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Co-morbidities associated with HIV and antiretroviral therapy

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Abstract

In the era of combination antiretroviral therapy (ART), parsing out the effects of HIV versus ART on health outcomes is challenging. Nadir CD4 count, a marker of the extent of immunosuppression, has significant long-term impact on an array of disease states in HIV+ persons; however, in the dental literature, reporting of pre-ART exposure to immunosuppression has largely been ignored and this limits the validity of previous studies. In Workshop A1 we explain fully the importance of nadir CD4, pre-ART immunosuppression, and identify a need to include specific variables in future research. The questions posed herein are challenging, typically not neatly addressed by any one study and require integration of the latest evidence from the wider medical literature. We consider topics beyond the confines of the oral cavity and examine oral health in the complex context of ART-era HIV-immunopathophysiology. We depict how variability in geographic setting and time period (pre and post-ART era) can impact oral conditions — influencing when HIV infection was detected (at what CD4 count), the type and timing of ART as well as social determinants such as strong stigma and limited access to care. We hope our Workshop will stir debate and energize a rigorous focus on relevant areas of future research in HIV/AIDS.

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Introduction

Understanding, treating and preventing deleterious effects of HIV on the oral cavity of PLWHA across the lifespan will be a central focus of oral HIV-related research in the coming decades. This is and will be a challenging task because determining the effects of combination antiretroviral therapy (ART) on the human host is complicated by the residual effects of HIV-infection (Serrano-Villar et al., 2014b, Serrano-Villar et al., 2014a). These effects include ongoing immune, inflammatory and metabolic dysfunction that may be linked to the degree of exposure to immunodeficiency (Longenecker & Triant, 2014). Another concern is *confounding by indication*: do the characteristics of the individual on a specific ART regimen drive associations to clinical manifestations—or is it the ART treatment itself (Ahdieh et al., 2000, Lau B, 2009)? For example, are people who are taking a protease inhibitor (PI) more likely to have had a lower nadir CD4 count and thus have higher levels of ongoing immune activation after ART initiation? How do we control for such HIV-related variables and place the determinants of oral health and disease in a meaningful context? Research from the wider medical community provides guidance.

Extensive research has been conducted regarding cardiovascular (CVD) risk in HIV infected adults (Longenecker & Triant, 2014). Importantly, there are distinct differences in individuals (i.e., their CD4 count, level of HIV RNA, inflammatory profile and resulting immune competence) prior to and during ART (Torriani et al., 2008, El-Sadr et al., 2006),. and, by extension, entire cohorts examined prior to and during ART, as findings can be influenced by the stage of HIV infection and the effectiveness of ART. Presently, risk for CVD is thought to involve exposure to viral replication (levels of and host response to HIV RNA) (Freiberg et al., 2013, Triant et al., 2010), immunodeficiency (lower nadir CD4+ count) (Ho et al., 2012, Longenecker & Triant, 2014), chronic inflammation (increased levels of interleukin-6, high sensitivity C reactive protein) (Kuller et al., 2008, Duprez et al., 2012), altered coagulation (d-dimer dysregulation) (Duprez et al., 2012) and toxic effects of ART (especially older classes of ART) (Bavinger et al., 2013, Kelesidis & Currier, 2014). These findings can inform research in oral health.

A central concern in comparing studies of HIV+ adults is whether investigators have reported and statistically analyzed the *immunological framework* of the cohort (Vernon et al., 2011, Vernon et al., 2013); that is, have investigators thoroughly examined HIV-related exposures that can vary across different cohorts (i.e., nadir CD4 count, time since first seropositive, time on ART, type of ART and percent of subjects with “undetectable” plasma HIV RNA)? Examination of such factors may reveal important associations and allow for nuanced comparisons across studies and historical time periods (Vernon et al., 2013). Thus, to help differentiate between the effects of HIV and ART, the variables mentioned above should be collected, analyzed and reported in future oral health-related studies—or, if not included, this should be mentioned as a study limitation. If there are social or logistical barriers to obtaining and reporting these data, then such barriers should be documented to help promote more effective communication between medical professionals and dental researchers.

Recent reports suggest that CD4/CD8 ratio (Serrano-Villar et al., 2014b, Li et al., 2014) and viremia copy-years (Mugavero et al., 2011) may also reveal important associations related to ongoing effects of HIV during ART. How these factors influence HIV-related oral conditions is unknown.

Question 1

Current ARV regimes. [1.1.] Does ART have a direct effect on oral health (to influence [1.1.1] fungal, [1.1.2.] bacterial and [1.1.3.] viral infections)? [1.2] Can we rank current ART regimes according to their risk of causing or exacerbating oral disease? 1.3] Is this mediated by immune reconstitution inflammatory syndrome (IRIS) [1.3.1.] or via wider ART-associated co-morbidities [1.3.2] such as liver and renal dysfunction, hypertension, hyperlipidemia, diabetes and disturbed bone homeostasis?

[1.1.]

Currently recommended ART regimens are individualized and based on antiviral efficacy, results of resistance testing, possible adverse events, patient comorbidities, clinical considerations and cost (US Department of Health and Human Services (USDHHS), 2015a). For recommended and alternative ART regimen options, see Table 6 (treatment-naïve patients) and Table 7 (specific clinical scenarios) of *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults* at AIDSinfo.nih.gov/guidelines; updated April 8, 2015 These current guidelines greatly emphasize the use of integrase inhibitors as first line ART (US Department of Health and Human Services (USDHHS), 2015a). Since World Workshop 6 in 2010, four new ART medications are available: rilpivirine (RPV)/Edurant® (2011) a non-nucleoside reverse transcriptase inhibitor (NNRTI); dolutegravir (DTG)/Tivicay® (2013) an integrase inhibitor, and two combination tablets: Complera® (2011; includes: emtricitabine, rilpivirine and tenofovir DF) and Stribild® (2012; includes: (Elvitegravir, Cobicistat, emtricitabine and tenofovir DF). For a complete list, see AIDSinfo.nih.gov/guidelines (US Department of Health and Human Services (USDHHS), 2015a).

