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Viral infections associated with oral cancers and diseases in the context of HIV: Workshop 3B

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Abstract

Human herpesviruses (HHVs) and Human papillomaviruses (HPV) are common in the general population and, in immunocompetent people, are mostly carried asymptomatically. However, once an individual becomes immunocompromised by age, illness, or HIV infection these dormant viruses can manifest themselves and produce disease. In HIV-positive patients there is an increased risk of disease caused by HHVs and HPV infections and cancers caused by the oncoviruses EBV, HHV-8, and HPV. This workshop examined four questions regarding the viruses associated with oral cancers disease in the HIV-positive and -negative populations, the immune response, and biomarkers useful for accurate diagnostics of these infections and their sequalae. Each presenter identified a number of key areas where further research is required.

Keywords

oral cancer; oncoviruses; Human Herpesvirus; Human Papillomavirus; HIV infection; biomarkers; immune response

The role of viral infections associated with oral cancers and disease in the context of human immunodeficiency virus (HIV) was the focus of Workshop 3B at the Seventh World Workshop on Oral Health and Disease in AIDS (November 2014, Hyderabad, India), which identified areas in need of further research (Tappuni & Shiboski, 2016). Whilst this area has

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been well covered by extensive reviews and ongoing research, such as that conducted by the International Agency for Research on Cancer, and was reviewed at the Sixth World Workshop on Oral Health and Disease in AIDS (April 2009, Beijing, China) much remains unsolved (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2009, Patton et al., 2011). This workshop underscored that the defined oral cancers should include those cancers of the whole head and neck region regardless of anatomical location. Oral cancers are not only those of the oral cavity, tongue and tonsils, (i.e. those visible upon a standard oral exam), but should include cancers of the entire head and neck region, including salivary glands, sublingual lymph nodes, as well as cancers that do not occur exclusively in the oral cavity. Therefore, the detection and management of opportunistic viral infections associated with oral cancers is the responsibility of the practicing dentist, especially in the context of HIV infection.

The majority of oral viral infections manifesting as oral diseases or cancers are caused by human herpesviruses (HHVs) and human papillomavirus (HPV). These diseases include herpes labialis [HSV-1 & 2], herpes zoster or shingles [VZV; HHV-3] infections, oral ulcers and retinitis/uveítis [HCMV; HHV-5], oral hairy leukoplakia (OHL; EBV) and oral cancers caused by the oncoviruses Epstein-Barr virus [EBV; HHV-4], Kaposi's sarcoma-associated herpesvirus [KSHV; HHV-8] and "high-risk" HPV's (especially HPV-16, 18, 31, and 33). Oral cancers include Burkitt's lymphoma (BL), Kaposi's sarcoma (KS), and a subset of upper aerodigestive tract cancers respectively (Johnson, 2010) (Table 1). Whilst the prevalence of these oncoviruses varies greatly, and in some regions can exceed 50%, only a small percentage of infected individuals will develop disease possibly due to the import role of the host cofactors. Many of these oncoviruses are transmitted through oral-oral contact and are readily detected in saliva. The exception is HPV where its detection is primarily in samples reflective of tonsillar tissue (tonsillar samples or gargles) (Duray et al., 2011). In addition, HPV is also likely transmitted through oral-genital contact (Pickard et al., 2012). These oncoviruses also work directly through several mechanisms, which include induction of cell proliferation, genomic instability, cell migration, and the inhibition of apoptosis (Table 2). On the other hand, hepatitis B virus (HBV) and hepatitis C virus (HCV) work indirectly through chronic inflammation.

Whilst some consider HIV to be an "oncovirus", its role is mainly indirect through increasing immunosuppression. HIV is also associated with immune activation, which can result in chronic inflammation and subsequent carcinogenic effects. Subsequently, this may result in an altered oral microbiome and loss of local immune surveillance and/or chronic inflammation. HIV may also directly induce B-cell activation by up-regulating activation-induced cytidine deaminase (AID) (He et al., 2006). Complicating the association with HIV are other co-factors associated with head and neck cancers (HNC). These include smoking (both cigarettes and smokeless tobacco), chewing betel quid, the use of alcohol and illicit drugs, as well as viral co-infections (Gupta & Johnson, 2014). Through increased immunosuppression HIV increases the risk of KS, non-Hodgkin's lymphomas, Hodgkin's lymphoma, anal and cervical cancer, oral cavity/pharyngeal cancer and liver cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2009).

In the HIV-positive individual, oral diseases may result from an increased risk of acquisition of virus or the emergence of disease due to reactivation from a pre-existing latent infection. Oral disease progression can be defined as a transition from asymptomatic to symptomatic chronic infection or a symptomatic disease that worsens over an accelerated time course (e.g. HPV-associated dysplasia to invasive carcinoma). Understanding these distinctions remains a challenge as the natural history of these viral infections in the oral cavity in general is not well understood.

Questions

Questions addressed by the workshop include the following:

Question 1: What are the viral associations with cancer and the co-infections EBV, HPV and HHV-8 in the head and neck?

Question 2: Are HPV-associated oral lesions including oral-pharyngeal cancers higher among HIV-infected men, women, and children?

Question 3: What alterations in immune responses to viral co-infections including EBV HPV and HHV8 are HIV specific?

Question 4: Are there biomarkers for oral clinical disease associated with viral co-infections in HIV infected persons?

Question 1: What are the viral associations with cancer and the co-infections EBV, HPV and HHV8 in the head and neck?

Presenter: Professor Marc Goodman.

