification are common symptoms associated with atopic dermatitis. The lung fields are usually clear to auscultation but upper airway transmitted sounds may be heard or mild rhonchi that clears with coughing. Though required in some cases, extensive testing (Table 1) and laboratory diagnostics should be limited to cases that fail to respond to standard therapy.²

With few exceptions, treatment for atopy in HIV+ is similar to HIV-.²⁴ Primarily, control of symptoms starts with control of environmental exposures to allergens. Minimizing exposure to the most common allergens—dust mites, cockroaches, pollens, molds, and irritants—is essential (See Table 2). Indoor allergens differ from outdoor, with exposure to indoor allergens somewhat more controllable. Seasonal symptoms are quite common and dependent on changes in regional flora as well as weather (humidity, temperature, wind). In all cases, providers need to assure patients have access to accurate data-driven

en information, training to employ strategic steps to control their environment, and support for being vigilant to potential exposures.

The range of pharmacotherapies that can be used in the management of atopy (Graph 1) include antihistamines (Table 4), decongestants, corticosteroids (Intranasal Table 5, Topical Table 6), mast cell stabilizers (Table 5), ipratropium bromide, anticholinergics, and anti-leukotriene agents (leukotriene receptor antagonists/LTRA).²²⁻²⁵⁻²⁶ This list does not include potential treatments for allergic asthma which is addressed in other resources. Hypertonic saline irrigation has been shown to reduce nasal-associated atopy symptoms including rhinitis and congestion.²⁷ Newer classes such as anti-IgE antibody (omalizumab) currently have a limited role in atopy treatment.²⁷ Selection of atopy treatment depends on symptoms (occurrence whether seasonal or perennial, frequency, persistence), predominant symptoms, response to previous therapies, adverse side effect profile, and administration (frequency, route). The individual's current HIV-associated treatment, antiviral therapy, and any comorbidities and treatments must also be considered. As advances are made in HIV treatments, clinicians must be vigilant regarding potential pharmaceutical interactions among atopy, HIV, and comorbidity pharmaceutical treatments (Table 7)

Overall, the referenced Joint Task Force on Practice reports that intranasal corticosteroids are the most effective class of medication for managing rhinitis, one of the most common atopy symptoms.²³ There are no apparent differences in efficacy among the various products and they have

few systemic adverse effects compared to oral versions.²³ Topical corticosteroids are also the primary recommendation for atopy skin manifestations (atopic dermatitis) (Table 6).²⁸ Although there is a theoretical possibility of increased risk of opportunistic infections (OIs) with the use of intranasal steroids in the HIV+ individual, this has not been documented.¹ However, corticosteroids are metabolized by cytochrome P450 3A4 (CYP3A4) and thus may have decreased metabolism and increased accumulation when administered along with ritonavir, a potent CYP3A4 inhibitor.²⁹ Fluticasone has the longest glucocorticoid receptor-binding half-life and is 300 times more lipophilic than budesonide and is more likely to cause adrenal suppression.²⁹ Cobicistat has a similar interaction.

Antihistamines are still considered primary treatment for many atopy symptoms, especially those affecting the upper airway. They are effective in reducing many atopy symptoms including rhinorrhea, sneezing, and itching but do not reduce nasal congestion. Intranasal antihistamines are effective for nasal congestion but are considered less effective than intranasal corticosteroids for rhinitis.²⁷ Most of the second generation oral antihistamines have reduced sedating effects; they vary in onset and duration profile.²³ LTRAs have gained an increased role in the treatment of atopy symptoms, especially when antihistamines fail to control symptoms.²⁷ Oral decongestants can reduce symptoms of nasal congestion associated with atopy and rhinitis, but are limited by adverse effects that can include insomnia, loss of appetite, irritability, and cardiac palpitations. They should be used with caution

in older patients and those with specific medical concerns, including heart disease, hypertension, diabetes, glaucoma, and hyperthyroidism.²³

Similar to HIV-, many HIV+ patients with atopy do not respond to avoidance or pharmacologic interventions. In such cases, HIV- may be offered allergen immunotherapy (AIT).³⁰ When allergens are correctly identified using skin testing (Table 1), AIT can result in clinical improvement in up to 95% of patients (decrease in symptoms, improved efficacy, or decreased amount of medications necessary for symptom control).^{1,31} However, the safety of AIT in HIV+ is unclear due to the theoretical potential of causing worsening HIV disease (decreased CD4 count and/or increased HIV viral load) due to AIT effect on T cells.^{1,3} Despite these hypothetical concerns, in a study by Coifman and Cox (2006), 40% of allergists/immunologists reported that they would start AIT on the HIV+ based on the knowledge that other vaccines have shown only minimal effects on CD4 and HIV viral load.³²⁻²⁴ More recently, case reports of AIT in HIV+ on HAART have all shown improvement in atopy symptoms and no change in CD4 or viral load as long as HAART is continued through the treatment.^{10,35,36} Guidelines have been proposed for AIT in HIV+ individuals who have no history of opportunistic infections or AIDS-defining illnesses, who have an undetectable or low viral load, who are able to maintain complete adherence to HAART, who cannot avoid allergens, and whose symptoms are not adequately controlled with pharmaceutical options.³⁷ If the option of using AIT in HIV-infected patients is considered, the potential risks

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Patients rate symptoms as more severe than their physicians do

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and benefits of AIT in HIV-positive patients must be assessed on an individual basis and close immune function/HIV disease monitoring is required.³

Though frequently considered a minor inconvenience, poorly controlled atopy substantially interferes with quality of life and daily functioning, including sleep disturbances with daytime fatigue and reduced productivity at school or work.³⁸ Furthermore, these minor symptoms can lead to more severe conditions including bronchitis, sinusitis, cellulitis, and even pneumonia. Unfortunately, many HIV+ patients frequently have various other minor ailments so that the addition of atopy symptoms can be “just one more thing wrong.” However, it is important for HIV clinicians to be aware that studies have found that patients rate their atopy symptoms more severely than their physicians do.³⁷ Though the treatment of HIV has dramatically improved over the last 20 years, with simplified regimes and decreased side effects, patients still experience numerous morbidities, many of which clinicians are not able to well control. Atopy symptoms are conditions that can be controlled with treatments that minimally affect HIV treatments. Control of these “small nuisances” may be minor in effort, but can have a profound effect on an HIV+ person’s quality of life and deserve our attention. ♦

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HIV online training
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Table 1. Specific Testing Used In Diagnosis of Atopy²

Indication: When symptoms are not able to be controlled using standard environmental/pharmacological interventions or standard interventions are not able to be employed due to environmental or health related constraints AND history is unable to identify causative allergens (triggers). Poor control of symptoms include recurrent need for antibiotics, high dose corticosteroids, or increased health care utilization. These tests provide information regarding potential allergens (triggers) so that focused attention/treatments may be used to improve symptom control.