Direct, clinically observable effects of ART on oral health (independent of HIV and/or ongoing immune deficits during ART) can be mediated by changes in the oral microbiome and are challenging to quantify. For example, although there have been recent basic science reports on this topic (Yohannes et al., 2011, Ghosh et al., 2013), suggesting ongoing immune, cellular and metabolic dysfunction on ART, the clinical relevance of these findings is unknown. A translational study by Li et al, 2014 found that among 10 HIV+ adults, levels of oral microbial diversity in saliva increased during ART as compared to before ART (Li et al., 2014). While interesting, the clinical significance of this finding is unclear. Future results by the Malumud group of “Crosstalk,” a longitudinal translational study that links basic science measures of blood, saliva, oral biofilms and skin with clinical findings, may help illuminate this area of research (Phelan et al., 2014): importantly, if immunological deficits found in blood correlate consistently with biomarkers in saliva on an individual level across time, then salivary samples may prove to be a non-invasive surrogate measure of systemic deficits and/or improvement in immune function on ART.

[1.1.1.]

Initiating effective ART reduces the prevalence of candidiasis (Hodgson et al., 2006, Taiwo & Hassan, 2010). The prevalence, incidence and re-occurrence of other HIV-associated oral lesions during ART appears to vary by historical time period (i.e., by degree of viral suppression over the past 30 years; prior to and after effective combination ART), percent of cohort on ART (as well as percent with undetectable plasma HIV RNA) and by the geographic location of the study cohort (Patton et al., 2013). A recent longitudinal study in Alabama (USA) by Tami-Maury et al, 2011 reported that 36% of patients had, across two years, at least one baseline, new or recurrent HIV-associated oral lesion while on ART (Tami-Maury et al., 2011); thus, ART may diminish but not necessarily eliminate the risk for existing or new HIV-related oral lesions, including candidiasis (Taiwo & Hassan, 2010, Tami-Maury et al., 2011). Furthermore, a limitation of the Taiwo & Hassan study was that the mean HIV RNA level at end of study was 13,900 ±52,352 copies/ml and the percent of subjects who were virologically suppressed (<50 copies/ml) was not reported (Taiwo & Hassan, 2010); likewise, in the Tami-Maury study, only baseline HIV RNA level was reported (viral load was not considered as a confounding variable in this longitudinal study) (Tami-Maury et al., 2011). Researchers in future studies should, therefore, appreciate that being on ART is not the same as being virologically suppressed and, if possible (i.e., the cell size is large enough), analyse their data using virological suppression as a categorical cut point and/or confounding variable.

[1.1.2.]

Effects due to shifts in bacterial balance await the study findings referred to above in 1.1.

[1.1.3.]

The reported increase in the prevalence of oral warts during the ART era is controversial: results have varied across time and geographical setting with few recent longitudinal studies examining human papillomavirus (HPV)-subtypes (Patton et al., 2013). Long-term prospective studies using standardized methodology (Patton et al., 2013) are needed: investigating behaviours which can transfer micro-organisms between oral/oropharyngeal and genital surfaces (D'Souza et al., 2009, D'Souza et al., 2014) and assessing the relationship to critical immunological variables (i.e., the cohort's *immunological framework* (Vernon et al., 2011, Vernon et al., 2013)) may clarify this topic. The interaction of HIV with oncogenic HPVs is discussed under Question 4.

A large study of 8 HIV+ cohorts in the USA initiating ART between 1996 and 2011 revealed that the incidence of Kaposi's sarcoma (KS) and EBV-related lymphoma was highest immediately after initiation of ART and then declined (Yanik et al., 2013). KS remains a major problem in Sub-Saharan Africa, although the increased availability of ART has substantially reduced the incidence (Bohlius et al., 2014). Seropositivity to HHV-8 does not reduce the efficacy of ART in relation to HIV response (Maskew et al., 2013). KS, however, is difficult to treat, particularly in resource-poor settings, requiring cancer chemotherapy in addition to ART (Borok et al., 2010). Conversely, IRIS-associated KS is a well-recognised, treatable disease (Speicher et al., 2013).

Regarding other diseases caused by Human herpesviruses: there is clearly a reduction in the prevalence of EBV-driven oral hairy leukoplakia [OHL] in patients on ART but most studies are retrospective with differing ART regimes. Males are affected more commonly, e.g., in India (Rao et al., 2012) and in Brazil (Dongo et al., 2013), and the mode of transmission is mainly sexual (Nittayananta et al., 2010b). Co-infection of EBV in OHL with low-risk HPV was described in 7/21 cases from Venezuela (Correnti et al., 2010).

An outbreak of mucocutaneous Herpes Zoster can be an important component of IRIS (Haddow et al., 2012, Jansen et al., 2013), but ART significantly reduces episodes in the longer term.

CMV viremia is common in HIV patients, even during ART, particularly in developing countries such as Thailand (Durier et al., 2013) and this can produce serious diseases; e.g. gastroenteritis, retinitis and encephalitis. Oral ulceration may occur, but documentation is limited. The oral and systemic clinical relevance of low level CMV viremia is unclear and requires more study.

[1.2.]

