An Assessment of the Impact of Highly Active Antiretroviral Therapy (HAART) on HIV-Related Eye Diseases

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Abstract:

People with HIV/AIDS have dealt with ocular complications of their disease since the beginning of the epidemic as recognized in 1981. Many studies were done describing incidence, prevalence, treatment and management of eye diseases caused by HIV in years before and after the introduction of the use of highly active antiretroviral therapy (HAART). This paper identifies studies directed at HIV related eye disease in the era after the introduction of HAART and finds evidence of the positive effects of HAART for some eye diseases. Examples of eye diseases with evidence of positive effects of HAART include cytomegalovirus retinitis and HIV retinopathy. Many populations have experienced a reduction in the incidence and prevalence of these and other HIV eye diseases in the era of HAART. While these trends are highly suggestive of the benefits of HAART for treating some HIV related eye diseases, further research is needed to strengthen the causal link for those conditions where improvements have been seen and to more clearly identify other ocular conditions that may benefit from HAART. Such evidence is critical when looking at the global picture of HIV eye disease because HIV eye disease is still a significant burden globally Many of the 34 million people in the world affected with HIV do not have access to treatment of HIV with HAART, and so it is important to look at the characteristics of individual HIV-related eye diseases and ascertain the impact of HAART use on these diseases, to build the evidence base for documenting the benefits of HAART in treating HIV ocular conditions, worldwide. An important step in identifying the benefits of HAART on specific HIV related eye diseases includes presenting a trend analysis comparing situations when HAART is used and when it is not used This information can then be used to inform practice and develop plans for further research. This paper presents the first steps in this research process by carefully reviewing these trends for a wide range of eye diseases that are

related to HIV. The findings described in this paper not only provide support for further studies, but also can serve as hypothesis generating results to help design such studies. The importance of undertaking such studies is directly related to practice based evidence that using widespread HAART could lessen the burden of HIV eye diseases in populations that have not currently adopted widespread HAART use.

The Use of HAART for Treatment of HIV/AIDS:

The World Health Organization (2013) reported that 34 million people were living with HIV at the end of 2011 and that 35 million people have died of AIDS globally as of 2011. The CDC (1992) defines AIDS as an HIV-infected person having a CD4 count less than 200 cells/mm^3, an HIV-infected person having CD4+ T-lymphocyte percentage of total lymphocytes less than 14, or an HIV-infected person having any AIDS-defining illness. Highly active antiretroviral therapy (HAART) is an aggressive treatment regimen given to patients with HIV/AIDS to suppress HIV viral replication and progression of HIV disease. The usual regimen is to combine three or more drugs aimed at reducing the amount of active virus. In some cases the level of virus becomes undetectable in blood plasma. The World Health Organization (2014) estimated that at least 15 million people were in need of antiretroviral therapy in 2011. The World Health Organization (2014) also provided recommendations defining when to initiate HAART in HIV-positive people. The WHO guidelines are listed below for various groups of HIV-positive people:

Adults and Adolescents:

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3 *(strong recommendation, moderate-quality evidence).*
- ART should be initiated in all individuals with HIV with CD4 count >350 cells/mmsup>3 and ≤ 500 cells/mmsup>3 regardless of WHO clinical stage *(strong recommendation, moderate-quality evidence).*
- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
  - Individuals with HIV and active TB disease *(strong recommendation, low-quality evidence).*
  - Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease *(strong recommendation, low-quality evidence).*
  - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners *(strong recommendation, high-quality evidence).*

Pregnant and Breastfeeding Women:

- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART *(strong recommendation, moderate-quality evidence)*.
- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment *(conditional recommendation, low-quality evidence)*.
- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased *(conditional recommendation, low-quality evidence)*.