Types of Testing

- **Skin Testing:** Standardized concentrations of key antigen (regionally and patient specific determined) injected directly into skin. This testing has higher positive predictive values for diagnosing allergic rhinitis and conjunctivitis than for diagnosing allergic asthma or food allergy; negative predictive value for food allergy is high. The most commonly used antigens are pollens (tree, grass, weed), molds, house dust mites, animal danders and sera, insect venom, foods, and β -lactam antibiotics. Certain drugs that can interfere with results must be stopped days/weeks before testing (H1 blockers/ antihistamines, tricyclic antidepressants, and monoamine oxidase inhibitors).
 - Two skin test techniques can be used:
 - Percutaneous (Prick): appropriate to detect HR-1 to most common allergies. A drop of antigen extract is placed on the skin, which is then tented up and pricked or punctured through the extract with the tip of a 27-gauge needle held at a 20° angle or with a commercially available prick device thus placing the allergen into the dermis.
 - Intradermal: More sensitive but less specific; used only when prick test results are negative or equivocal. Using ~0.02 mL of an antigen, a 1-2 mm bleb created intradermally with a 27-gauge short-bevel needle.
 - For patients who have had a recent (< 1 yr) generalized reaction to the test antigen, begin testing with highly diluted reagent (100-fold) and increase (10-fold to standard concentration).
 - Both should include diluent alone as a negative control and histamine (10 mg/mL for prick tests, 0.01 mL of a 1:1000 solution for intradermal tests) as a positive control.
 - A skin test is considered positive if a wheal/flare reaction is 3 to 5 mm > the negative control after 15 to 20 min. False positives occur in dermatographism (a reaction due to stroking or scraping the skin).
 - False negative results can occur due to contaminated or degraded allergen extract.
 - Caution with patients on β -blockers: this indicates risk of increased reaction severity (Use of drugs indicates limited cardiopulmonary reserve including coronary artery disease, arrhythmias, and older age which increases risk associated with reaction). β -blockers can also interfere with treatment of severe reactions by blocking response to β -adrenergic agonists such as epinephrine
- **Allergen-specific serum IgE tests/Radioallergosorbent Testing (RAST):**
 - Indication: Used when skin testing may be ineffective, concurrent skin conditions (ie, eczema, psoriasis) would interfere with results, or other contraindication (in patients on β -blockers or drugs that interfere with test and cannot be stopped).
 - Method: Uses labeled anti-IgE that will bind to allergen specific serum IgE. Allergen is immobilized on a synthetic surface. A colorimetric fluorescent or chemiluminescent substrate for the labeled anti-IgE is added. Testing involves detecting substrate.
 - RAST: uses radioactive "I-labeled" anti-IgE antibody
 - ASIgE Tests: does not use a radioactive label, (frequently referred to as RAST)
- **Provocative testing**
 - Indication: for diagnosis of specific food allergy or when a reaction to a specific allergen is required (eg, for occupational or disability claims)
 - Method: direct exposure of the mucosae to allergen to document specific reaction. Examples: exercising to diagnose exercise-induced asthma, ice to skin to diagnose cold-induced urticaria.



Table 2. Management of Atopy via Environmental Control Measures³⁹

The primary treatment for atopy is avoiding the most common triggers including pollens, fungi, dust mites, furry animals, and insect emanations.