Cancers of the head and neck arise from the lining of the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasopharynx. Globally the incidence and mortality of HNC is increasing. Based on the GLOBOCAN estimates for 2012 there were 686,328 new cases with 375,665 deaths worldwide (Ferlay et al., 2012). Of these, 300,373 are from the oral cavity, 156,877 from the larynx, 142,387 from other pharynx, and 86,691 from the nasopharynx (Figure 1). Head and neck malignancies represent 6.9% of cancers in men and 2.6% of cancers in women.

Kaposi sarcoma-associated herpesvirus (HHV-8)—HHV-8 is the aetiological agent of KS, multicentric Castleman's disease and primary effusion lymphoma. There are four clinical-epidemiological variants of KS: classic, endemic (African), iatrogenic (transplant-associated) and HIV/AIDS-associated (epidemic). These variants can be distinguished by the severity and presentation of clinical symptoms, manifestations that vary by (i) the extent of anatomical involvement, (ii) the aggressiveness of lesion formation and progression, (iii) patient risk factors (i.e. ethno-geographic origin, age of onset, and gender), and (iv) the association with patient morbidity and mortality. However, all epidemiological forms of KS are histopathologically identical (Ablashi et al., 2002). KS is AIDS defining and the most frequent AIDS-associated neoplasm worldwide due to the underlying HHV-8 prevalence, limited access to antiretroviral therapy (ART) and the health delivery infrastructure in many developing nations (Dittmer & Damania, 2013).

Globally, the prevalence of KS usually mirrors the seroprevalence of HHV-8 and HIV, except for in the Amazon Amerindians populations of South America and in India. In the HIV-negative Amazon Amerindians populations of Brazil, Ecuador and French Guiana HHV-8 is endemic (i.e. 75.4% seroprevalence) but clinical KS is rare (Borges et al., 2012). In 2012 the Government of India estimated that 2.40 million Indians are living with HIV with an adult prevalence of 0.31% (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014). However, KS has only been documented a total of 7 times in the literature (Vaishnani et al., 2010, Dongre & Montaldo, 2009, Kharkar et al., 2009, Kura et al., 2008, Soufiane et al., 2010) with the first recorded case from YRG CARE (Kumarasamy et al., 1996). In 1999, Ablashi *et al.* found a 4% HHV-8 seropositivity rate in blood collected from 108 healthy individuals at blood bank facilities in Bombay, Chennai, and New Delhi (Ablashi et al., 1999). These results are comparable to those found in blood donors in the USA (5.2%; 7/135) as reported in the same study. Further studies have shown that the seroprevalence of HHV-8 in the HIV-positive ART-naive population in India ranges between 10.64% (Speicher et al., 2014a) and 26% (Munawwar et al., 2014). These results suggest that HHV-8 is present in India but it may not express itself as KS.

In the USA, one third of KS cases develop in patients (mostly older men) on suppressive ART (Krown et al., 2008). While cutaneous KS is more common, oral KS is present in up to 60% of KS cases with up to 45% of cases involving both oral and cutaneous lesions. Oral KS is associated with a higher death rate with mortality occurring 24 months after diagnosis, compared to 72 months as seen in cutaneous lesions (Jindal et al., 1995). Molecularly and histologically indistinguishable iatrogenic KS can also develop in solid organ allograph recipients irrespective of HIV status. HIV is not likely to contribute directly to the pathology of the disease above inducing immunosuppression and thus increasing the rate of disease progression.

Treatment regimens of HIV/AIDS play a huge role in KS pathology. The use of ART causes remission of many, but not all KS lesions. Following the release of ART, the incidence of KS was reduced in the USA from 333 cases/million in 1987 to 28 cases/million by 1998 (Ziegler et al., 1997). Since 2000 no further decline in KS was observed and the number of new cases plateaued. ART was so effective that 90% of AIDS-KS cases displayed complete remission of cutaneous lesions within six months as well as an 81% reduction in mortality (Ziegler et al., 1997). However, in a small subset of patients, the initiation of ART can cause an intense rebound of inflammatory responses including those to non-HIV viral infections, a situation now widely recognised as immune reconstitution inflammatory syndrome (IRIS). IRIS occurs in two forms. If an opportunistic infection worsens despite successful treatment of HIV this is called *paradoxical IRIS*, whereas the emergence of a previously absent infection is called *unmasking IRIS* (Tappuni, 2011). When KS is associated with IRIS, this is called KS-IRIS. KS-IRIS can occur in up to 11% of newly diagnosed HIV-positive patients initiating ART (Speicher et al., 2013, Achenbach et al., 2012). The appearance of KS-IRIS should be treated by maintaining ART and treating the KS with liposomal doxorubicin.

In summary, HHV-8 is associated with all epidemiological variants of KS, multicentric Castleman's disease and primary effusion lymphomas. AIDS-KS commonly affects the oral

cavity with the oral mucosa being the initial site of clinical disease in ~22% of patients (Mesri et al., 2010). Whilst ART has successfully decreased the prevalence and incidence of AIDS-KS worldwide, in parts of Sub-Saharan Africa clinical KS and HHV-8 infection remain endemic (Dittmer & Damania, 2013, Butt et al., 2008). The use of ART may also cause KS to either regress or flare up as either unmasking or paradoxical KS-IRIS (Speicher et al., 2013, Achenbach et al., 2012).