Children:

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.
  - Infants diagnosed in the first year of life *(strong recommendation, moderate-quality evidence)*
  - Children infected with HIV one year to less than five years of age *(conditional recommendation, very-low-quality evidence)*.
- ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤500 cells/mm^3, regardless of WHO clinical stage.
  - CD4 count ≤350 cells/mm^3 *(strong recommendation, moderate-quality evidence)*
  - CD4 count between 350 and 500 cells/mm^3 *(conditional recommendation, very-low-quality evidence)*.
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count *(strong recommendation, moderate-quality evidence)*.
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection *(strong recommendation, low-quality evidence)*

There is evidence that HAART is effective at treating HIV. Contarelli (2012) looked at two cohorts of HIV-positive patients on HAART and determined that in one cohort, the percentage of undetectable HIV viral load at the first year of treatment was 84% and in the other cohort studied the percentage of undetectable viral load at the first year of treatment was 82%. Looking at these cohorts demonstrates that HAART is successful in lowering HIV viral load. Studies have also shown that HAART is capable of increasing CD4 counts, which is associated with more robust immune functioning in HIV-positive patients. Dravid (2011) reported in a study of CD4 count

follow-ups on rural patients on HAART that the median CD4 counts of patients in the beginning of the study was 137 cells/mm^3 of blood. After two years of completion of HAART the median CD4 count of the cohort was 365 cells/mm^3 of blood. This study shows the rise in CD4 counts in patients treated with HAART. One drawback to HAART is patient compliance. A meta-analysis showed that the average rate of reporting ≥90% HAART adherence is 62% (Ortego, 2011). Adherence refers to patients following their prescribed regimen of therapy. Such less-than-ideal adherence issues could lead to treatment failure and progression of HIV. Patient compliance also could differ among groups, such as men who have sex with men vs. injection drug users.

There are differences in the availability of treatment with HAART given to HIV patients globally. Some countries provide antiretrovirals free-of-charge to HIV-positive persons and HAART use is more widely used. Other countries rely on insurance programs or patients to pay for antiretrovirals. Cost also can be an issue that affects availability of the antiretrovirals to HIV-positive people. Nunn (2009) reported that by 2009 only four million of ten million people needing HAART in developing countries received the therapy. In the US, one study reported that between 2000 and 2008 the proportion of participants in the study receiving HAART rose to 83% (Athoff, 2012). Thus, one can see based on examples of the US and developing world there is evidence of disparities among HIV patients receiving HAART. Another consideration is the fact there is HIV-1 and HIV-2. HIV-1 is the predominant form of HIV, and HIV-2 is a type that contributes approximately a third to the prevalence of HIV in West Africa (Peterson, 2011). HIV-2 is also present in other areas around the world, but it is much less common overall than HIV-1. Some of the medications currently available that are useful in treating HIV-1 are not effective in treating HIV-2 (AIDS Info, 2011). As such, populations affected by HIV-2 have

differences in HAART therapy than those with HIV-1. As mentioned previously, even in populations with widespread availability of HAART, there is still the issue of poor compliance and use of HAART medications. If the compliance is low, then the beneficial effects of HAART may not be realized even when HAART is available to a given population.

Ocular Complications of HIV/AIDS:

Kestelyn (2001) reported that ocular complications of HIV/AIDS affect 50-75% of these patients during some point of their illness. Thus, the issue of eye diseases is significant among those infected with HIV. It is important to look at ways to prevent and/or improve outcomes of eye disease among people infected with HIV.   HAART's ability to restore immune function has led to changes in incidence, natural history, management, and sequelae of HIV ocular complications (Goldberg, 2005). A good way to look at the burden of HIV eye disease globally is to look at the epidemiology of particular eye diseases affecting HIV-positive people, discuss the incidence and prevalence of these eye diseases particularly in HIV-infected populations, and to ascertain if widespread HAART use can decrease the burden of various eye diseases on affected populations. Literature was searched related to the epidemiology of HIV eye diseases and also how HAART has impacted these diseases, including pertinent studies done prior to the initiation of HAART as well as after the initiation of HAART.

One goal of this paper is to describe various ocular conditions affecting people with HIV, including the epidemiology of the conditions and where available, comparing the era before and after the initiation of HAART. A second goal is to look at the specific ocular conditions that occur in HIV/AIDS patients and identify the conditions that are less of a problem in HAART-treated populations in comparison to conditions that are not changed as a result of HAART use. The ultimate goal of this paper is to describe how public health leaders can better understand the

established benefits and need for future study of HAART, to prevent and treat ocular complications of HIV/AIDS.