- **Clinically effective dust mite avoidance requires a combination of humidity control, dust mite covers for bedding, high-efficiency particulate air (HEPA) vacuuming of carpeting, and the use of acaricides.**
 - Use only synthetic polyester-fill pillows *and* comforters (never feather or down). Encase pillows, mattresses, and box springs in zippered dust mite-proof covers (available at allergy-supply stores and many department and discount stores). Keep covers clean by vacuuming or wiping them down once a week.
 - Wash sheets and blankets once a week in very hot water (130°F or higher) to kill dust mites.
 - Avoid upholstered furniture, window mini-blinds, and carpeting as much as possible. They can collect dust and harbor dust mites (especially carpets).
 - Use washable throw rugs on vinyl or hardwood floors and wash rugs in hot water frequently.
 - Use washable curtains and vinyl window shades that can be wiped down. Wash curtains in hot water frequently.
 - Dust and vacuum weekly. If possible, use a vacuum cleaner with a HEPA (high-efficiency particulate) filter to collect and trap dust mites that become airborne during vacuuming.
 - Reduce the number of dust-collecting houseplants, books, and knickknacks.
 - Using central or room unit air filters such as HEPA filters or electrostatic filters are **ONLY** effective in reducing dust mite allergens when used along with other environmental control measures. When using such filters, the appropriate size should be used to filter the entire room. Ozone air purifiers or ionizers are not effective
 - Decrease humidity to below 50% when possible: moist air promotes dust mite infestation. Monitor humidity in the home with a humidity gauge (hygrometer) so additional precautions can be taken if >50%.
- **Cockroaches are a significant cause of nasal allergy; reducing exposure should include:**
 - Remove/control all food and water sources that can attract cockroaches. Assure frequent sweeping/vacuuming in areas where food particles may be found. Limit areas where food is found in home: eat only in specific areas that can be easily cleaned. Assure all food is kept in airtight containers. Keep trash and garbage in tightly sealed containers removed frequently from the home and away from the house.
 - Eliminate "non-food" sources that can attract cockroaches: cardboard, accumulated paper areas that are moist (plants, cleaning supplies, rags, leaking pipes)
 - Use a suitable pesticide that is effective but does not cause further harm. Assure they are used at appropriate frequency to maintain control.
 - Seal any cracks in walls and floors where cockroaches may enter.
- **Fungi are ubiquitous organisms, many of which produce clinically important allergens. Reduction of indoor fungal exposure involves removal of moisture sources, replacement of contamination materials, and the use of diluted bleach solutions on nonporous surfaces.**
 - Avoid humidifiers and maintain a low humidity environment if possible. If a humidifier is required, change the water every day and clean with bleach 2-3 times a week to prevent mold growth.
 - Ventilate bathrooms, basements, and other dark, moist places that commonly grow mold. Consider keeping a light on in closets and using a dehumidifier in basements to remove air moisture.
 - Air conditioning does assist in removing excess air moisture; assure filters are changed/cleaned once a month.
 - Avoid wallpaper and carpets in bathrooms since mold can grow under them.
 - Use a weak bleach solution consisting of 1 cup of bleach per gallon of water to kill mold in bathrooms and other areas.
- **The types of pollen responsible for atopy vary widely with locale, climate, and introduced plantings. Highly pollen-allergic individuals should limit exposure to the outdoors when high pollen counts are present.**
 - Air conditioning does assist in removing pollen from the air, filters should be changed once a month.
 - Keep windows and doors shut during pollen season.
 - Consider bathing/changing clothes after coming into home on high pollen count days or after doing yard work
 - Take extra precautions when doing yard work including using a hepa-filter mask, gloves, eye protection, and long sleeves
 - Drive with windows closed and air conditioning on during high pollen days
 - Monitor weather and beware of conditions that will increase air pollen: decreased humidity, wind
- **Controlling exposure to chemical irritants**
 - Do not allow cigarette smoke in the house: smoke will become trapped in upholstery and carpets.
 - Limit the use of wood burning fireplaces or stoves.
 - Avoid strong odors from paint, perfume, body sprays/cosmetics, disinfectants, chemical cleaners, air fresheners, and glues.
 - Beware of increased atopy symptoms associated with seasonal exposures: Christmas trees, barbecue fires, swimming pool chlorine
- **Avoidance is the most effective way to manage animal sensitivity. Animals can also be a sources of pollen exposure as they can carry large amounts from the outside on their coats.**
 - Even after a pet is removed from the home it may take several months before all the dander is cleared.
 - Animal dander/attribution pollen can be reduced if the animal is frequently washed (weekly).
 - Limit the pet's exposure to certain rooms (bedrooms) or rooms where dander cannot be easily removed
 - If someone in the home has atopy, do not bring an animal into the home. Even if there is no known allergy to pet dander, exposure can trigger reactions.
 - Central or room unit HEPA filters may be more effective in removing airborne pet dander than in recovering dust mite allergens.

Graphic 1: Pharmacological Management of Allergic Rhinitis²⁷

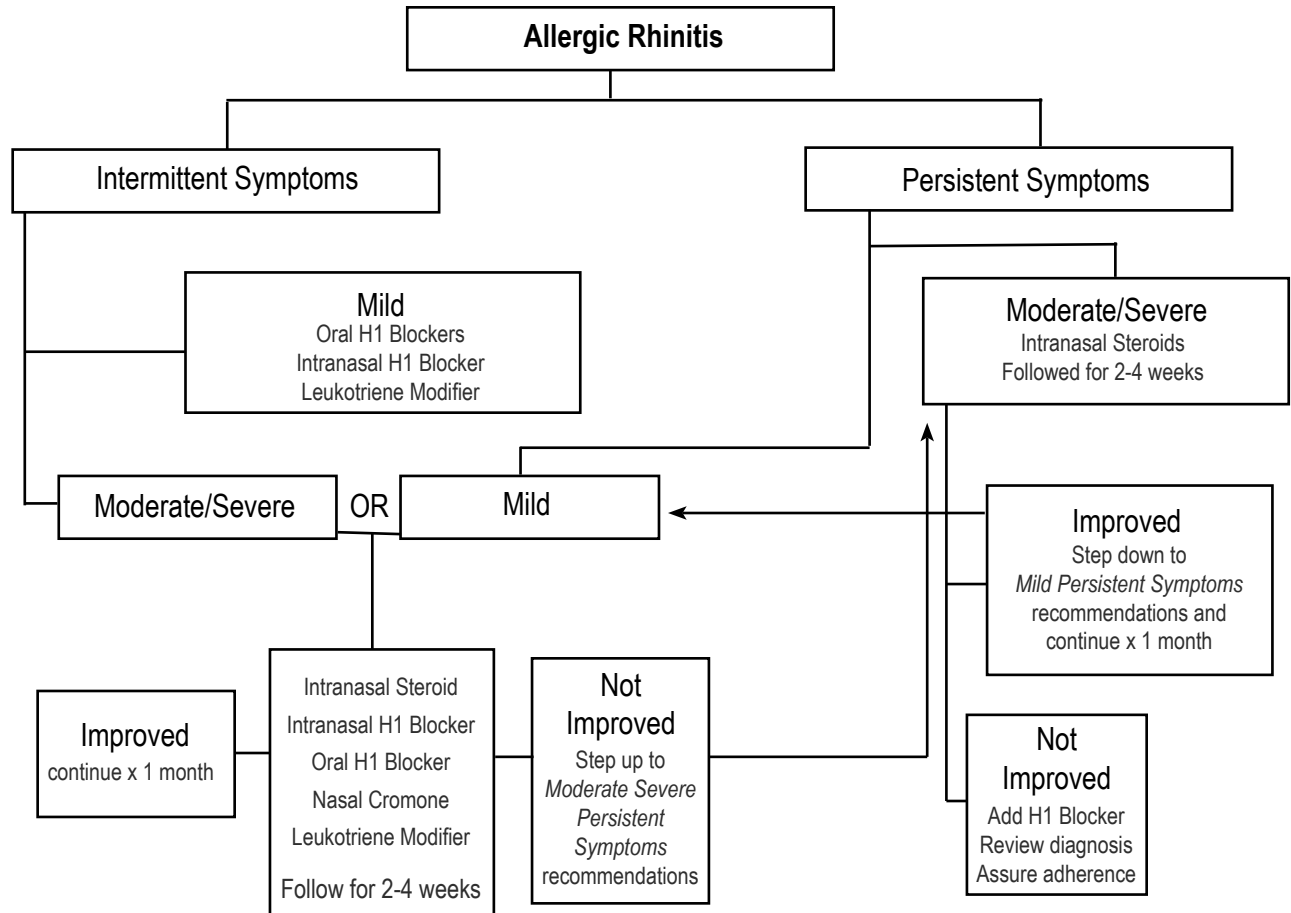


Table 3. Potential Treatments for Atopy Symptoms

	Topical	Oral	Intranasal	Inhaled	Ocular
Antihistamines		X	X		X
Decongestants		X	X		
Corticosteroids	X	X	X	X	X
Mast cell stabilizers		X	X	X	X
Anticholinergics			X		
Anti-leukotriene agents		X		X	