From a clinical perspective, ART-associated side effects or diseases may be ranked according to severity of impact on patients' health and quality of life. A working list for clinicians to consider includes: i) life threatening conditions; while rare, some oral IRIS-related conditions [Kaposi's sarcoma (Papagatsia et al., 2009), lymphoma], viral-related oral cancers (Gillison, 2009), cutaneous toxicities (Stevens-Johnson syndrome (SJS)/severe erythema multiforme), as well as serious side effects/interactions with concomitant medications (US Department of Health and Human Services (USDHHS), 2015a, Diz Dios & Scully, 2014) must be managed promptly, ii) severe, treatment-refractory side effects (gastrointestinal disturbances, renal or hepatic injury, rashes, hypersensitivity reactions, insulin sensitivity and lipoatrophy/lipohypertophy) (Calmy et al., 2007, US Department of Health and Human Services (USDHHS), 2015a) could interfere with ART compliance and — as per the SMART Study (Lundgren et al., 2008) — treatment interruptions can accelerate negative systemic and thus oral consequences, iii) chronic oral conditions that negatively impact a patient's quality of life including, for example, hyperpigmentation on lips of African patients — i.e., noticeable lesions that can reveal HIV-status; (for a comprehensive list, see Diz Dios and Scully, 2014, Tables 2–5 (Diz Dios & Scully, 2014), iv) xerostomia due to it's being a common side effect of many antiviral medications and/or concomitant medications (Patton, 2013, Diz Dios & Scully, 2014); can increase risk for dental caries, fungal infections and periodontal disease (Ram et al., 2011), and, v) other benign or superficial conditions that do not bother the patient (e.g., intra-oral hyperpigmentation, not visible to others). Practitioners and researchers alike should be careful to avoid bias in linking a benign condition to HIV (unless it can be established that the condition occurred following HIV-infection and/or abates on ART). The above list should be considered relative, fluid and evolving. For treatment recommendations, see Patton's 2013 review (Patton, 2013).

[1.3.1]

The topic of (IRIS) was well covered at World Workshop 6 (see Tappuni, 2011 and Ramirez-Amador et al, 2011) (Tappuni, 2011, Ramirez-Amador et al., 2011). Briefly, IRIS is a transient, newly-emerging or worsening clinical condition occurring during a steep decline in HIV viremia, typically during initial, effective ART (Tappuni, 2011). Oral conditions in IRIS are not well studied. Ramirez-Amador et al, (2009) reported, in a longitudinal study, that oral candidiasis, hairy leukoplakia and recurrent oral ulcers are possible oral manifestations of IRIS (Ramirez-Amador et al., 2009); however, such conditions could also occur by coincidence, as suggested by Tami-Maury et al, 2011 (see above) (Tami-Maury et al., 2011). Further defining oral lesions related to IRIS, including their onset, duration and clinical presentation, is an open area of research.

[1.3.2.]

Elevated rates of liver (Price & Thio, 2010) and kidney (Islam et al., 2012) diseases, hypertension (Peck et al., 2014), diabetes (Zhang et al., 2014) and disturbed bone homeostasis (Barkhordarian et al., 2011, Arora et al., 2010, Ofotokun & Weitzmann, 2011) in HIV+ adults are well documented. These systemic diseases are influenced by HIV and ART; however, persons with HIV infection may also have high levels of traditional risk factors (Volberding & Deeks, 2010) such as (older) age, male gender, smoking, genetic predisposition/family history, being overweight, dietary contributions and a lack of physical activity (US Department of Health and Human Services (USDHHS), 2015b)); thus, these potential confounding variables should be examined to avoid spurious associations between these conditions and ART. Regardless, the degree to which these secondary systemic illnesses (resulting from HIV-infection) further contribute to oral disease is presently unknown and may be difficult to measure.

ART clearly improves immune and systemic health in previously ART-naïve subjects with a compromised immune system (Volberding & Deeks, 2010). In a large study by the AIDS Clinical Trial Group (ACTG), 20% of ART-naïve subjects had metabolic syndrome (MetS) at baseline and after 96 weeks on ART, 37% of these cases no longer met the definition of MetS: this decrease in MetS was largely mediated by increased HDL cholesterol (Krishnan et al., 2015). Torriani et al, 2008, established that ART initiation improves flow mediated dilation (FMD; i.e., endothelial function, as measured in the brachial artery) in previously ART-naïve subjects (Torriani et al., 2008). However, even with these health improvements, HIV can have lingering detrimental effects, both immunological and physiological, during ART and these probably contribute to premature age-related diseases (Volberding & Deeks, 2010).

[1.3.2.]

Immunodeficiency, viral replication and ART can all contribute independently to dyslipidemia in HIV+ adults (Kelesidis & Currier, 2014). ART-promoted alterations in lipid profiles can vary between and within classes of ART (Kelesidis & Currier, 2014). Lipid alterations can have a direct or indirect immunoregulatory effect by contributing to immune activation, inflammation and insulin resistance (Kelesidis & Currier, 2014) that can increase the risk for cardiovascular disease (Kelesidis & Currier, 2014): whether such changes can

increase the risk for oral diseases is, to our knowledge, unknown. Longitudinal changes in HDL cholesterol level may be an important variable on which to focus (Krishnan et al., 2015) during future oral health-related research.

Question 2

What are the particular effects of ART on hard tissues, especially maxillofacial bones [2.1.1.] and teeth [2.1.2.], and how does this influence the progression of periodontal disease [2.2.], risk of osteonecrosis [2.3.1.] and dental caries [2.3.2.]?

[2.1.1.]

HIV-associated immunopathology has been related to reduced bone mineral density (BMD) (Gutierrez & Masia, 2011, Arora et al., 2010), resulting in an increasing risk for osteoporosis (Brown & Qaqish, 2006) and bone fracture in HIV-infected individuals (Triant et al., 2008). For example, both HIV and ART may disturb the osteoclast-osteoblast equilibrium that, in sum, favors the destructive forces of osteoclast activity (Barkhordarian et al., 2011, Ofotokun & Weitzmann, 2011). A recent, singular report found that mandibular BMD in menopausal HIV+ women may be reduced in comparison to older HIV-negative women (Caputo et al., 2013).(Caputo et al., 2013). While low BMD (osteopenia) of the hip and spine in HIV+ adults has been studied extensively (Cotter & Mallon, 2014, Erlandson et al., 2014, Compston, 2014), orofacial bones have not been studied in the same detail.

[2.1.2.]

Direct clinical effects of HIV on teeth are largely unknown; however, HIV (Nittayananta et al., 2010a) and/or ART-associated xerostomia (Nittayananta et al., 2010c) could increase the risk for dental caries (Ram et al., 2011). Further, it is presently unknown whether immunosuppression-associated gingival recession (Vernon et al., 2009, Vernon et al., 2013, McKaig et al., 1998, Robinson et al., 1996, Alves et al., 2006) (especially when coupled with xerostomia) could increase the *long-term* risk for root caries and/or tooth loss.