HIV Eye Conditions for which HAART Seems to Lessen Incidence/Prevalence:

HIV Retinopathy:

HIV retinopathy is regarded as an anomaly of HIV-infected people. Studies of HIV retinopathy show that HIV retinopathy is clinically apparent in 70% of those with advanced HIV disease, approximately 40% of those with symptomatic intermediate stage HIV disease, and only 1% of those with asymptomatic HIV infection (Jabs, 1988 and 1989). More severe stages of HIV eye disease are inversely correlated with CD4 counts. Higher counts are associated with asymptomatic infection. Lower CD4 counts are associated with symptomatic infection and then even lower with advanced HIV disease. Thus, one can see that as HIV worsens in a population, the prevalence of HIV retinopathy increases in that population. HIV retinopathy is a microvascular disorder resulting in cotton-wool spots and hemorrhages in the retina. The condition is generally not a vision-impairing disorder like many other HIV eye diseases. Treatment of the condition does not include a specific modality aimed directly at fighting the condition. Treatment, per se, is basically restoring immune function in patients through HAART. HAART's goal is to decrease viral load in patients and to increase the CD4 count. Previously discussed was a study demonstrating that HAART is effective at increasing CD4 counts in populations. If HAART is used in an effective, widespread manner in a population, we can expect the incidence and prevalence of HIV retinopathy to lessen based on the studies mentioned about prevalence of the condition. This belief stems from the likelihood that fewer HIV-positive people in the population treated with HAART will have advanced disease and

fewer will have intermediate stage disease. By moving those with advanced and intermediate stage disease into the category of asymptomatic HIV infection with HAART, then less of the population will experience the condition of HIV retinopathy (as only 1% of those with asymptomatic HIV infection were said to have HIV retinopathy as discussed by Jabs).

Cytomegalovirus Retinitis:

Because of the possibility of development of visual impairment or blindness, cytomegalovirus retinitis (CMV retinitis) is of significant concern in the public health and ophthalmic communities. Cytomegalovirus is a herpes virus that affects a large percentage of the population worldwide. This virus is well-controlled by the immune system in immunocompetent people, who are generally exposed early in life and never have any consequences of having the virus. It is when the immune system is weakened by things like chemotherapy, disease, or transplants that CMV causes problems. There is also the issue of newly acquired CMV in HIV/AIDS patients that can pose a problem because of their immunocompromised status and the fact that the immune system cannot keep the virus at bay. CMV in AIDS patients can result in conditions like CMV retinitis, especially when the CD4 count is below 50 cells/mm^3 of blood (Hoover, 1993). CMV is still a problem because of HIV-positive patients who have failed antiretroviral therapy, have poor compliance with therapy, or are not on therapy and have low CD4 counts. Ford (2013) carried out a meta-analysis on CMV retinitis among HIV-positive people in various settings around the world. Ford found that the prevalence of CMV retinitis among HIV-positive people was highest in Asia, 14%. Therefore, CMV retinitis is still a problem in certain areas of the world.

Treatment specific to CMV retinitis is required to help prevent progression of the disease and resulting blindness. Raising the CD4 counts in HIV-positive persons via HAART would be

considered an indirect treatment, whereas in HIV retinopathy HAART treatment would really be the only type of treatment modality.

Because CMV retinitis is a short-lived disease and is not chronic in nature, it is better to study incidence of the condition rather than prevalence. In summarizing the incidence of CMV retinitis, one source reported that before the initiation of HAART therapy 30% of AIDS patients developed CMV retinitis but HAART has reduced the incidence by three-quarters (Smith, 2013). Several studies have looked directly at incidence (pre-HAART). The Multicenter AIDS Cohort Study determined that during four years of follow-up there was a 25% chance of the development of CMV retinitis among patients in their study whose CD4 counts fell below 100 cells/mm^3 of blood (Hoover, 1996). Thus, patients whose HIV disease progresses and the immune system fails seem to have a high incidence of CMV retinitis. Since a large number of the population of HIV/AIDS patients globally do not take HAART, overall the global decrease in incidence and prevalence of CMV retinitis may not be reality. Populations in countries with widespread HAART may realize a decrease, but this pattern is not globally substantiated. Spector (1996) looked at incidence of CMV retinitis in his study involving oral ganciclovir for the prevention of CMV disease in AIDS patients. He studied AIDS patients with CD4 counts less than 50 cells/mm3 or those with CD4 counts less than 100 cells/mm3 along with an AIDS-defining opportunistic infection. He randomized one group to CMV prophylaxis with oral ganciclovir and the other group to placebo. In the placebo group, he found that the incidence of CMV retinitis after 12 months of study was 24%. Thus, his study agreed with the Multicenter AIDS Cohort Study and found incidence of around one out of four. Since these two studies were carried out over short periods of time (one study was done over one year and another over four years), it is believable that Smith's report of 30% of pre-HAART patients developing CMV

retinitis (western population) is realistic. Patients can have HIV/AIDS for longer periods of time than one to four years, and so the cumulative incidence in pre-HAART populations likely would increase over longer time periods.