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Table 4: Oral Antihistamines²

Drug	Usual Adult Dosage
Brompheniramine*	4 mg q 4–6 h or 8 mg q 8–12 h
Chlorpheniramine *	2–4 mg q 4–6 h
Clemastine*	1.34 mg (1.0 mg of base) bid to 2.68 mg tid
Cyproheptadine*	4 mg tid or qid (maximum 0.5 mg/kg/day)
Dexchlorpheniramine*	2 mg q 4–6 h
Diphenhydramine *	25–50 mg q 4–6 h
Hydroxyzine*	25–50 mg tid or qid
Promethazine*	12.5–25 mg bid
Acrivastine/pseudoephedrine	8/60 mg bid or tid
Cetirizine	5–10 mg once/day
Desloratadine	5 mg once/day
Fexofenadine	60 mg bid or 180 mg once/day
Levocetirizine	5 mg once/day
Loratadine	10 mg once/day
Mizolastine	10 mg once/day

*Sedating. All sedating antihistamines have strong anticholinergic properties. Caution when used in the elderly, glaucoma, benign prostatic hyperplasia, constipation, delirium, dementia, or orthostatic hypotension. Common side effects include dry mouth, blurred vision, urinary retention, constipation, and orthostatic hypotension.

Table 5. Intranasal Corticosteroids and Mast Cell Stabilizers²

Drug		Dose per Spray	Initial Dose (Sprays per Nostril)
Inhaled Nasal Corticosteroids	Beclomethasone	42 mcg	6–12 yr: 1 spray bid
	Budesonide	32 mcg	≥ 6 yr: 1 spray once/day
	Flunisolide	29 mcg	6–14 yr: 1 spray tid or 2 sprays bid
	Fluticasone	50 mcg	4–12 yr: 1 spray once/day
	Mometasone	50 mcg	2–11 yr: 1 spray once/day
			≥ 12 yr: 2 sprays once/day
	Triamcinolone	55 mcg	> 6–12 yr: 1 spray once/day
Mast cell stabilizers	Azelastine	137 mcg	5–11 yr: 1 spray bid



Table 6. Treatment for Atopic Dermatitis²⁸

Intervention	Use	Recommendation	Anticipated Benefits	Potential Harms	Comments
Topical corticosteroids (TCS)	First-line treatment for patients of all ages with moderate-to-severe atopic dermatitis	Use the lowest effective potency; use only mild preparations on the face, neck, and intertriginous areas; q day is as effective as BID; use for the duration of a flare; use potent preparations intermittently (e.g., twice a week) to reduce flares in moderate/severe disease; do not use continually as may cause skin thinning; occlusion may enhance response	Reduced itching Improves skin integrity. Effectiveness directly related to potency, tx duration, type of vehicle base.	Potency dependent; short-term; stinging with application. Medium to long-term on skin: stria thinning, tolerance, contact sensitization, glaucoma (periocular use). Systemic effect: hypothalamic pituitary adrenal axis suppression/Cushing's	Optimal methods of use (in terms of potency, frequency, and duration of application) are unclear.
Emollients	First-line treatment for patients of all ages with very mild atopic dermatitis; adjunctive therapy for use with other TCS or systemic treatments	Use to control skin dryness that occurs with inflammation and/or TCS; thicker emollients are needed for thicker skin (hands/feet); apply in the direction of the hair to avert follicle occlusion.	Reduces skin dryness, itching. May reduce ability for irritants/allergens to penetrate skin by preventing cracks/breakdown. May reduce need/enhance effect of TCS.	Stinging on application; residue on the face and hands	Different mechanism per prep White soft paraffin: traps moisture Aqueous: introduces moisture Urea: increases skin's moisture holding capacity
Topical tacrolimus	For moderate/severe cases unresponsive intolerant to TCS. Only in age > 2 years. 2-16 yrs: 0.03% >16 years: 0.1%	Use BID until clear; use intermittently to prevent flares; do not use when infection is present. Can be used with TCS.	Same as TCS magnitude of benefit of 0.1% equal to potent TCS/ 0.03%, is less effective than TCS	Short-term: mild stinging/burning. Long-term (>5 years): safety unknown; use with caution in excess exposure to ultraviolet light.	Useful in "TCS sensitive" locations (face, neck, axillae), reduces risk of skin thinning. Efficacy is unclear in TCS intolerant/unresponsive.
Topical 1% pimecrolimus	For moderate/severe cases unresponsive intolerant to TCS. Only in age > 2 years.	Use BID until clear; use intermittently to prevent flares; do not use when infection is present. Use early to prevent flares.	Same as TCS but not as effective	Same as topical tacrolimus	Efficacy is unclear in cases of TCS unresponsive/intolerant. May be useful on delicate sites (ie, face).
Refined coal tar	For patients with mild-to moderate cases	Use BID on affected areas	Reduced itching, redness and lichenification	Itching and stinging, odor, staining of skin and clothes	Limited data on effectiveness; other tar preparations might also be effective. Irritation and cosmetic acceptability from odor and staining is an issue.
Topical doxepin	Adjunctive therapy for patients older than 12 years	Apply cream thinly TID-QID (max 12 g daily).	Short-term reduced itching	Drowsiness, transient stinging with application	Limited data on reduced itching in the first 24-48 hrs. No data re symptoms/disease improving over time.
Oral antihistamines	Adjunctive therapy	Unclear	Possible reduced itching and improved sleep	Drowsiness/anticholinergic effect	Frequently used, but evidence of benefit is unclear
Oral corticosteroids	For patients with severe flare. Optimal dosage is unknown.	Use intermittently, short term in severe cases. Case should be referred to specialist.	Relief from itching and skin redness and infiltration, reduced oozing	Short-term: Increased appetite, psychosis, dyspepsia. Long-term: HTN, osteoporosis, adrenal suppression, striae, muscle atrophy	No evidence of effect from randomized trials but clinical experience suggests beneficial in short term use for severe flare.