[2.2.]

Exposure to HIV-related immunosuppression (i.e., a low nadir CD4 count) can strongly influence risk for adverse clinical outcomes including CVD (Hsue et al., 2004, Ho et al., 2012), low BMD (osteopenia) (Ofotokun & Weitzmann, 2011, Barkhordarian et al., 2011) and periodontal disease (PD) (Vernon et al., 2009, Vernon et al., 2013, Pattrapornnan & DeRouen, 2013). In a cross-sectional study of 112 HIV+ adults in the USA, Vernon et al, 2009 found that a CD4 count <200 cells/μl had nearly twice the (negative) effect on clinical attachment level (CAL) ($p<0.001$) than did smoking, a well-established risk factor for PD (Vernon et al., 2009). Importantly, the median nadir CD4 count of this cohort was 172 cells/μl (Vernon et al., 2009), which reflects, across continents around the entire world, the median CD4 count at start of ART in the past decade (Egger, 2007). Likewise, other studies support the association between reduced CD4 count and increased gingival recession and/or clinical attachment loss (McKaig et al., 1998, Robinson et al., 1996, Alves et al., 2006). A recent study by Aichelmann-Reidy et al, 2010, did not support this association (Aichelmann-Reidy et al., 2010); however, this group did not report nadir CD4 count, a critical variable

linking HIV to PD (Vernon et al., 2013). Overall, ART appears to minimize the detrimental effects of HIV on periodontal disease; however, the *long-term* effects (i.e., >5 to 10 years) resulting from pre-ART associated gingival recession (Vernon et al., 2009, Vernon et al., 2013, McKaig et al., 1998, Robinson et al., 1996, Alves et al., 2006) on PD progression and tooth loss are not known.

[2.3.1.]

Evidence linking ART to osteonecrosis of the jaws (ONJ) is limited. Only recently has the use of bisphosphonates as a strategy to reduce bone loss in HIV+ adults been studied longitudinally; thus, longer-term adverse consequences of this treatment strategy are still unclear (Pinzone et al., 2014, Lin & Rieder, 2007). There has been a case series report from West Africa of five HIV+ individuals with osteonecrosis or osteomyelitis of the jaw (Khullar et al., 2012) and, further, one case report from the USA of focal osteonecrosis developing after intraosseous anesthesia with related iatrogenic trauma (Woodmansey et al., 2009). Since case reports and case series reports represent a low level of evidence, these associations should be considered with caution until stronger evidence has been published. Corticosteroid use (Wallis et al., 2003) especially while taking protease inhibitors may increase the risk for osteonecrosis (Penzak et al., 2005). At present, the long-term risk for ONJ in HIV+ persons is unknown.

[2.3.2.]

In general, the topic of dental caries in HIV+ *adults* has not been well studied and remains controversial (Nittayananta et al., 2010c). (For dental caries in children, see Workshop A2.) Liu et al, 2012 found higher levels of *mutans streptococci* and lower levels of salivary flow in HIV+ adults compared to HIV-negative adults; this group also found a positive correlation between increased CD8+ counts and increased levels of *mutans streptococci* (Liu et al., 2012). The clinical significance of these associations is not yet known.

Finally, it should be noted that currently there is no evidence to suggest that different ART agents have differential effects on maxillofacial bones and teeth.

Question 3

What oral soft tissue conditions are caused or exacerbated by ART [3.1]? How can these risks be minimised and how should the conditions be managed [3.2]?

3.1

The recent review by Diz Dios and Scully, 2014 notes that clinically-observable side effects on orofacial soft tissues related to ART are based on few clinical studies, case reports and package inserts (Diz Dios & Scully, 2014):information regarding this topic has serious limitations. Extra-oral complications linked to ART include erythema multiforme, perioral paraesthesia, parotid lipomatosis and facial lipoatrophy; whereas, intra-oral complications include hypersensitivity reactions, oral ulcers, xerostomia, parotid lipomatosis and taste disturbances. (Diz Dios & Scully, 2014). Clinical presentations may vary by geographic locations. For example, settings using older generation ART (i.e., stavudine, didanosine and

zalcitabine) and/or treat patients at a lower nadir CD4 count, may experience higher levels of facial lipoatrophy, a stigmatizing condition that can further impact a patient's quality of life (Nair et al., 2011).

Severe ART toxicities are possible. Prior to initiating abacavir, genetic screening for the presence of HLA-B*570 is essential, as this gene is strongly linked to abacavir hypersensitivity syndrome (AHS) in both black and white populations (Pavlos & Phillips, 2012) (US Department of Health and Human Services (USDHHS), 2015a); AHS can cause a rapidly progressing multi-organ system failure that can cause death related to hypotension (Introcaso et al., 2010a). Case reports have linked nevirapine to oral ulcers and generalized exanthematous pustulosis that resolve upon drug discontinuation; SJS is also associated with nevirapine, which is one of the more common causes of SJS in the developing world where it is used more frequently (Introcaso et al., 2010b). For more information on access to effective ART, see question 6, below.

While ART can improve oral conditions, it is not a panacea (see 1.1.1, above). In a longitudinal cohort of Nigerian HIV+ adults initiated on ART, Taiwo and Hassan (2010) found that pseudomembranous candidiasis strongly declined at one month and all forms of candidal infections disappeared by month three; other lesions such as OHL, oral hyperpigmentation, parotid gland enlargement and KS decreased slowly in size or extent but few (except some OHL cases) had completely resolved by six months (Taiwo & Hassan, 2010).