As mentioned previously, fortunately the incidence of CMV retinitis has decreased during the era of HAART. Sugar (2012) looked at CMV retinitis incidence in the era of HAART by following 1,600 participants with AIDS and performing ophthalmoscopic examinations. The findings were 29 incident cases out of the 1,600 in the cohort (incidence rate of 0.36/100 person-years). Because 29 incident cases out of 1,600 was drastically lower than in studies previously mentioned that were done in the era before HAART, it can be hypothesized that there is an association between HAART used and large decreases in the incidence of CMV retinitis. Looking at these numbers discussed, about 25% of HIV-positive patients developed CMV retinitis prior to initiation of HAART. On the other hand, 29 of 1,600 developed CMV post-HAART (1.81%). Even though the incidence drastically decreased, CMV retinitis still poses a problem even in HAART-treated populations.

Pertaining to CMV, there is the phenomenon of immune reconstitution inflammatory syndrome (IRIS). In this phenomenon, patients are placed on HAART therapy when they are severely immunocompromised. As their CD4 count rises, the CMV retinitis regresses but the body starts reacting to the remaining cytomegalovirus. Inflammation of the vitreous and other structures of the eye subsequently occurs. This phenomenon may occur in up to 63% of patients with regressed CMV and elevated CD4 counts from HAART therapy (Copeland, 2013). This curious side effect of treatment, however, does not warrant discontinuation of HAART. The side effects of treatment thus do not outweigh the benefits of treatment in this scenario.

HIV Eye Conditions for Which it is Unknown if HAART Lessens Incidence/Prevalence:

Toxoplasma Retinochoroiditis:

Another condition affecting the retina in patients with AIDS is toxoplasma retinochoroiditis. Schmitz (1991) found toxoplasma retinochoroiditis as the second most common opportunistic infection of the eye among AIDS patients they studied in the period prior to the introduction of HAART(they diagnosed 7 cases in 261 AIDS patients in their study). Thus, in Schmitz's study, 2.7% of AIDS patients in their study were affected with toxoplasmosis retinochoroiditis by the study's conclusion. These percentages seem consistent with other data showing that 1-2% of HIV patients with HIV are affected by ocular toxoplasmosis (Jabs, 1989). Toxoplasma retinochoroiditis is not a disease isolated to patients with AIDS, but it worthy of concern in this population. Likely for the reason that toxoplasma retinochoroiditis is not isolated to AIDS patients, it is not listed as an AIDS-defining condition (CDC, 1992). To illustrate that toxoplasma retinochoroiditis is generally a problem in advanced HIV patients with CD4 counts <100, one source reports that toxoplasma prophylaxis is needed only when CD4 counts in an HIV-positive patient are below 100 and there is a positive T. gondii specific antibody Ig G test result (Clinical Key, 2012). Keeping the CD4 counts above 100 is thus likely associated with less risk of toxoplasmosis retinochoroiditis,

Acquired toxoplasmosis is associated with ingestion of undercooked meat contaminated with cysts of *T. gondii* or in water contaminated with oocysts of Toxoplasma gondii. Acquired *T. gondii* may also occur from unpasteurized milk, blood products, or tissue transplants. Cats are the only species to shed the infectious stage of *T. gondii* in their feces (fecal oocysts). A possible route of transmission is human contact with cat feces such as cleaning/changing litter boxes. Studies have shown that up to two-thirds of people who have ocular toxoplasmosis

acquired the infection after birth (Gilbert and Stanford, 2000). Ocular toxoplasmosis is self-limiting in immunocompetent individuals. However, in AIDS patients with CD4 deficiency (less than 100 as previously suggested), toxoplasma chorioretinitis is known to be severe and progressive because of presumed retinal necrosis caused by unhindered spread of parasites (Wallace and Stanford, 2008). As with congenital infections, the bradyzoite form of *T. gondii* can encyst in the retina and lead to reactivation later. During chronic infection with *T. gondii*, T cells have an important role in the control of toxoplasmosis. Two subsets of T cells, CD4 and CD8, contribute to this protective role (Wallace and Stanford, 2008). Conditions resulting in deficiencies of CD4 and CD8 cells could result in reactivation of the condition. Some of the patients affected in this setting of immunodeficiency/reactivation later of the condition include patients on chemotherapy, transplant patients, and AIDS patients.