See *Atopy* next page

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Table 7: Potential Treatments for Atopy that Interact with HIV Antivirals⁴⁰

Concomitant Drug	HIV Antiretroviral	Effect on ART or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Beclomethasone (Inhaled)	DRV/r	RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ Cmax 1.6-fold	No dosage adjustment necessary.
		(DRV 600 mg plus RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ Cmax 19%	Significant interaction between beclomethasone (inhaled or intranasal) and other RTV-boosted PIs is not expected.
Budesonide (Systemic)	All PIs	↓ PI levels possible/ ↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. Do not co-administer unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.
Budesonide (Inhaled/Intranasal)	All RTV-boosted PIs	↑ glucocorticoids	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. Do not co-administer unless potential benefits of inhaled or intranasal budesonide outweigh the risks of systemic corticosteroid adverse effects. Consider alternative therapy (e.g., beclomethasone).
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	EVG/cobi/TDF/FTC	↓ EVG and cobi possible	Co-administer with caution, monitor HIV virologic response
	RPV	Significant ↓ RPV possible	Contraindicated with more than a single dose of dexamethasone.
	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Fluticasone (Inhaled/Intranasal)	EVG/cobi/TDF/FTC	↑ fluticasone possible	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. Consider alternative therapy (e.g., beclomethasone), particularly for long-term use.
	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ Cmax 25-fold	Co-administration can result in adrenal insufficiency, including Cushing's syndrome. Do not co-administer unless potential benefits of inhaled or intranasal fluticasone outweigh the risks of systemic corticosteroid adverse effects. Consider alternative therapy (e.g., beclomethasone).
Prednisone	LPV/r	↑ prednisolone AUC 31%	Use with caution. Co-administration can result in adrenal insufficiency, including Cushing's syndrome. Do not co-administer unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.
	All PIs	↑ prednisolone possible	
Methylprednisolone, Prednisolone, Triamcinolone (local injections, including intra-articular, epidural, intraorbital)	EVG/cobi/TDF/FTC	↑ glucocorticoids expected	Co-administration may result in adrenal insufficiency, including Cushing's syndrome. Do not co-administer.
	All RTV-boosted PIs		Consider alternative non-steroidal therapies. If intra-articular corticosteroid therapy required, change to alternative non-CYP3A-modulating ART (e.g., RAL, DTG).

The timing of ART initiation is crucial to the patient's survival

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goals: 1) help HIV+ patients reach viral suppression; 2) comply with the three goals of the National HIV Strategy which are: a) reducing the number of newly HIV-infected people; b) increasing access to care; and c) reducing HIV-related health disparities. Fear of knowing one's HIV status and the prospect of taking HIV medications for a lifetime are the challenges to "test early, treat early."

Fear leads to late HIV testing and entry to care. HIV-infected individuals may wait too long until their immune system is almost depleted of all its defense mechanisms. When they have opportunistic infections, the time becomes critical to seek treatment and care. According to the Centers for Disease Control and Prevention, the recommendations for routine HIV testing are that routine HIV screening should be done on all clients aged 13-64 years old by their primary care providers after providing notification to the patient that HIV screening will be performed and after the patient has given written consent. The HIV screening cannot be done if the patient declines (opt out screening) or if the state law prohibits routine HIV screening (opt in screening).¹ What will it take to get people aged 13 and up to get tested early and be treated early to increase their survival rate? In an attempt to bring awareness to the need for early HIV testing and early entry to care, we have searched for and reviewed recently published studies on "HIV Testing and Disease Progression," "Early HIV Treatment," "Evaluation of HIV Elite Controller Definitions," and "Survival Rates with the Use of ART," and here present study findings that better justify the therapeutic need of the approach "Test early, treat early" in the absence of an HIV cure and vaccine.

Methods: Justification

Studies selected for use in this review come from Taiwan, United States and Europe. Some common criteria that led to the choice of these studies were: the use of highly active antiretroviral therapy (HAART), the timing of use of HAART (1997 in Taiwan and 1996 in the US), the participants' characteristics (newly- versus late-diagnosed HIV patients), study types, (animal study, cohort, and cross-sectional studies), cases (Mississippi Baby, Berlin Patient,

Boston Patients), a review of HIV cure research (advances and prospects), and an evaluation of the definition "HIV elite controller" and the viewpoint of other experts in the HIV field. The study on HIV testing was chosen because it explained the acute HIV infection phases and the related diagnostic methods used to detect HIV antigens and antibodies, the time range when these HIV markers could be detected, the limit of detection, the eclipse period, and the time range for the establishment of early chronic infection. The "Mississippi Baby" and "Boston Patients" cases were used to: illustrate that 1) so far an HIV cure is not yet available and 2) the effort put in by the scientific community to search for the cure. "The Berlin Patient" case was discussed to show that it was an exception that could not yet be replicated. The review of "HIV Cure Research: Advances and Prospects" was selected because of its comprehensive use of 164 studies that illustrate the challenges of finding an HIV vaccine and cure. The review of all these published studies and their conclusions demonstrate that up to the present the therapeutic approach of using combination antiretroviral therapy (CART) is by far the preferred method with the end point of viral suppression. The use of "An Evaluation of HIV Elite Controller Definitions within a Large Seroconverter Cohort Collaboration" in this review shows that the term and existence of 1% of "HIV elite controllers" were scientifically evaluated within a Large Seroconverter Cohort Collaboration using a pool of data from a CASCADE (Concerted Action on SeroConversion on AIDS and Death in Europe) study funded by the European Union Seventh Framework Programme (FP7/2007-2013) and published in the journal PLOS One, January 28, 2014. This also illustrates the research challenge of searching for elite controllers within a small pool of population (1% in 99% of the HIV-infected population worldwide). The recommendations for HIV treatment are included to show that HIV/AIDS is at the center of policy issues. HIV education and prevention is also taken into account to show that fighting HIV/AIDS requires a multidimensional approach. Lastly, these studies were chosen because of their recent time of publication (2014) except for two studies, Wang *et al.*, (2007) and Andrew J. Michael *et al.*, (2010). The format of this paper is an analytical review.