Epstein Barr Virus (EBV)—EBV can manifest in the oral cavity and/or head and neck region as BL, mononucleosis and OHL with disease severity and prevalence increased in individuals co-infected with HIV. Mononucleosis is common irrespective of HIV status and is associated with a primary EBV infection during adolescents and young adulthood. However, age of primary infection varies greatly worldwide. OHL is a manifestation EBV reactivation detected in association with immunosuppression. OHL is often asymptomatic, and is the only pathologic manifestation of permissive EBV infection. OHL is not confined to HIV infected people, but was detected in solid organ transplants and bone marrow transplant recipients (Itin et al., 1988, Epstein et al., 1991, King et al., 1994). OHL serves as a clinical biomarker for HIV infection and progression to AIDS. Even in the HAART era, the prevalence of OHL is 12% of the HIV population (Shiboski et al., 2015). This is of particular importance because OHL may serve as an oral indicator, not only of new HIV infections, but of ineffective ART. OHL demonstrates an interesting pattern of gene expression with a combination of lytic and transforming genes (Webster-Cyriaque et al., 2000). While transforming genes are expressed in OHL, the lesion has not been associated with malignancy in the context of HIV. Mutalima *et al.* (2008) found that HIV status increased the risk of BL by 12-fold (Mutalima et al., 2008). Among HIV-negative individuals, high levels of antibodies for EBV and malaria increased the risk of BL by 12 and 2.5 fold respectively. These EBV-positive Hodgkin's and non-Hodgkin's lymphomas may manifest in the head and neck. Nasopharyngeal cancers (NPC) are also head and neck cancers associated with an EBV infection. NPC, however, is not typically detected as an EBV-associated AIDS defining cancer. Hazard ratios for developing NPC associated with anti–EBV viral capsid antigen immunoglobulin A: low antibody levels have elevated odds ratio (OR) of 9.5 (range: 2.2 to 40.1) and high antibody levels have an OR of 21.4 (range: 2.8 to 161.7) (Hsu et al., 2009). Transmission of HIV during pregnancy or birth adds complexity to the aetiology of EBV-associated cancers and virus-associated oral transmission. In many developing countries HIV is acquired prior to the first infection with a human oncovirus and increases the risk of disease. Whether HIV has direct biochemical effects on EBV-associated disease beyond modulation of transmission and "seeding" of the latent reservoir of EBV remains a subject of debate.

Human Papillomavirus (HPV)—In many countries the incidence of HNC is increasing mostly due to the increase of HPV-associated oropharyngeal cancers (e.g. tonsils, base of tongue and other parts of the oropharynx) (Marur et al., 2010). HPV-associated HNC also tend to respond better to standard therapy than HPV-negative HNC. HIV infection can increase incidence and alter pathology by three mechanisms. Firstly, HPV acquisition is increased by high-risk sexual behaviour in those populations considered at higher risk of HIV acquisition. Secondly, HPV persistence is increased in HIV-positive individuals due to

immune dysfunction; even in individuals on long-term, successful ART. Lastly, the direct biochemical effects of HIV proteins on the oral epithelial cell physiology may enhance, sustain or modulate HPV infection in the oral cavity (Tugizov et al., 2013).

The prevalence of HPV DNA detection orally can be up to 31% in the HIV-positive population compared to 6% in the general population (Beachler et al., 2014, Antonsson et al., 2014, Parisi et al., 2011). Several prevalence studies have shown that the number of oral sex partners is directly proportional to the risk of HPV infection irrespective of HIV status. In the HIV-positive population Kreimer *et al.*, reported that the odds of having an oral HPV infection increased greatly with more than two recent HIV-seropositive oral sex partners (OR: 12.8; 95% CI; 3.1–52.7) compared to having one or fewer (OR: 1.0) (Kreimer et al., 2004). In the HIV-negative population, D'Souza *et al.* reported a similar pattern in that the risk of oral HIV infection increased from one or fewer (OR: 1.0) to eleven or more (OR: 5.20; 95% CI; 1.13–24.7) lifetime number of oral sex partners (D'Souza et al., 2009). This correlation was confirmed by Pickard *et al.* who reported that five or more lifetime open-mouth kissing (OR, 4.0; 95% CI: 1.1–14.8) or lifetime oral sex (OR, 4.0; 95% CI: 1.3–11.9) partners were associated with infection (Pickard et al., 2012). Prospective studies have been inconsistent in determining an association between oral sex behaviours and oral acquisition of HPV (Kreimer et al., 2013b, Edelstein et al., 2012). Further studies are needed to determine (1) the mechanistic interactions between oncoviruses and HIV, (2) the cost-effectiveness of current HPV vaccines towards HNC in population–based studies, and (3) the effect of smoking and drinking on the risk of HPV-associated HNC.

Question 2: Are HPV-associated oral lesions including oral-pharyngeal cancers higher among HIV-positive men, women, and children?

Presenter: Dr. Velia A. Ramírez-Amador.

HPV-associated oral lesions—HPV-associated oral lesions have been called HPV-associated oral warts (HPV-OW) in different studies (King et al., 2002, Greenspan et al., 2001, Patton et al., 2000). HPV-OW is a nonspecific generic term that refers to a group of benign lesions that includes: squamous cell papilloma (SCP), verruca vulgaris (VV), condyloma acuminatum (CA), and focal epithelial hyperplasia (FEH) (Syrjanen, 2003). In 2001, an increase in oral warts was described in adult HIV-infected individuals from 5% in individuals without ART, to 15% in patients on ART other than highly active antiretroviral therapy (HAART), and to 23% in those on HAART (Greenspan et al., 2001). Similarly, other studies have mentioned an augmented incidence of these lesions in HIV-infected population (King et al., 2002, Patton et al., 2000).