Existing data on xerostomia during ART come largely from a few cross-sectional studies in the early 2000's; thus, these data maybe based on outdated and/or not fully effective ART regimens. Navazesh et al, (2000) found that HIV+ women had higher rates of dry mouth complaint, absence of saliva upon palpation and zero unstimulated whole saliva (p=.02) than HIV-negative women (Navazesh et al., 2000). Bretz et al, (2000) found that HIV+ patients on ART had lower salivary flow rates than those not on ARV (p=0.00001) and subjects on ARV had fewer dental caries (as compared to 1990 NHANES data); however, approximately 40% on ART were also on antimicrobials (Bretz et al., 2000). There are more recent cross-sectional studies: Jeganathan et al, 2012, found increased dental caries and poorer oral health related quality of life in HIV+ adults from Australia who reported xerostomia (38 of 100 patients) — of which, 87% had HIV RNA <50 copies/ml (Jeganathan et al., 2012). Nittayanata et al, 2010 found unstimulated and stimulated salivary flow rates of HIV+ adults on ART in Thailand were significantly lower ($p<0.05$) than those not on ART (Nittayananta et al., 2010a). The long-term effects of reduced salivary quantity and/or quality on oral conditions in HIV+ adults on ART are unclear.

[3.2.]

For oral disease management and treatment options, see Patton, (2013) (Patton, 2013). For the management of xerostomia and salivary gland-related pathologies, see Nittayananta et al, (2013) (Nittayananta et al., 2013)

Question 4

Do HIV-infected patients have a higher risk of developing oral and/or oropharyngeal cancer? [4.1] What are the mechanisms? [4.2] (Distinguish between common cancers of ageing in PLWHA enjoying increased lifespans, and the associated lifestyle risk factors, versus biological synergisms with HIV disease) [4.3] What are future research needs? [4.4]

AIDS-defining vs non-AIDS defining cancers in HIV positive populations

[4.1]—Annually there are 14 million new cases of cancer and over 8 million people die from cancer worldwide, with 60% of deaths in Africa, Asia and Central and South America (World Health Organization (WHO), 2015a). AIDS has made a significant impact on the types and distribution of such cancers. There is inconsistency in the literature as to which neoplasms should be regarded as AIDS defining. The distinction is important in an era when effective ART is available to many, so that the common cancers of ageing are rising in incidence in PLWHA due to their increased life expectancy and exposure to environmental carcinogens. There are considerable geographical differences in the epidemiology.

AIDS-defining cancers are those which are rare in HIV-negative populations, and/or have much earlier age of onset in PLWHA. The susceptibility to these cancers is greatly enhanced by immunosuppression: in other words, they are caused by an infectious agent, predominantly viruses. Understanding any molecular synergisms between oncogenic viruses and the biology of HIV itself is an important field of research, that between Human Papillomaviruses [HPV] and HIV being an important example.

A “short-list” of cancers with increased risk in PLWHA in the USA includes (Carr, 2013):

- Kaposi’s sarcoma [KS]: Increased risk by a factor of several thousands; aetiological agent HHV-8
- Non-Hodgkin lymphoma [NHL]: Increased risk ~>77; EBV
- Anal squamous cell carcinoma: X ~29; oncogenic genotypes of HPV [predominantly HPV 16, 18]
- Hodgkin lymphoma: Increased risk ~11; EBV
- Cervical squamous cell carcinoma: Increased risk ~6; HPV 16, 18
- Hepatocellular carcinoma: Increased risk ~5; HBV, HCV
- Non-small cell lung cancer: Increased risk ~3

The scientific community was slow to recognise the role of infectious agents in human carcinogenesis, in spite of knowledge in experimental animals. We now know that a substantial burden of human cancers are caused by viruses, more than two million cases per annum worldwide (Oh & Weiderpass, 2014). ART has dramatically decreased the incidence of KS and NHL, but non-AIDS-defining malignancies, such as lung cancer, hepatocarcinoma, anal cancer, head & neck and skin cancers, remain a major cause of morbidity and mortality in the HIV-infected population (Gobert et al., 2014). A recent systematic review (Cobucci et al., 2015) has calculated that HAART has reduced the risk for

the development of KS to a relative risk of 0.30 (95% CI: 0.28–0.33) and NHL by half (RR=0.52, 95% CI: 0.48–0.56), but less so for invasive cervical cancer (RR=1.46, 95% CI: 1.09–1.94). For non-AIDS-defining cancers, the overall risk has doubled (RR=2.00, 95% CI: 1.79–2.23). This latter imposes a considerable public health and cost burden, particularly for the African continent (Adebamowo et al., 2014). KS, Burkitt and other lymphomas are a major burden in HIV-positive children in Africa (Davidson et al., 2014).

Apart from viruses, there is renewed interest in the importance of a wider microbiome, including the bacteriome, in the pathogenesis of oral cancer (Wang & Ganly, 2014).

Kaposi's sarcoma and other HHV-8 related disorders as AIDS-defining: implications for the oral/dental research community

HHV-8 is the definitive aetiological agent of KS, of Multicentric Castleman's disease [MCD], and Primary Effusion Lymphoma. KS is the most common, and AIDS-associated KS is particularly common in the head and neck, including the oral cavity. Small dusky vascular patches on oral mucosa of the palate and gingiva have frequently been a first sign of HIV disease. We have shown that KS and MCD can exist in the same lymph node and have hypothesised a progressive model of HHV-8 disease (Speicher, 2013).

The diagnosis of KS in the oral cavity is challenging because the clinical appearances can be similar to non-specific inflammatory or reactive lesions such as pyogenic granuloma. Histopathology alone does not always allow confident diagnosis and this can create problems in countries with a high prevalence of HIV. Confirmation of the presence of HHV-8 can be obtained by PCR (Speicher & Johnson, 2012, Speicher & Johnson, 2014) and by immunochemistry with monoclonal antibodies to unique HHV-8 antigens [the anti-LANA-1 antibody is most satisfactory]. However many countries, e.g., across Sub-Saharan Africa, are resource-constrained: neither tool may be available and we have shown that PCR is dangerous because of contamination in busy laboratories (Speicher et al., In Press).

For reasons not yet understood, KS is extremely rare in the Indian subcontinent. We were the first to show a significant sero-prevalence of HHV-8 amongst HIV-positive patients in South India, ~11% (Speicher et al., 2014), recently confirmed in a North Indian cohort (Munawwar et al., 2014).