Analytical Review

The use of human immunodeficiency virus highly active antiretroviral therapy (HAART) is a promising step to HIV treatment. From 1996 to the present, HAART is averting more than 6.6 million AIDS-related deaths across the globe.² Life expectancy for HAART-adherent HIV-infected patients is now approaching that of the non-HIV-infected individuals. Wang *et al.*'s cohort study³ (May 1997-April 2003) done in Taiwan on 3,351 newly HIV-diagnosed patients showed a 5-year survival rate of 58% in patients with AIDS at diagnosis compared to 89% in non-AIDS group. According to the study, the estimate mean survival time was 10.6 years for the AIDS group and 21.5 years for the non-AIDS group after diagnosis. The use of HAART is extending the life of all individuals infected with the virus, even for perinatally HIV-infected newborn and adolescents. The time of ART initiation is crucial to the patient's survival and mostly to curbing the spread of the virus at the cellular level as the following study indicates.

Gandhi T. Rajesh and Jonathan Z. Li⁴ cite Luzuriaga and colleagues' comparative study in which they followed four perinatally-infected infants who received early treatment (ET) between 0.5-2.6 months of age and monitored them for 13.9-17.5 years. They compared them to four late-treated (LT) children with established infection at 6-14.7 years of age and on therapy for 4.5-10.7 years. The purpose of the study was to find out if early therapy might limit the spread of HIV infection in the longest living T-cell memory. They checked for HIV-1 RNA copies in both groups after setting the limit of detection to twenty copies/mL. The study found that the ET group had undetectable plasma HIV-1 RNA while the LT group had a median of eight copies/mL. Also, the researchers checked for levels of HIV-1 DNA in the peripheral blood memory cells (PBMC). The ET group had lower levels than the LT group. When they checked for viruses capable of replicating in both groups, the replication-competent virus was detectable in one child in the ET group and in all four of the LT group. The ET youth's HIV-1 DNA was declining for over 13 years of HIV therapy despite not having a strong HIV-specific T-cell immunity. However, they had a higher

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Early testing needed to offset exponential rate of HIV replication

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percentage of pro-viral reservoirs in the transitional memory cells (TMC). This study shows that early HIV therapy reduces HIV-1 reservoir size in perinatally-infected children. If newborn infants with HIV on HAART can reach an undetectable level with a presumably non-existent HIV immunity, HIV-infected adults tested early and treated early can as well.

The main issue causing delay in early HIV testing and therefore early treatment is the prospect of staying on HAART for a lifetime. The case of the Mississippi Baby as explained in the following report by Gus Cairns in "*Reappearance of HIV in "Mississippi Baby" poses questions for early treatment*"⁵ demonstrates the cost of stopping taking HIV medications. This report was published on July 22, 2014. The Mississippi baby girl, who was started at 30 hours of life on early HAART therapy (first therapy Zidovudine, Lamivudine and Nevirapine switched to Zidovudine/Lamivudine and boosted Lopinavir), who had cleared HIV from her system at 18 months old, and whose treatment was stopped due to her mother's dropping out of care, was brought back to care 11 months later by the mother. At her return, the baby had the same viral load of <20 copies/ml as when she was four months old. This case brought hope in the research community that a possible HIV cure was on the horizon but during the 20th International AIDS Conference (AIDS 2014) it was reported that the Mississippi baby had returned to care again at 3 years, 9 months, and 24 days and was found to have a viral load of 16,750 copies/mL, and antibodies to p24 (viral protein that makes up the core of the virus) and gp 160 (HIV envelope proteins called glycoproteins). Within a week, the Western blot assay had confirmed her to be HIV positive again. It was reported that she had the same type of HIV that had disappeared 27 months earlier and the HIV was 98% similar to her mother's. The baby is back on treatment after a 27 month viral remission. Still, the challenge is to understand "the unpredictable nature of viral rebound." Nevertheless, early treatment and full HIV medication adherence (without interruption) leads to HIV undetectable levels.

Gandhi Rajesh *et al*,⁶ while reviewing Luzuriaga *et al*'s study, took notice of other issues worth mentioning: the difference in duration on ART therapy of the two groups: the early-treated (ET) group was on therapy for 16.7 years and the late-treated youth group 9.6 years. This is a difference of 7.1 years. The median CD4⁺ T-cell count for the early treated (ET) group was 943 cells per mm³ and 476 cells per mm³ for the late-treated (LT) group. The median difference is 467 cells per mm³. There is also a big difference in the number of blood cells tested among youth and adults: in the youth the range of blood cells that can be tested is only 10-24 million cells per assay while for an adult hundreds of millions or billions cells per assay can be tested. Beyond the fact that HIV laboratory monitoring is based on blood measurements, which are able to show undetectable levels of HIV-1 RNA or HIV-1 DNA (4th generation testing), there is no measurement available for tissue reservoirs where high levels of HIV hide. Nevertheless, the study has the merit of showing that early HIV treatment helps perinatally-HIV infected children reach undetectable levels despite their not-yet-established immunity. It also shows that HAART does not reach HIV hidden in the reservoirs. So for the sake of survival, staying on HIV treatment seems to be the best option to avoid viral rebound and resistance.

The next study reveals where HIV hides, particularly in the mucosal tissues of colon, the existence of pools of virions, and describes another form of HIV transmission: direct cell-to-cell HIV transmission. Ladinsky *et al*⁷ used the electron tomography (ET) to take images of HIV-1 in gut-associated lymphoid tissue (GALT) of HIV-1-infected humanized mice. The ET revealed different types and stages of HIV-1 virions in the GALT: budding immature virions and free mature and immature viruses. Ladinsky and his team used the immuno-electron microscopy to verify if the virions were HIV-1 and the status of CD4 in the endoplasmic reticulum of infected cells. The immuno-electron microscopy showed sequestered (altered) CD4 cells, most HIV-1 infected cells, and budding virions were localized into the intestinal crypts (glands found in the epithelial lining of the small intestine and colon⁸) with pools of free virions concentrated in spaces between cells. Fewer infected cells were

found in mucosal regions and the lamina propria. They also found pools of both immature and mature free virions within infected tissue. These pools contained mostly mature or immature particles, and analyses of their proximities to the cell of origin showed a pattern of semi-synchronous waves of virion release. In addition to HIV-1 transmission by pools of free virus, they found evidence that HIV-1 transmission was occurring via virological synapses. They also noticed that there were differences between cultured cells and tissue model of HIV-1 infection. The study revealed another aspect of HIV-1/AIDS disease: it is a disease of mucosal tissues.