Currently, in the context of HIV, information related to oral HPV-OW frequency and behaviour is scarce. Studies published during 2008–2012 reported a prevalence of oral HPV-OW from 0.5% (8/1,595) to 6.9% (55/787) in HIV-positive patients from Brazil (Ortega et al., 2009) and Mexico (Anaya-Saavedra et al., 2013) respectively. In the HIV-negative population most data on HPV-OW comes from case reports (Nagaraj, 2013, Liu et al., 2012, Falaki et al., 2009). However, three large population-based studies reported a prevalence of ≤0.3% in Swedish adults (Robledo-Sierra et al., 2013, Salonen et al., 1990, Axell, 1976),

which is similar to a 0.37% (89/23,789) prevalence reported in the Mexican HIV-negative adult population (Castellanos & Diaz-Guzman, 2008). Due to immune dysfunction the risk of developing HPV-OW is higher in the HIV-positive population compared to the general population (Table 3). In HIV-positive adults the prevalence of oral HPV infection ranges from 16% (Videla et al., 2013) to 40% (Beachler et al., 2012), which is higher than in the general population. Population studies have also shown that the prevalence of HPV-OW in HIV-positive children (1.6%) is also slightly higher than in HIV-negative children (0.51%) (Nabbanja et al., 2013).

For the purpose of this review, studies on the frequency of FEH in children have not been considered because FEH may be present only in specific ethnic groups and geographical regions, particularly in childhood, independently of the HIV status (Bennett & Hinshaw, 2009, Said et al., 2013, Akoglu et al., 2015).

While the majority of studies have emphasized the benign nature of HPV-OL in HIV-positive patients, others have shown a range of high-risk HPV types (HR-HPV) in these lesions. Some studies that have shown HR-HPV mainly HPV-16, 18 and 31, have been also identified in these lesions (Estrella, 2015, Anaya-Saavedra et al., 2013, Ma et al., 2004). The prevalence of HR-HPV found in HPV-OL displays the potential for a malignant change in these lesions, particularly considering the increased risk of HPV-associated malignancy among HIV patients (Beachler et al., 2014). Consequently, longitudinal studies based on viral transcriptional activity are warranted.

Oral-pharyngeal Cancers—Based on standardized incidence ratios (SIRs) the incidence of oral-pharyngeal cancer in HIV-infected individuals is higher in HIV-positive individuals than that of the age-and gender matched general population. One study in Italy showed an increased risk of tonsil cancer (SIR = 10.9, 95% CI: 1.2–39.4) in HIV-infected men (Franzetti et al., 2013). Another study from Puerto Rico found an increased risk of oral-pharyngeal cancer in HIV-infected women (SIR = 10.9, 95% CI: 1.26–37.6) (Ortiz et al., 2014). Other studies have reported significant albeit lower risks than these two studies – ranging from an SIR of 1.6 (95% CI: 1.2–2.1) in the United States (Chaturvedi et al., 2009) to 1.9 (95% CI: 1.8–2.1) in Northern Italy (Calabresi et al., 2013). Engsis et al reported an incidence rate ratio (IRR) of 5.1 (95% CI: 2.28–11.44) in a Danish HIV-cohort study (Engsig et al., 2011). In the USA a prospective study determined that the standardized incidence of HPV-related and -unrelated head and neck squamous cell cancers (HNSCC) were both 3-fold higher in HIV-positive individuals than the general population (Beachler et al., 2014).

Data must be taken with caution as most studies either lack information or could not be adjusted for the effect of confounders such as smoking, alcohol use and viral co-infections. A large non-registry study has shown that the risk factors for developing HNSCC are similar between the HIV-positive and –negative populations for both HPV-related and tobacco/alcohol-related HNSCC (D'Souza et al., 2014). In order to elucidate the incidence and risk of HPV-associated oral lesions in the HIV-positive population further studies are needed (i) to develop detailed case definitions, which would constitute a starting point for clinical studies to arrive at true population-specific incidence rates, (ii) to determine if the increased

incidence in these benign oral lesions is associated with greater risk or faster progression to oral cancer, (iii) to identify the HPV types involved in oral lesions and determine the role and importance of high-risk and atypical types, and (iv) to develop collaborative and multicentric studies to perform randomized controlled trials for HPV-OL treatment.

Question 3: What alterations in immune responses to viral co-infections including EBV, HPV, and HHV8 are HIV specific?

Presenter: Associate Professor Jennifer Webster-Cyriaque.

It is not well understood what different immune modulating events contribute to an individual's risk of developing oral lesions, how they change the pathophysiology of oral lesions, their progression to cancer, response to intervention or how immune modulation affects transmission via the oral cavity. Whilst it is know that acute HIV infection or end stage AIDS contribute to transmission rates, disease incidence, and outcome, currently there is insufficient evidence to support the notion that, on a molecular and pathophysiological level, oral cancer, HNC, or any cancer differs from the same cancer that develops in an HIV-negative person.

Modulation of the immune response by HIV and its associated therapies occurs at many different levels. HIV itself disarms lymphoid and macrophage subsets and their effectors, which are critical to control other viral infections. Furthermore, innate immune responses to viral co-infections are compromised by both HIV infection and ART. Type I interferon (IFN) is critical to control viral infections. A viral infection results in the downstream activation of type 1 IFN with rapid induction of IFN stimulated genes (ISGs) that encode proteins with direct antiviral and immunomodulatory activities (Acchioni et al., 2015, Gibbert et al., 2013). However, persistent HIV-1 infection disables this response such that IFN, although produced, cannot block infection facilitating chronic IFN-mediated immune activation and inflammation (Zheng et al., 2014). IFN responses against opportunists are then compromised and the chronic immune activation characteristic of HIV infection may facilitate oncoviruses like EBV, KSHV, and HPV. HIV-associated therapies may further alter immune responses that affect viral co-infections as seen in HIV-positive individuals treated successfully with ART who succumb to IRIS. IRIS is characterized by heightened HIV specific B and T cell responses and enhanced chronic immune activation (Tappuni, 2011). It is thought that chronic immune activation facilitates these opportunistic infections. IRIS typically occurs in the first few months of ART and is accompanied by worsening of clinical status in spite of improved $CD4^+$ T cell counts. The accompanying proinflammatory response may result in the pathologic manifestations of these opportunistic infections. These IRIS associated oral manifestations have been described in the context of DNA oncoviral infections. KS-IRIS is well described in both the mouth and on the skin. Oral KS-IRIS has been described in a series of case reports (Speicher et al., 2013, Papagatsia et al., 2009, Feller et al., 2008, Feller & Lemmer, 2008, Englert et al., 2014). EBV-associated IRIS has been described both in the context of permissive infection and of EBV-associated malignancy. There has been one report reviewing oral manifestations in the context of IRIS that determined three of eight patients with IRIS-associated oral disease had hairy leukoplakia (Ramirez-Amador et al., 2009). Hodgkin's Lymphoma, is associated with EBV