Toxoplasmosis retinitis is an important manifestation of toxoplasmosis in patients with HIV/AIDS. The disease can also affect the optic nerve, resulting in optic neuritis or papillitis that is associated with edema. HIV-positive patients and other immunocompromised patients with toxoplasmosis may have a different presentation than in immunocompetent persons. HIV-positive patients may not have much of a vitreal reaction due to impaired immune function, and thus few to no vitreous cells may be present in HIV patients.

Dry Eye Syndrome:

Dry eye has been found to be associated with HIV/AIDS. DeCarlo (1995) found a prevalence of dry eye of 38.8% in HIV-positive males in her study. She also concluded that patient symptoms are not adequate predictors of dry eye in HIV disease. She promoted the need for diagnostic dry eye testing as part of routine testing during eye examinations. DeCarlo's study was done in the age before the use of HAART. A repeat study could be done on patients treated

with HAART who have undetectable plasma HIV RNA to compare the prevalence of dry eye. Such a study could help investigators and clinicians to understand if dry eye is prevalent in HIV-positive people in the age of HAART and to look at mechanisms for this dry eye if it is still associated with HIV in patients on HAART. It is generally thought that dry eye in HIV-positive patients is due to lymphocytic infiltration of the lacrimal gland (Biswas, 2008). To illustrate the significance of dry eye among HIV-infected males in the pre-HAART era, looking at prevalence of dry eye in the general and male populations (cross-sectional) can be done. Moss (2000) found in a study that the overall prevalence of dry eye was 14.4%. In the male population of this study the prevalence was 11.4%. Thus, comparing these studies, DeCarlo's study showed that dry eye in pre-HAART era HIV-positive males was approximately 3.4 times the prevalence of dry eyes in males in the study by Moss. Geier (1995) found that this increased frequency of decreased tear production (dry eye) is not associated with the CD4+ count, or related to the severity of HIV disease. Further tests in the post-HAART era simply are needed to confirm the prevalence of dry eye and the morbidity associated with dry eye.

Herpes Simplex Keratitis:

Herpes simplex keratitis is a condition that can occur in any person and can occur as epithelial keratitis or stromal keratitis. Patients may complain of foreign-body sensation, photophobia, decreased vision and redness. Looking at the condition among HIV-positive patients, Hodge and Margolis (1997) found that the incidence and clinical course of herpes simplex keratitis were no different among HIV-positive people and HIV-negative people. The only difference in the disease among HIV-positive people and HIV-negative people was the recurrence rate. The recurrence rate was 2.48 times more frequent among the HIV-positive patients than among the HIV-negative patients. The fact that the recurrence rate is significantly

higher among HIV-positive people may change the clinical management of these patients. For example, HIV-positive people with recurrent herpes simplex keratitis may need prophylactic drugs at a greater frequency in an attempt to prevent frequent recurrences of the disease. Examples of such drugs to prevent recurrence of herpes simplex keratitis include acyclovir and valacyclovir. The study done by Hodge and Margolis was done before widespread use of HAART. Repeat studies concerning the recurrence rate of herpes simplex keratitis in situations of widespread HAART use would help to determine if the recurrence rate of this condition normalizes to that in the general population or if it remains higher in the HIV-positive population in the situation of widespread HAART use.

Molluscum Contagiosum:

Molluscum contagiosum can pose a problem in HIV-positive people, and ocular complications do occur. Molluscum contagiosum is a condition caused by a poxvirus. Molluscum contagiosum can occur in HIV-negative and HIV-positive people, but the difference in how it affects HIV-positive people is that it occurs commonly and the lesions can become quite large and are often more numerous and more rapidly growing than they are in HIV-negative people. The lesions also do not commonly occur on the face in HIV-negative people like they do in HIV-positive people. In HIV-negative people treatment is generally not necessary, since the lesions often resolve on their own within a few months. The prevalence of molluscum contagiosum in patients with HIV is reported to be 5-18%, and, if the CD4 cell counts are less than 100, the prevalence of molluscum contagiosum is reported to be as high as 33% (Bhatia, 2012). Eyelid involvement may occur in up to 5% of HIV-infected patients, and they are usually multiple, bilateral, confluent, and tend to recur 6 to 8 weeks after removal (Lima, 2004). There is no immunity to a patient against reinfection after the lesions have