1. The Use of Mice Model in the Study of HIV-1 Transmission in the Mucosal Tissues

Mice are grafted with humanized immune systems by transferring human fetal thymic and liver organoid tissues, along with CD34-positive human stem cells, into immunocompromised mice. The results are humanized bone marrow/liver/thymus (BLT) mice. This model is called BLT model, a tractable, cost-effective way of studying HIV-1 infection in mucosal lymphoid tissue. BLT mice rebuild new human lymphoid immune cells: T and B cells, monocytes, dendritic cells, and macrophages in peripheral blood and organs including the gastrointestinal (GI) tract.^{9,10} Through this system, the following aspects of human HIV-1 infection are tracked: T cell depletion in the gut and peripheral blood, and both systemic and mucosal virus transmission during the course of the disease.

2. Landisky *et al*'s Study Description

BLT mice with enough human immune tissue and cells (>25% of peripheral blood cells; >50% of cells in the lymphocyte; >40% of human T cells in the lymphocyte gate) were infected with HIV-1 and compared to non humanized and HIV-1 non- infected BLT mice (control group). Ten to twenty weeks post infection, the mice were killed and segments of small intestine and colon were excised to analyze the spread of HIV. Landisky and his team found that the human CD4 T cells were depleted from the lamina propria (layer of connective tissue that lies under the epithelium of

a mucous membrane) and p24 proteins of HIV-1 were localized primarily in CD4+ cells in regions near the crypts. In contrast, the non-humanized infected control mice did not have any human cells or HIV-1 infection.

3. Discussion of the study

In the discussion section, Ladinsky *et al* said that they were unable to correlate the relative abundance of virions detected in GALT with the viral load measured in the blood. They reported that only two examples of virions within blood vessels of BLT mice were detected compared with hundreds of virions within mucosal tissues. They concluded that this finding was consistent with reports highlighting a discrepancy between blood viral load and HIV-1 levels in tissues. This study finding is in line with Gandhi *et al*'s statement that blood measurements do not reflect what is going on in the tissue reservoirs.

4. Identification and Quantification of Intracellular Pools of HIV Virions

In addition, the authors described how they were able to find pools of HIV virions within dilated regions of intercellular spaces in approximately 10% of HIV-infected crypts. Ladinsky *et al*'s definition of pools is "a population of virions within an intercellular space that is continuous within a given 3-D volume." A range of 5-200 free virions was found within intercellular pools and most pools contained 10-40 particles. The authors found more than 100 pools had hundreds of virions. They also classified pools as mostly mature (90%) and immature (10%) pools. Again, this confirms that HIV hides in the reservoirs. This may explain why HIV rebound occurred in the Mississippi baby and in undetectable HIV patients who take holidays from HIV medications. Caroline P. Passaes and Asier Sáez-Cirión¹¹ cited Fernandez Guerrero *et al.*, (2005); Steingrover *et al.*, (2008) and Wit *et al.*, (2005) as follows: "Treatment interruption in patients who started cART (combination antiretroviral therapy) during chronic phase leads to viral rebound within weeks, with viral loads frequently reaching pretreatment set-point levels." This is additional evidence that HIV has the capability of reappearing at any time when HIV medications are stopped. The only exception known so far is "the Berlin Patient," who, after receiving double blood transplantations for leukemia from a donor with a CCR5 Δ 32 allele, showed no sign of HIV after six months

follow up without being on therapy. The same procedure was later performed on two Boston patients with unsuccessful results: according to the report of the 6th Internal Workshop on HIV Persistence, Reservoirs and Eradication Strategies, the Boston patients had a strong viral rebound several months after treatment interruption.^{12, 13} The same attempt was done on a pediatric HIV patient at the University of Minnesota in April 2013, but the patient died two months after transplantation. Transplantation does not appear to be promising. "Treat early" does not completely eliminate HIV from the human body. Therefore, staying on HIV treatment as long as possible seems to be clinically justified to minimize viral rebound.

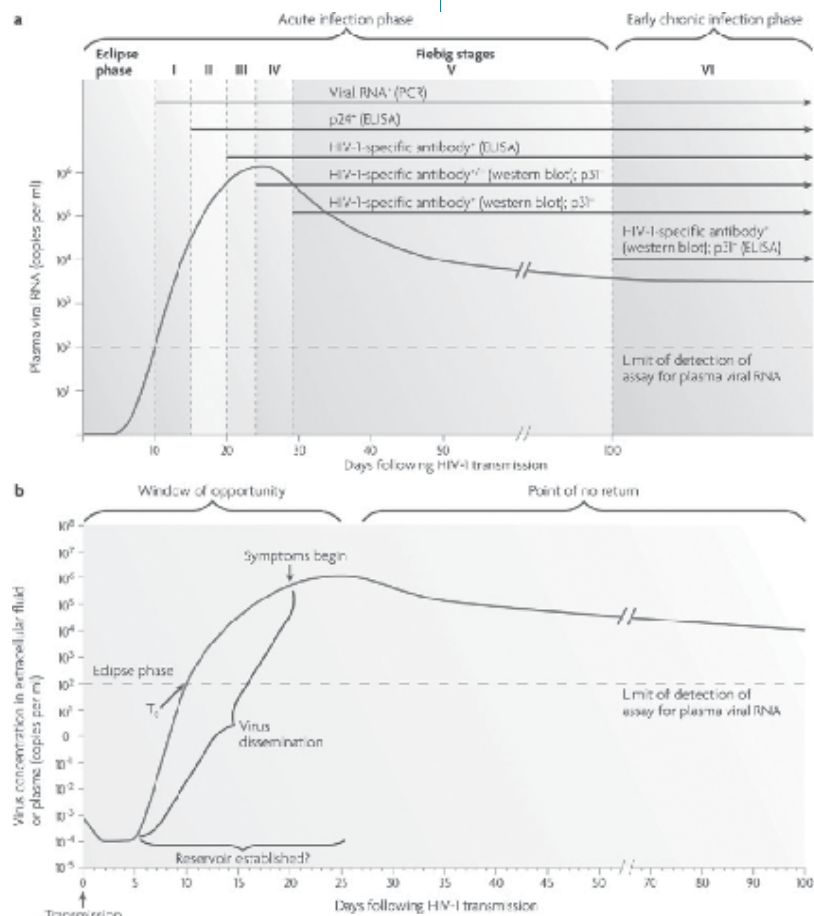
5. Direct Cell-to-Cell HIV Virus Transmission