infection and its risk was higher in the first 12 months (IRR=2.02, 95%CI=1.32–3.10) after cART initiation (Kowalkowski et al., 2013). In a recent study of HIV subjects undergoing IRIS, the most common oral manifestation was parotid enlargement (57.14%) (P = 0.019) (Ortega et al., 2008). This parotid enlargement has recently been associated with permissive human polyomavirus BK (BKPyV) infections; an oncovirus that is a well described opportunist in the kidney transplant setting (Jeffers et al., 2009, Burger-Calderon et al., 2014). The existence of HPV-associated IRIS is not clear. Cervical (Rositch et al., 2013, Shrestha et al., 2010) and skin HPV infections (Lowe et al., 2012) were not affected by IRIS. The increase in oral warts subsequent to the inception of ART suggested a role for IRIS (Greenspan et al., 2001, King et al., 2002). The OHARA trial A5272 asked this question and determined that while warts were not associated with rising CD4+ counts, oral HPV shedding did increase post-ART (Shiboski, personal communication). Hence it appeared that while there may not be an HPV pathologic manifestation, associated with IRIS in the skin, cervix or oral cavity – HPV shedding may be associated with immune reconstitution.

Few studies discuss the relationship between oral innate immunity and HPV, EBV or KSHV infection. However, human natural killer (NK) cells have been suggested to restrict viral infections. Recent studies show that early differentiated human NK cells limit lytic EBV replication (Munz, 2014). In the context of HIV, regardless of ART therapy, there are functional defects and numeric shifts in NK cell subsets that lead to decreased frequencies IFN-γ-producing NK (Dillon et al., 2014). Furthermore, AIDS patients show lowered ratios between fold increase in ligand expression on CD4+ T cells upon in vitro stimulation and respective NK cell receptor expression (Bisio et al., 2013). Cellular pathogen sensing is also critical to innate control of opportunistic viral co-infections. Abnormal expression and function of cytosolic IFI16 DNA sensors was detected in HIV-positive patients. IFI16 expression was correlated with CD38 a marker of immune activation as well as with a high viral load and low CD4 (Nissen et al., 2014).

Both innate and humoral responses are compromised in the setting of HIV. Cellular editing enzymes like AID/APOBEC are important to the innate immune responses to viral infection. Cytidine induced deaminases have recently been shown to be important to control of KSHV, EBV and HPV (Vieira & Soares, 2013, Bekerman et al., 2013). Cytidine induced deaminases hypermutate and deaminate viral genomes resulting in compromised infection by upregulation of NK ligands and formation of misfolded/truncated viral proteins that initiate CTL responses. However, HIV targets AID/APOBEC for proteosomal degradation further compromising responses against opportunistic viral co-infections. HIV may also diminish viral co-infection specific humoral responses. Antibody function depends on somatic hypermutation of variable regions of immunoglobulin heavy chain genes. AID is specifically induced in germinal center B cells to perform somatic hypermutation and class-switch recombination. The antigen-binding hypervariable regions and hypervariable complementarity determining regions of IgG class-switched and antigen-binding V_H3 CDR genes, from B cells of HIV-1-infected patients demonstrated decreased mutation frequencies (Bowers et al., 2014). Lower levels of somatic hypermutation in IgG class-switched B cells from HIV-1-infected patients may contribute to the increased risk of viral opportunistic infections. In order to elucidate the immune response to viral co-infections further studies are needed (i) to determine the oral innate immune responses in both the oral mucosa and in

saliva, and their relationship to HPV, KSHV and EBV, (ii) to determine oral IgA associated humoral responses to oral viral co-infection, and (iii) to clearly define oral IRIS.

Question 4: Are there biomarkers for oral clinical disease associated with viral co-infections in HIV infected persons?

Presenter: Dr David J. Speicher.

Viral biomarkers are measurable substances indicative of a viral infection and usually predictive of disease such as cancer. Biomarkers can identify active disease, effective immunity or increased risk of disease. Active disease is often identified by histological or molecular diagnostic biomarkers, whereas effective immunity has been measured traditionally by serological biomarkers. Increased risk of disease is associated with a variety of markers usually associated with pathogenesis. Useful biomarkers must have clinical relevance and be cost-effective.

Both histopathology, employing both H&E and IHC stating, and molecular assays are useful for identifying HHVs and HPV from lesional tissue and assigning causality. Whilst, in most HHV infections, viraemia will precede disease and viral shedding can be detected, this is not always true. Asymptomatic shedding is common in individuals with HSV-1 or -2 making it essential to detect the virus in anogenital and oral swabs (Mertz, 2008). It is also unwise to diagnose oral lesions solely upon clinical appearance and tissue morphology revealed by H&E staining. IHC stains are available for all HHVs and HPV (Table 4). Whilst IHC, in-situ hybridization and molecular assays are available for HPV, studies have shown that p16 immunohistochemistry is the best test for the identification of high-risk HPV associated high grade lesions (Lewis et al., 2010, Wittekindt et al., 2005).