resolved. Lesions may recur particularly when CD4 counts decrease, for example (Bardenstein, 1995). Topical therapy may be used for molluscum contagiosum. Surgical treatment may also be used and include cryotherapy, curettage, and laser treatments. Because the prevalence of molluscum contagiosum increases to as high as 33% when the CD4 count is below 100, there is thus evidence that advanced HIV disease is a risk factor for molluscum contagiosum. By having population CD4 counts higher (particularly in this case above 100), there is less likelihood of morbidity from molluscum contagiosum (although it is mainly cosmetic morbidity).

Kaposi Sarcoma:

Kaposi sarcoma is another condition affecting the eyes of people with HIV/AIDS. Kaposi sarcoma is thought to arise from endothelial cells, and is a spindle-cell proliferation tumor. It is associated with human herpes virus 8, HHV 8 (Casper, 2004). Kaposi sarcoma lesions may involve the skin, mucosa, lymph nodes, and visceral organs. Cutaneous lesions may occur at any location. Mucous membranes may be involved, affecting the palate, gingiva, and conjunctiva. Gastrointestinal lesions can occur anywhere in the gastrointestinal tract, where they are generally asymptomatic.   Pulmonary lesions can occur and be asymptomatic, but they also can be associated with cough, dyspnea, hemoptysis, and chest pain.   Treatment of Kaposi sarcoma includes entities like radiation, cryotherapy, surgery, chemotherapy, and using HIV HAART therapy as a method to restore the immune system and allow the condition to be more indolent or to regress spontaneously. There are prior studies that show that AIDS-associated Kaposi sarcoma is less aggressive and more localized when HAART therapy is used (Nasti, 2003).

AIDS-associated Kaposi sarcoma is associated with a more aggressive course of disease. Extensive lesions may occur in AIDS patients. Visceral involvement can be widespread, for

example. AIDS-associated Kaposi sarcoma is one of the AIDS-defining illnesses as previously discussed in the case definition of AIDS (CDC, 1992). It is the most common malignancy seen in HIV-infected patients, and this is especially true where HAART therapy access is limited (DeVita, 2008). In the United States, the risk of Kaposi sarcoma among sexually active HIV-infected men who have sex with men is much greater than among others infected with HIV (Scadden, 2003). The CDC (2002) reported that Kaposi sarcoma occurs in approximately 24% of patients with AIDS and in 35% of all homosexual men with AIDS.

The mucosa and skin varieties of Kaposi sarcoma affect the eyes of patients with HIV/AIDS. They rarely are found inside the orbit—there is one case of choroidal involvement that was reported (Pantanowitz, 2008). Ophthalmic involvement occurs in 20-24% of patients with Kaposi sarcoma, so it obviously occurs as an ocular manifestation in a significant proportion of patients affected with the condition (Freudenthal, 2012). Freudenthal (2012) also reported that the ophthalmic presentation was the initial manifestation of AIDS-related Kaposi sarcoma in 4-12% of patients. Of these ophthalmic manifestations 10-75% of patients had conjunctival lesions, and 25-80% of patients have eyelid lesions.

Mansour (1993) reported that lesions tend to be indolent, but, as a tumor or tumors grow, it/they can alter ocular adnexal structures and the ocular surface. For example, the mass of the tumors affecting the eyelids can result in mechanical entropion or ectropion. Trichiasis, lagophthalmos, and irregular astigmatism can result because of lid changes. Blocking of the visual axis could occur if the weight of the tumor(s) holds down the eyelids enough. Also, epiphora, poor tear film, recurrent corneal abrasions, dry eyes, and photophobia may occur. Exposure of the cornea and trichiasis could lead to corneal infection, scarring, and opacification. Conjunctival involvement may include hemorrhage, chemosis, and conjunctival injection.