Furthermore, Ladinsky and colleagues discovered that HIV virus transmission in the GALT was occurring through direct cell-to-cell transmission within tissues whereby a virus buds from an infected cell and directly contacts

and infects an adjacent uninfected cell through virological synapses. Virological synapses may not always be present due to CD4 cells depletion or down-regulation. Yet, infection via free virus or direct cell-to-cell transfer can happen because of the existence of natural recombinant HIV-1 strains, which may re-infect a cell already infected with a different viral strain¹⁴ or a residual infected CD4 cell surface can allow infection through the same process (free virus/direct cell-to cell transfer).

Clinical Stages of HIV-1 infection

Moreover, we learn from Andrew J. McMichael *et al*'s¹⁵ publication "The immune response during acute HIV-1 infection: clues for vaccine development", in Nature Reviews Immunology,^{10, 11-13} (January 2010) that patients with HIV-1 infection go through clinical stages called Fiebig I-VI. The following two graphs (a, b)¹⁶ from the journal Nature Reviews Immunology are a good illustration of HIV infection clinical stages (disease progression) and diagnostic methods.



Early treatment limits establishment of reservoirs and dissemination

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These stages correspond to specific times when HIV-1 can be detected by specific diagnostic methods: viral RNA measured by PCR, p24 and p31 viral antigens measured by enzyme-linked immunosorbent assay (ELISA), HIV-1-specific antibody detected by ELISA and HIV-1-specific antibodies detected by western blot. Progression from acute infection to early chronic stage takes about 100 days from the time of HIV exposure. By 100 days, the plasma viral load begins to plateau.

During acute HIV-1 infection, the following events take place: first the virus replicates locally in the mucosa, then it is transported to the lymph nodes, and from there it starts spreading. The window of detection varies: from 0-10 days, the virus cannot be detected even though it is the initial phase of infection. This period is called the eclipse period. Between 21-28 days, the HIV rate of replication is at its peak. The CD4+ T-cells start depleting in the mucosa and reservoirs of HIV virions establish in the cells. The patient starts having symptoms.

Discussion

The graph illustrating how the immune system responds to acute HIV-1 infection is concise. It shows all the phases of HIV-1 infection, from the eclipse period where no HIV testing method is going to detect either HIV antigens or antibodies to the early chronic phase when the symptoms of illness appear. The early chronic phase may be a time of confusion for the patient when he or she thinks it is stress, fatigue, or another health condition. "Test early, treat early" time would probably be best in the interval of 10-100 days of HIV infection/ disease progression for a patient with no other chronic health conditions. For a patient with other chronic diseases or for pregnant women, testing early and going on treatment right away are recommended. The Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents states: "ART is also recommended for HIV-infected individuals to prevent transmission of HIV. The strength of and evidence for this recommendation vary by transmission risks: perinatal transmission (AI); heterosexual transmission (AI); other transmission risk groups (AIII)"¹⁷.

But, what is the likelihood that this can be done for people aged 13 years old and up, assuming stigma, fear, HIV medication cost, health care access, and health care disparities are no longer barriers?

In the absence of ART, HIV multiplies, destroys CD4 cells and eventually leads to death. However, a small group of HIV-positive individuals not on HIV medications do not progress towards AIDS. They have stable CD4 cell counts over a long period of time. This group is called "Elite Controller." Ashley D. Olson *et al*¹⁸ did an evaluation of the definition of "elite controller" through a systematic review of 28 cohorts consisting of 25,629 seroconverters from Europe, Canada, Australia and Sub-Saharan Africa. In the evaluation study, they divided their participants into three elite controller definition groups based on these markers: 1) HIV-RNA levels <75 copies/mL for at least one year (elite controllers); 2) No previous HIV-RNA levels >1000 copies/ml (adaptation of elite controller definition); 3) Individuals HIV positive ≥ 10 years with ≥ 2 years HIV-RNA measurements and ≥ 90% with < 400 copies/ml. From these three groups, three more groups were again derived: a) individuals who fulfilled the definition; b) individuals who did not; and c) those for whom EC (elite controller) could not be determined. The participants had the following characteristics: the median year of HIV seroconversion was 1999 (1992-2005), median age at seroconversion was 31 years (25-37), MSM (55%), IDU (14%) and male (78%). The result of the evaluation study was that elite controllers made up only 1% of individuals regardless of definition used. This group could be of research interest. Yet, the challenge is to locate who is among that 1% of elite controllers among 99% of non-HIV controllers worldwide.

Conclusion

The above studies show that HIV testing is the only way to detect HIV infection. Clinical symptoms alone are not strong indicators of HIV infection and are easily overlooked because of their similarities to other diseases (fever, weight loss, fatigue, etc). The rate of HIV replication is exponential (see graph). This explains why the progression from HIV infection to CD4+ T-cells depletion to acquired immunodeficiency syndrome is fast, yet unknown to the non-HIV tested individuals. On top of the rapid progression to AIDS, these studies reveal

other events that occur inside the human body following HIV exposure: exponential HIV replication, formation of reservoirs, HIV moving to lymph nodes, direct cell-to-cell transmission within the gut tissues either through virological synapses or free virus transfer. HIV testing and treatment recommendations are clear and up-to-date. Since there is neither an HIV vaccine to stop these processes nor a cure, testing early allows early detection; treating early eventually limits the establishment of reservoirs and virus dissemination within the body. The use of other preventive methods (condom use and practicing) are the best tools available to curve the spread of HIV. Fear, stigma and other psychosocial factors will be overcome in the long run by continuous HIV education and HIV prevention messages. ♦

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