In developed countries, these biomarkers are common practice. On the other hand, in many resource-constrained settings lesions are often diagnosed solely by clinical appearance and H&E staining thus increasing the risk of misdiagnosis other reactive and neoplastic vascular proliferations. Two examples where a misdiagnosis is possible are Sub-Saharan Africa where KS is endemic, and India where clinical KS is very rare. In one study, Speicher et al found that in Nairobi, Kenya (where KS is endemic), whilst all cutaneous KS were correctly diagnosed, 12/28 oral KS lesions were misdiagnosed and were re-diagnosed as either pyogenic granulomata (n=6), deep mycosis (n=1), inflamed mucosa (n=2) or “uncertain but not KS” (n=3) (Speicher et al., 2015b). Therefore, even where molecular assays are not available it is essential that HHV-8 immunohistochemistry be used for the correct diagnosis of oral KS.

In India, the presence of KS has only been documented a total of 7 times (Vaishnani et al., 2010, Dongre & Montaldo, 2009, Kharkar et al., 2009, Kura et al., 2008, Soufiane et al., 2010, Kumarasamy et al., 1996). However, caution must be given as all but one of the reported cases of KS were diagnosed solely on the H&E staining. Thus the presence/absence of HHV-8 in India cannot be confirmed nor denied and work is needed to determine the true status of HHV-8 in India.

Molecular biomarkers for the presence of HHVs typically focus on the identification of states of viraemia and/or confirm histological findings. As HHVs establish undetectable latent infections it is the presence of viraemia that appears immediately prior to clinical disease thus molecular assays (i.e. PCR assays) are useful for monitoring disease progression and treatment efficacy (Speicher et al., 2014b). Viraemia can be determined from either plasma or peripheral blood mononuclear cells depending on whether the virus circulates as cell-free intact virion or cell-associated virus (Table 4). All diagnostic molecular assays should use two genomic targets to rule out false positives and be designed to conserved regions to rule out false negatives (Whiley et al., 2008). This is especially true when detecting HCMV due to two glycoprotein B splice variants (Nye et al., 2005).

The molecular detection of HPV has been primarily from cell scrapings collected from mucosal surfaces with DNA detected predominately by L1 general or consensus (i.e. GP5+/6+ or MY09/MY11) primers and “high-risk” and “low-risk” types determined by sequencing the amplicon (de Roda Husman et al., 1995). Today, molecular testing for HPV DNA or RNA in conjunction with cytology are commonly used in cervical cancer screening starting at age 30 years Recently the FDA approved the HPV DNA test, Roche Cobas, for primary screening starting at 25 years of age. HPV genome testing is also used in a variety of algorithms for management of abnormal cytology. HPV infections do not normally produce viraemia. However, whilst still controversial with uncertain clinical relevance, HPV can be detected in blood where the virus is attached to the outside of blood cells and can also be isolated from B-cells, dendritic cells, NK cells and neutrophils (Chen et al., 2009). As mentioned earlier, p16 staining is now used routinely to define high grade disease since CIN 2 is often over or under called. P16 INK4 positive staining is considered the hallmark of a significant high grade lesion. More recently the combination of p16 INK4 and Ki67 is being used with excellent sensitivities and specificities—both are commercially available (Wentzensen et al., 2012, Ikenberg et al., 2013). P16 and HPV DNA are not used routinely in cancer diagnoses. However, it is often used to define HPV type causality using laser capture microdissection. Currently oral HPV DNA testing is not used for the detection of oral cancers clinically but is now of great interest in associating causality.

Saliva is a diagnostic fluid with great potential: it is abundant, collection is easy and non-invasive, and represent a much lower risk of exposure of the health care worker to blood-borne infectious agents. Saliva is ideal for the detection of HHV-8, especially for screening patients prior to disease development. Not only is HHV-8 transmitted via saliva, but the epithelium of the oropharynx is the site of primary infection with the tonsils and adenoids being a reservoir of infection (Mbulaiteye et al., 2004, Taylor et al., 2004, Chagas et al., 2006). However, in saliva biomarkers are present in lower concentration than in blood, and the presence of various nucleolytic enzymes, such as endonucleases, ribonucleases, and bacterial proteases, are detrimental (Park et al., 2006, Bardon & Shugar, 1980). Traditionally, unstimulated WMF has been collected by dribbling into a chilled collection cup (Al-Otaibi et al., 2009), or by collecting throat-gargles (TG) with either phosphate buffered saline (Webster-Cyriaque et al., 2006) or commercial mouthwashes (Marshall et al., 2007). While these methods work well, samples must immediately be stored at −80°C to slow enzymatic activity, in resource-constrained settings this is usually not possible. It has also been shown that after storage for 14 months at −80°C DNA extracted from saliva is

highly degraded (Speicher et al., 2015a). The DNA Genotek OMNIgene™·DISCOVER OM-501 and OM-505 kits have been designed for the collection and stabilization of microbial DNA and RNA from saliva stored at room temperature. Whilst DNA Genotek claim RNA is stable for up to 3 months, DNA is stable much longer. After 14 months of storage at room temperature extracted DNA showed little or no degradation (Speicher et al., 2015a). The OMNIgene™·DISCOVER kits are also useful for the accurate quantitation of HHV-8 in saliva and should be useful for any virus shed orally (Speicher & Johnson, 2014).