Kaposi sarcoma, including ocular complications, may still pose a problem in countries that have adopted widespread use of HAART. People who are HIV positive may not opt for treatment until their CD4 count falls to a significantly low level. Other people may not know they are HIV positive. Kaposi sarcoma could show up suddenly in these people infected with HIV. Kaposi sarcoma, in fact, can occur when CD4 counts are at higher levels. Crum-Cianflone (2010) reported that over one-third of the cases of AIDS-associated Kaposi sarcoma occurred in HIV patients with CD4 counts above or equal to 350 cells/mm3 from 2002-2008. HIV-positive people with robust CD4 counts thus could experience Kaposi sarcoma

Rare Ocular Conditions:

Several rare ocular conditions affect HIV-positive people, and it is unknown how HAART affects the incidence and/or prevalence of these conditions. Studies are limited likely due to low incidence and prevalence of these conditions. Examples include *Candida albicans* endophthalmitis, *Cryptococcus neoformans* infection, endogenous bacterial retinitis, bacterial and fungal corneal infections, microsporidial keratitis and *Pneumocystis jiroveci* choroidopathy, Further studies concerning the incidence and prevalence of these conditions in the age of HAART need to be done to ascertain if HAART has an impact on these conditions.

HIV Eye Conditions in which it is Thought HAART Does Not Decrease Incidence/Prevalence:

Ocular Syphilis:

The incidence of ocular syphilis has not decreased in the HAART era like other ophthalmic manifestations of HIV have decreased in the HAART era (Gonzales-Lopez, 2009). A confounding variable is simply that the number of syphilis cases has increased in recent years,

and this fact may be skewing the data concerning ocular syphilis during the age of HAART. The CDC reported that between 2011 and 2012, the number of reported syphilis cases increased 12.1 percent. The CDC also reported that in 2012, 75% of the reported syphilis cases were among men who have sex with men (MSM). One study of patients with ocular syphilis who had HIV versus those with ocular syphilis who were not immunocompromised from HIV or other immunocompromising conditions showed that the HIV-infected group had more extensive ocular disease than the immunocompetent group (Becerra, 1989). The findings of ocular syphilis include entities such as anterior uveitis, interstitial keratitis, lesions of the skin of the lids, diffuse papillary conjunctivitis, temporary loss of eyebrows, scleroconjunctivitis, chorioretinitis, retinal perivasculitis, intraretinal hemorrhage, papillitis, and panuveitis. An HIV-positive patient with ocular conditions should raise high suspicion for syphilis regardless of CD4 count (Wender, 2008). Likewise, patients with ocular syphilis should raise a suspicion for HIV. Wender (2008) also discussed that HIV-positive patients are more likely to have a more severe, atypical course of ocular syphilis. Posterior uveitis is significantly more common in patients with CD4 counts below 200 cells/mm^3, and such patients with CD4 counts below 200 cells/mm^3 also typically had lower risk of panuveitis and anterior uveitis (Tucker, 2011).

Herpes Zoster Ophthalmicus:

Herpes zoster ophthalmicus affects both the anterior and posterior segments of the eyes (virtually all of the eye and surrounding tissues) in patients with and without HIV. Herpes zoster is caused by human herpes virus 3, which is the same virus that causes chickenpox. Herpes zoster ophthalmicus represents up to 25% of all cases of herpes zoster (Shaikh, 2002). Risk factors of herpes zoster ophthalmicus include immunosuppression or older age. Examples of immunosuppression include HIV, malignancy, systemic lupus erythematosus, and the use of

immunosuppressive agents. Herpes zoster ophthalmicus may be the initial manifestation of HIV. HIV-positive people have 15–25 times the prevalence of zoster as compared to the general population (Pavan-Langston, 2002). A longitudinal study demonstrated an incidence of 29.4 cases of herpes zoster per 1000 person-years among HIV-seropositive persons, as compared with 2.0 cases per 1000 person-years among HIV-seronegative controls (Buchbinder, 1992).

Gebo et al (2005) looked at the incidence of, risk factors of, and sequelae of herpes zoster among 239 HIV patients in the era of HAART. This study found that the incidence rate of herpes zoster among an urban cohort of HIV patients, 3.2 per 100 person-years of follow-up, was unchanged from the pre-HAART era. Thus, herpes zoster is still a significant problem for HIV patients in the age of HAART according to this single study. The study also found that patients on HAART and those with CD4 counts between 50 and 200 cells/mm^3 seemed to be at the highest risk of a herpes zoster event. The CD4 counts between 50 and 200 cells/mm3 indicates the condition occurs at moderate levels of immunodeficiency and not severe immunodeficiency. When HAART is used, the CD4 level generally rises and profound immunodeficiency is generally avoided. Many patients on HAART may simply be situated in an ideal window regarding their CD4 counts for herpes zoster to occur (depending on how many HIV patients on HAART recover and to what level). The study also found that the complication rate among the incident zoster cases in HIV-positive patients (particularly post-herpetic neuralgia), was markedly higher than that expected in a similar-age HIV-negative population.