[4.2] Head and Neck squamous cell carcinomas in the ART era

Parkin calculates that the burden of cases of head and neck cancer in the UK population, in 2010, attributable to HPV was ~8% for the oral cavity, 11% for the larynx and ~14% for the oropharynx (Parkin, 2011). HPV-related HNSCC is increasing dramatically in most Western countries, where it is now regarded as a sexually transmitted disease. Fortunately, most of these respond well to treatment, particularly to radiotherapy, so that such cases have a relatively good prognosis, permitting de-intensification of treatment protocols. However there are fewer data on this situation in patients who also happen to be PLWHA. Large clinical trials are needed. In the USA there exists the AIDS Malignancy Consortium which manages such trials and they continue to recruit (ClinicalTrials.gov, 2015). There are treatment guidelines from Britain (Bower et al., 2014). There is a need for such trials in Africa and Asia.

In Kenya, oral SCC presents earlier than usual in PLWHA (Butt et al., 2012).

Quantifying the increased risk of H&N SCC in an HIV-positive subject requires further work. The contribution to risk profile from carriage of an oncogenic strain of HPV, degree of immunosuppression/HIV-disease profile, presence of “traditional” risk factors including tobacco use, alcohol abuse, marihuana use, poor diet, limited access to care, *inter alia*, requires more large studies. The mix of risk factors is likely to vary from country to country and between different routes of having acquired HIV. Perhaps somewhat surprisingly, a large population/cohort study from Denmark showed no interaction between smoking and HIV in risk for cancer (Helleberg et al., 2014). Detection rates will also be sensitive to method of sample collection and method of identifying, quantifying and typing HPV.

The risk of H&N SCC, as with anal and other HPV-driven cancers, is increased in MSM with persistent carriage of oncogenic HPV (Brickman & Palefsky, 2015). In a study of 500 MSM in Melbourne, half of whom were HIV-positive, HPV of any genotype was detected in the mouth in 19% of HIV-infected men and 7% of HIV-negative men: oncogenic HPV-16 in 4.4% of positive but only 0.8% of HIV negative men. Oral carriage of HPV was associated with current smoking, time since tooth-brushing, and number of both lifetime tongue-kissing partners and lifetime oral-penile sex partners. HPV 16 and 18 persisted in 10 of 12 men after a median six months, indicating risk of cross infection (Read et al., 2012).

In a smaller study in Thailand by the Nittyananta group (Amornthatree et al., 2012), using qPCR for detection of the HPV-16, E6 oncogene in stimulated saliva samples, a much higher carriage rate was recorded. Of 46 HIV-positive subjects, 37 (80%) were positive for E6 compared to 9/46 (20%) of HIV-negative controls. The use of ART and its duration did not significantly affect the prevalence and the copy numbers of the virus.

Interactions between chemotherapy for cancer and for HIV disease

For effective treatment of AIDS-defining neoplasms such as NHL and KS, ART alone may suffice: both a nucleoside analogue and a protease inhibitor are necessary (Clayton et al., 2006). For non-AIDS neoplasms, efficacy and side-effects may vary widely according to type of ART and the particular cancer chemotherapeutic agent. Cytotoxic agents further depress immunity in AIDS patients, encouraging the search for targeted molecular anticancer therapies–consistent with the current drive to personalized medicine. However for the most common H&N malignancy of concern to the dental/ oro-maxillofacial community, namely SCC, the only FDA-approved molecular therapy is, at the time of writing, monoclonal antibodies against EGFR [epidermal growth factor receptor].

Pharmacological interactions between antiretroviral and antineoplastic therapies were comprehensively reviewed by Rudek et al in 2011 (Rudek et al., 2011) but limited guidance is available to clinicians even now (Beumer et al., 2014). Multidisciplinary teams are needed to co-ordinate patient care. Multicentre trials are clearly needed to provide an evidence base for H&N/oral physicians [see section 4.3].

[4.3.] Molecular synergisms between HPV and HIV

As Konopnicki et al summarise: *HIV infection favours HPV at the molecular and cellular levels during the various phases of the HPV cycle, including penetration of HPV into the target cell, HPV replication and HPV immune escape from host defences (2013).*

- *In ex vivo models of oral and cervical epithelial cells in tissue explants from HIV-uninfected patients, the adjunction of HIV proteins (tat and gp120) with cytokines produced by HIV-infected cells (TNF-[alpha] and IFN-&gamma) induces disruption of epithelial tight junctions and potentiates HPV penetration into basal epithelial cells, which are HPV targeted cells* (Tugizov et al., 2013).
- *It has long been known that during HPV replication, HIV tat protein significantly enhances HPV transcription and thus the expression of the HPV E oncogenes and L capsid proteins in cell cultures*, including studies utilising human oral keratinocytes (Syrjanen, 2011, Kim et al., 2008).
- *To escape immune surveillance, HPV is able to induce a shift to T helper-type (Th) polarization from Th1 to Th2, with a parallel shift into cytokine production. When HIV infection progresses to AIDS, the same shift from Th1 to Th2 cytokine profile occurs in cervico-vaginal secretions, and may contribute to HPV persistence* (Goncalves et al., 2009). Clearly the same mechanism could occur in the upper aero-digestive tract (Fakhry et al., 2013).

Molecular synergisms between HIV and HHVs

HIV-associated disruption of tight and adherens junctions of oral epithelial cells facilitates HSV-1 infection and spread (Sufiawati & Tugizov, 2014). Reciprocally, HSV-2, and presumptively HSV-1, increase the likelihood of HIV entering [genital and] oral epithelia by the production of microlesions, allowing interaction of HIV with dendritic cells and the acquisition of HIV infection (Suazo et al., 2014): Proinflammatory cytokines are generated, enhancing disease with both viruses.