Biomarkers of effective immunity have traditionally been detected via the serological measurement of antibodies (i.e. IgM for current infections and IgG for previous exposure via infection or vaccination). Whilst serological assays are usually relevant for epidemiological studies, their clinical interpretation is more complex. One problem with serology is that asymptomatic patients will exhibit seropositivity due to a past infection, but this reactive result doesn't correlated well with disease. This is seen globally as the IgG seroprevalence of EBV, HCMV and VZV in adults is between 80–100%, thus making any clinical interpretation impossible. Regarding HHV-8, seroconversion precedes and often predicts disease and ranges from 3–6% to 20–40% in the general population in the USA and Sub-Saharan Africa respectively (Ablashi et al., 1999, Dollard et al., 2010). In the HIV-positive community the HHV-8 seroprevalence is much higher. Whilst there are no standardized HHV-8 serological algorithm both the CDC and NIH algorithms work (Dollard et al., 2010, Mbisa et al., 2010).

HPV serological tests are available, and cervical cancer patients often have serum antibodies against the HPV genotype found in the tumour. Those who have been vaccinated will be seropositive for those vaccine types. Therefore, most research assays examine antibodies to HPV L1, E2 E6 or E7, but prevalence ranges widely to each of these antigens in different populations. The majority of individuals with cervical HPV infections other than HPV-16 do not seroconvert (Marais et al., 2008, Giuliano et al., 2015). Approximately 75% of women with HPV-16 will seroconvert (positive anti-HPV-16 L1) within 12 months – other HPV types have much lower seroconversion rates ranging from 10–35% (Giuliano et al., 2015). Interestingly seroconversion is more common in women than in men suggesting that men have superficial infections resulting in poor immune responses. This may be one explanation as to why HPV-associated HNC are much higher in men than women. Recent data show that anti-HPV-16 E6 is highly predictive of HPV-associated oral cancers (Kreimer et al., 2013a). There is a great need for better, properly validated, biomarkers indicating the risk of pre-cancer and HPV-HNC, which are not affected by seropositivity due to the vaccination.

Biomarkers that show increased risk of disease include immunosuppression, poor health, other opportunistic infections and low humoral immunity. A patient's HIV status and/or age is superfluous for the presence/absence of viral biomarkers for active disease and effective immunity as these are virus specific, but the presence of HIV does suggest immunosuppression and thus an increased risk of viral co-infections. Poor health due to an inactive (lack of exercise) and/or unhealthy lifestyle (excessive smoking and alcohol use) also lowers the immune system and increases the risk of disease. Other diseases, such as diabetes and cardiovascular disease, as well as low humoral immunity suggest a weakened immune system and thus an increased risk of disease.

In summary, diagnostic biomarkers usually focus on measuring viral nucleic acids and antibodies. Unfortunately, these tests often lack sensitivity and specificity to identify oral cancers. Challenges include the lack of standardized endpoints, limitations of disease ascertainment, impact on risk stratification. Whilst saliva as a diagnostic field is emerging, more work is needed to standardize collection, storage and testing of saliva. Once standardized these assays may assist in understanding the salivary transmission of viruses and be used to predict disease. There is also a need for better, properly validated biomarkers that indicate the risk of pre-cancer and HPV-HNC, which are not affected by seropositivity due to the vaccination. Regardless of the diagnostic platform the assays must be available to those who need them the most. Therefore, low cost diagnostic assays are urgently needed for resource-constrained countries. Finally, there is a need for studies that show how viral biomarkers are affected by immunosuppression caused by HIV infection. Long-term efficacy studies in HIV infected persons are important.

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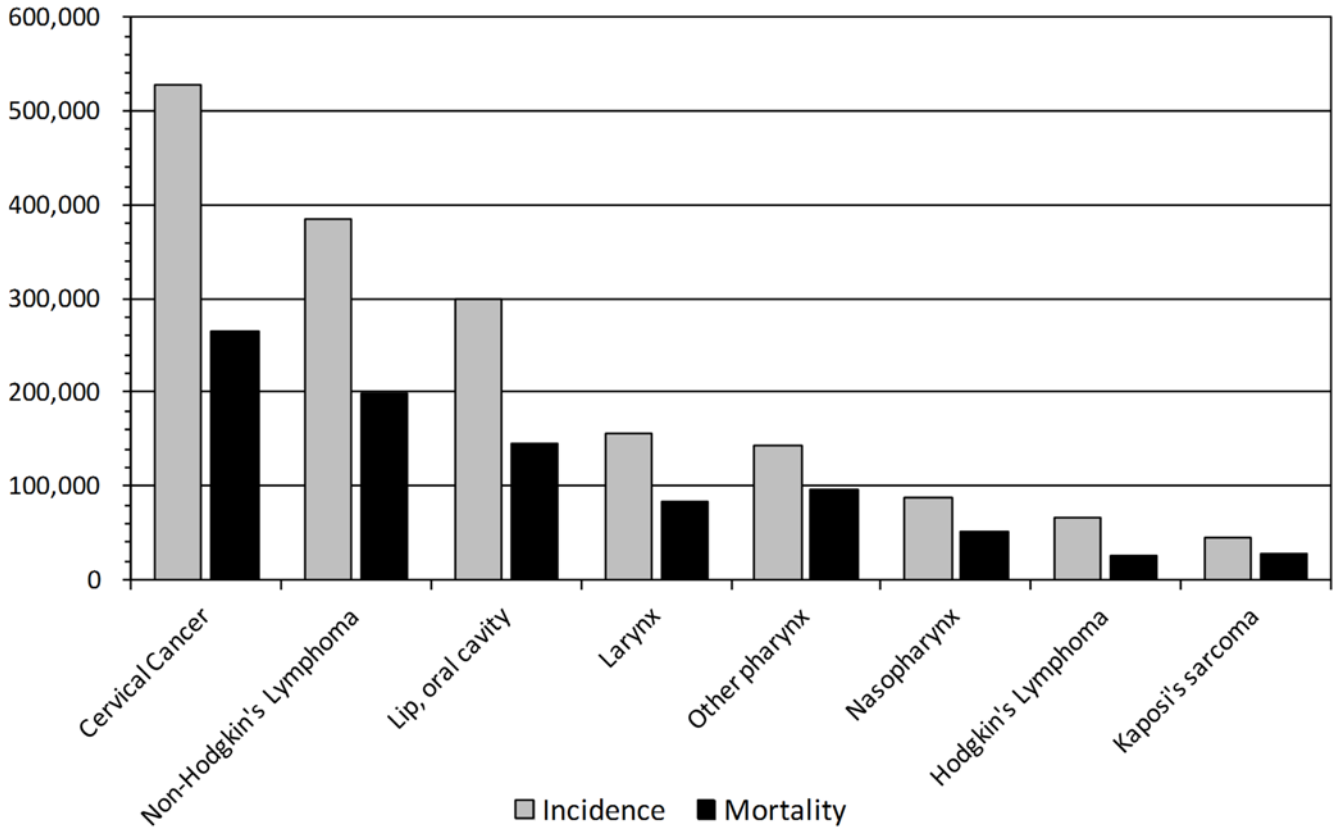