Herpes zoster ophthalmicus can also result in ocular issues other than just a characteristic rash. Involvement of the tip of the nose (Hutchinson's sign) has been thought to be a clinical predictor of ocular involvement of the condition. Although patients with a positive Hutchinson's sign have twice the incidence of ocular involvement, one third of patients without the sign

develop ocular manifestations (Harding, 1987). Corneal involvement can result in significant visual loss in those affected by herpes zoster ophthalmicus. Corneal complications occur in approximately 65% of cases of herpes zoster ophthalmicus (Baratz, 1988). Deep stromal keratitis is uncommon but can develop months to years after the initial acute episode (Baratz, 1988). Neurotrophic keratopathy can develop from decreased corneal sensation.

Acute retinal necrosis can occur in herpes zoster ophthalmicus. The condition is serious because it can lead to uveitis, retinal detachment, and blindness. Retinal detachment is a complication in approximately 50% of cases (Lau, 2007). Patients may complain of signs and symptoms such as red eye, ocular pain, decreased vision, floaters, and decreased color vision. Acute retinal necrosis can also be caused by herpes simplex virus types 1 and type 2. Treatment of the condition consists of antivirals, such as acyclovir, valacyclovir, and famciclovir. However, in immunosuppressed patients the condition is much more recalcitrant to such treatment (Ahmed, 2006). Anti-inflammatory therapy and anti-platelets also used. Retinal detachment prophylaxis is also utilized. Vitrectomy procedure may also be necessary.

Progressive outer retinal necrosis (PORN) is another retinal condition that may result indirectly from herpes zoster ophthalmicus. The condition is generally associated with severely immunocompromised patients, such as AIDS patients and those on chemotherapy.   Most patients with PORN have a poor ophthalmologic prognosis, because the retinal necrosis tends to be followed by retinal detachment. Antiviral therapy with acyclovir has not been effective because of the patients' severely immunosuppressed state (Van den Horn, 1996). Prophylaxis against retinal detachment using laser retinopexy has not been useful in most cases (Holland, 1994).

Conclusion:

In conclusion, there is strong evidence that HIV can affect the eyes in a multitude of ways. It has also been observed that higher incidence and prevalence of HIV eye-related conditions seems to be most related to lowering of CD4 levels in HIV patients. Therefore, it is thought that HAART, which impacts the CD4 levels, can indirectly impact the incidence and prevalence of various ocular conditions associated with HIV/AIDS. Looking at how these ocular diseases affect HIV-positive people is important in following the epidemic's impact globally. There are numerous studies and observational data to show varying degrees of evidence about the impact of HAART on HIV eye disease; these have been summarized in this paper. HIV eye conditions that seem to demonstrate the strongest evidence of improved outcomes due to HAART include HIV retinopathy and CMV retinitis. In contrast, some conditions are not improved after initiation of HAART—examples include ocular syphilis and herpes zoster ophthalmicus. There are also some conditions where the association between use of HAART and HIV eye diseases is less well understood but cannot be assumed to be negative. These include dry eye, herpes simplex keratitis, Kaposi sarcoma, toxoplasmosis retinochoroiditis, molluscum contagiosum, and several rare HIV-caused ophthalmic conditions—further studies may give rise to information to determine if widespread HAART use would decrease distribution and determinants of these diseases in the HIV-infected population.

Since there are clear trends indicating that several of the HIV-related ophthalmic conditions are less of a burden for patients on HAART, an argument for use of HAART in HIV-infected persons can be made. However, further studies are needed to create a stronger evidence base for those conditions where a strong beneficial pattern has been observed, but also to establish the evidence base for other conditions where the benefits of HAART are less well

established. The findings described in this paper not only provide support for further studies, but also can serve as hypothesis generating results to help design such studies. The importance of undertaking such studies is directly related to practice based evidence that using widespread HAART could lessen the burden of HIV eye diseases in populations that have not currently adopted widespread HAART use.

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