[4.4] Research needs

Future research needs include large-scale epidemiological studies, with multiple arms, to quantify the: 1) increased risk of H&N SCC in diverse HIV-positive populations,, 2) effects of HPV vaccination on H&N cancer incidence: population studies, 3) efficacy of preventative/therapeutic HPV vaccination against HPV in both males and females: cohort studies, 4) carriage of oncogenic HPVs in mouth and oropharynx of HIV-positive versus HIV-negative — and effects of ART on carriage using a nested within-subject pre/post ART study design, 5) assessment of treatment regimens for HPV-related HNSCC in PLWHA: multi-centre clinical trials, 6) carriage/shedding/infectivity/synergisms of HPV, EBV, KSHV, HSV, HCV in/from upper aearodigestive tract — and risks for and mechanisms of increased infectivity between HIV and other viruses: translational studies, and 7)to closely monitor HPV vaccine trials for the likely reduced incidence of H&N SCC. Further, basic science studies should be conducted on: 8) the molecular mechanisms of HPV/HIV synergy, 9) the way various clades of HIV-1 and HIV-2 interact with oncogenic HPVs and with HHVs:

especially in cell and organotypic cultures and in animal models. Regarding all of the above, there is a need to: 10) translate pertinent results into public health policy.

Question 5

What is known about reservoirs of HIV RNA and DNA [5.1] in different anatomical compartments: CNS [5.2]; lymph nodes [5.3]; MALT [5.]; bone marrow, thymus; spleen [5.5] and genital fluids [5.6]? With a focus on Waldeyer's ring, what is the risk of shedding competent virus into oral fluids and what are the implications for transmission [5.7]?

[5.1.]

HIV reservoirs, both cellular and anatomical, contain latent but viable HIV RNA and DNA that evade ART and the immune system (Smith et al., 2012). Cellular reservoirs primarily include resting central/transitional memory CD4+ T cells, and, while controversial, may also include naïve T cells,, monocytes and macrophages, astrocytes and follicular dendritic cells (Keele et al., 2008, Smith et al., 2012). Anatomical sites include Mucosa Associated Lymphoid Tissue (MALT)—which includes the gastrointestinal (GI) tract and Gut Associated Lymphoid Tissue (GALT)—a major anatomical reservoir for HIV (Lafeuillade et al., 2014)–and lymphoid organs/tissues, blood, bone marrow(Carter et al., 2010), central nervous system (CNS), genitourinary (GU) tract and lungs (Smith et al., 2012, Jambo et al., 2014). The ring of Waldeyer, a component of MALT, consists of the palatine tonsils, pharyngeal tonsils (adenoids), lingual tonsils, tubal tonsils and lateral pharyngeal bands (Hellings et al., 2000), is rich in lymphoid tissue and is important given its proximity to the oral cavity and its potential for HIV shedding and transmission (see 5.7., below).

Even with regimen intensification, ART cannot entirely eliminate HIV from the human host (Lafeuillade et al., 2014). Once ART is stopped, the virus is thought to rebound in all patients (Lafeuillade et al., 2014). A French cohort, however, has identified 20 people, termed post-treatment controllers—persons who initiated ARV early during primary HIV infection—and were able to maintain undetectable levels of HIV RNA for several years after discontinuation of ART; such a finding offers hope for long-term control off ART on a broader scale (Saez-Cirion et al., 2013, Rouzioux et al., 2015). Regardless, viral persistence —ongoing viral replication, activation or homeostatic proliferation (Lafeuillade et al., 2014)) —occurs due to latently infected cells containing integrated but dormant HIV provirus (Smith et al., 2012). ART can inhibit viral replication (Marsden & Zack, 2013) and stop the virus from spreading to new cells but has no direct effect on an integrated HIV provirus (Marsden & Zack, 2013). ART classes may have differential effectiveness on different cell types (eg. T cells v macrophages) (Smith et al., 2012); further, compartments (blood, genital tract and saliva) can have different levels of detectable HIV RNA and these levels can vary by gender (most notably in the genital tract—i.e. seminal fluid v endocervical wicking and cervical vaginal lavage) (Kantor et al., 2014).

[5.2.]

The CNS is regarded as a reservoir because the blood-brain barrier restricts access of ARVs and HIV-specific immune cells (Smith et al., 2012, Churchill & Nath, 2013). Further, the

HIV resides in microglial cells and possibly also in astrocytes, some of the longest living cells in the human body (Churchill & Nath, 2013). Thus, compartmentalized in the brain, HIV evolves to more effectively infect macrophages (cells with low CD4 expression), becoming more neurovirulent (Churchill & Nath, 2013) and potentially leading to clinically significant neurocognitive impairment despite optimal ART treatment (Heaton et al., 2011).

[5.3.]

Lymphocytes (T cells and B cells) are concentrated in lymph nodes and lymphatic tissue. Resting $CD4^+$ T cells containing integrated HIV DNA circulate through lymph nodes making lymphatic tissue an important, albeit understudied, reservoir (Smith et al., 2012). Several ARVs (i.e., emtricitabine triphosphate, atazanavir, efavirenz) may not reach the lymphoid tissues effectively, allowing continued viral propagation at levels potentially insufficient to select for resistance but perhaps sufficient to replenish the reservoir (Cohen, 2011, Fletcher et al., 2014).

The GI tract and the spleen are significant reservoirs wherein concentrations of HIV DNA, as well as cell-associated unspliced HIV RNA—are ~5–10 times higher than in peripheral blood mononuclear cells (Smith et al., 2012). While GALT is a key reservoir, the GI tract, according to a phylogenetic study by Lerner et al, 2011, is not the primary source of rebound (post-ART interruption) viremia (Lerner et al., 2011).

[5.4.]

For MALT, see 5.1, 5.6 and 5.7.

[5.5]

While an ex-vivo experiment found that HIV-1 was able to utilize the CXCR4 chemokine receptor to infect long-lived hematopoietic stem cells (Carter et al., 2010), the finding was largely discredited by an in-vivo study that did not find HIV DNA in highly purified cell fractions of bone marrow aspirates taken from persons with HIV infection; thus, there is no evidence that hematopeietic progenitor cells can form a reservoir in-vivo (Durand et al., 2012). Once HIV RNA is detected in peripheral blood, the HIV reservoir persists (Wightman et al., 2010, Fabre-Mersseman et al., 2011). Importantly, lymphocytes travel among most other cells; they circulate in blood and lymph and are present in large numbers in the thymus, bone marrow, lymph nodes, spleen and appendix. However, only a small proportion of resting memory CD4+ T cells contain integrated viral genome (Eriksson et al., 2013).