Figure 1.
Incidence and mortality of cancers caused EBV, HHV-8, and HPV in both genders worldwide (Globocan 2012).

Table 1

Cancers caused by oncoviruses with sufficient and limited evidence according to the IARC criteria.

Virus	Cancers with sufficient evidence	Cancers with limited evidence
EBV	Nasopharyngeal carcinoma Burkitt's Lymphoma Immunesuppression-related non- Hodgkin lymphoma, Extranodal NK/T cell lymphoma (nasal type), Hodgkin's lymphoma	Gastric carcinoma Lympho-epithelioma-like carcinoma Plasmablastic lymphoma Diffuse large B-cell/immunoblastic lymphoma (DLBCL)
HHV-8	Kaposi's sarcoma Primary Effusion Lymphoma (classic and solid variants) Plasmablastic lymphomas	Extracavitary KSHV positive solid lymphoma Early PEL Germinotrophic lymphoproliferation
HPV-16	Cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil	Cancer of the larynx
HPV-18, 31, 33,35, 39, 45, 51, 52, 56, 58, and 59	Cervical cancer	

Table 2

Established carcinogenic mechanisms of oncogenic viruses.

Mechanism	Oncovirus	Carcinogenic Properties
Direct	EBV	Cell proliferation, Inhibition of apoptosis, Genomic instability, Cell migration
	HHV-8	Cell proliferation, Inhibition of apoptosis, Genomic instability, Cell migration
	HPV	Immortalization, Genomic instability, Inhibition of DNA damage response, Anti-apoptotic activity
	HTLV-1	Immortalization and transformation of T cells
	HIV	Induce B-cell activation
Indirect through chronic inflammation	HBV	Inflammation, Liver cirrhosis, Chronic hepatitis
	HCV	Inflammation, Liver cirrhosis, Liver fibrosis
Indirect through immunosuppression	HIV-1	Immunosuppression

Table 3

HPV-related oral lesions in adult patients

Authors & year	N	Gender (%)	Age (years-old)	HAART (%)	HPV-OL	
					Prevalence %	Type
HIV/AIDS adult patients						
(Estrella, 2015)	29	Male (93.1)	32.5–44	(89.6)	3.4	SCP, MEH, VV, CA
(Anaya-Saavedra et al., 2013)	787	Male (93.4)	27–40	(30.9)	6.9	SCP, MEH, VV
(Lourenco et al., 2011)	388	Male (61.6)	Mean: 38	(79.9)	0.6	MEH, CA
(Ortega et al., 2009)	1595	ND	ND	(57.9)	0.5	CA
(Giuliani et al., 2008)	130	Male (54.6)	Mean: 39.6	(79.2)	4.6	HPV-OL
(Kakabadze et al., 2008)	732	Male (82.2)	ND	ND	5.0	Oral warts
(Nunes Mde et al., 2008)	129	Male (100)	31–50	(77.8)	2.3	2 CA, 1 VV
NON HIV/AIDS adult patients						
(Robledo-Sierra et al., 2013)	6,448	Male & female	Adults	ND	<0.1	SCP
(Castellanos & Diaz-Guzman, 2008)	23,785	Male (31.2)	15–97	ND	0.29	SCP

SCP = squamous cell papilloma; MEH = multifocal epithelial hyperplasia; VV = verruca vulgaris; CA = condyloma accuminatum; ND = no data; HPV-OL = HPV-associated oral lesions.

Table 4

Histological antibodies and molecular targets and bodily fluids useful for the diagnosis of viral co-infections

	Histological Assays	Molecular Assays	
Virus	**Immunohistochemical Markers**	**Target**	**Specimen**
HSV-1	anti-HSV-1/2 pAb (CP108)	US5 Region	WMF, Plasma
HSV-2	anti-HSV-1/2 pAb (CP108)	Glycoprotein D (US6)	Plasma
VZV	anti-VZV gE mAb (ORF68, C90.2.8)	MBP (ORF29) / gpI (ORF67)	PBMC, Plasma
EBV	EBV-EBER and EBV-LMP	EBNA-1 / BALF5	WMF, PBMC
HCMV	anti-HCMV clone DDG9 + CCH2 mAb	UL83 gene / MIE region	WMF, PBMC, Plasma
HHV-8	NCL-HHV8-LNA (13B10)	ORF26 & ORF73	WMF, PBMC, Plasma
HPV	P16 IHC (p16INK4A); HPV16 IHC	Latent Protein 1	WMF, PBMC *

PBMC = peripheral blood mononuclear cells

* HPV is detectable in PBMC's but is controversial.