In a study of rhesus macaques infected with recombinant simian immunodeficiency virus containing the RT coding region from HIV-1 (RT-SHIV) and treated with ART, the predominate reservoirs of viral RNA and DNA were found in the spleen, lymph nodes and GI tract (North et al., 2010).

[5.6.]

During ART, i.e., when virus was suppressed in the plasma, HIV RNA was detected in semen in 8%–10% of men and in genital tract secretion from 54% of women—suggesting a

residual reservoir.. However, the exact source (i.e., the testes or prostatic fluid of ejaculate) of this virus remains unclear (Smith et al., 2012).

[5.7]

Waldeyer's ring is MALT located at the gateway of the respiratory and alimentary tract. To date, studies implicating Waldeyer's ring have focused on oropharyngeal fluids and basic science experiments using cell lines.

Pavlinac et al, 2012 found that 63% of ART-naïve subjects had detectable HIV in saliva; this study also linked the level of HIV RNA in saliva to plasma HIV viral load, as have others (Pavlinac et al., 2012). Previous studies that included participants both on and off ART have shown 38–100% detection rates of HIV-1 RNA in saliva; however, whether the detected HIV genome was viable for transmission was not assessed.

Kohil et al, 2014, exposed oral epithelial cell lines to HIV-1 and found no integration of the viral genome into the epithelial cellular machinery and no de novo viral production; however, when using an endocytic entrance pathway, these cells could support and transfer HIV-1 infection to adjacent permissive cells (see Workshop B1 or B2) (Kohli et al., 2014). Similar results have been reported using oral keratinocytes (Herzberg et al., 2011). These studies (Herzberg et al., 2011, Kohli et al., 2014) and others (Johnson et al., 2014) suggest that, under certain circumstances, transmission via oral fluids may be possible. However, anti-HIV mechanisms found in saliva are well documented (Weinberg et al., 2011) and the available data suggest that the oral transmission rate of HIV is low (Patel et al., 2014). Nonetheless, in order to better understand the potential for mouth to mouth and oro-genital sexual HIV transmission, the biological mechanisms involved in oral transmission and resistance to infection should be further explored.

Question 6

Changing concepts of cure: Eradication of HIV v Functional Cures/Remission [6.1]. How does the [uneven] availability of ART increase or ameliorate inequalities in oral health around the world [6.2]? How can such inequalities be addressed [6.3]?

[6.1]

Eradicating HIV vs Functional cure:

The concept of eradicating HIV has gained much attention lately because combination anti-retroviral therapy (ART) is extremely effective in suppressing viral replication; however, it is not curative (De Crignis & Mahmoudi, 2014).

While patients are on ART, reservoirs of latent HIV infected cells persist at both the anatomical and cellular levels. With such persistent and stable reservoirs, the virus is able to escape from the effects of the ART medicines and continue to release its progeny into the blood; thus, a cure of complete eradication is not achievable (De Crignis & Mahmoudi, 2014, Finzi et al., 1999). Targeted delivery using nanoparticles is a promising development

to infiltrate these reservoirs. Without suppressive therapy (ART), viral rebound would occur, thus patients need to be on a lifelong medication regimen (Finzi et al., 1999).

Efforts to achieve a cure have been boosted by reports of the “Berlin patient” who was transplanted with hematopoietic stem cells harboring a mutated form of the CCR5 receptor (Josefsson et al., 2013, Allers et al., 2011). This patient showed undetectable levels of HIV RNA, DNA or replication-competent virus after discontinuing ART for multiple years (Henrich et al., 2013). The “Mississippi baby” depicts another case wherein high-dose ART was administered 30 hours after birth and there were no signs of viral replication for 2 years after discontinuance of ART — however, a viral rebound was later noted (Persaud et al., 2013, National Institutes of Health (NIH), 2014).

The above cases illustrate that a cure is achievable in HIV patients, either constituting complete eradication of the virus (sterilizing cure), or the control of viral load in the absence of ART for prolonged periods of time (functional cure) (De Crignis & Mahmoudi, 2014). This implies that a cure can only be achieved by reducing the size of the latent reservoirs in HIV infected patients or by complete eradication of the latent reservoirs.

[6.2]

Global inequalities in oral health persist, both between and within different regions and societies and they undermine the fabric, productivity and quality of life of many people around the world (Sgan-Cohen et al., 2013). For equitable health delivery, all sectors must be engaged in determining health issues (Sheiham et al., 2011). This calls for an understanding of the social determinants of health and the social gradient in order to better address multi-layered, underlying causes of disease linked to social hierarchy and the resulting socially determined conditions in which people live and interact (Sgan-Cohen et al., 2013, Marmot & Bell, 2011). Studies from both the Americas and Europe have reported a decrease in the frequency of HIV-related oral manifestations of 10–50% following the introduction of ART. Studies from both the Americas and Europe have reported a decrease in the frequency of HIV-related oral manifestations of 10–50% following the introduction of ART (Tappuni & Fleming, 2001, Hodgson et al., 2006); however, a more recent study in 2010, noted that 36% of subjects on ART had HIV-related oral lesions (Tami-Maury et al., 2011). For more discussion, see section 1.1.1, above.

[6.3]

Inequalities can affect all aspects of oral health. The uneven availability of ART adversely affects the general health of affected populations and further concentrates severe HIV-related illnesses in resource limited settings that are least able to mount an effective response—thus magnifying inequality. These inequalities can be ameliorated by addressing the social determinants of health (Watt, 2005, World Health Organization (WHO), 2015b) and by integrating oral health with general health.

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Questions

1. Current ARV regimes: Does ART have a direct effect on oral health? Can we rank current ART regimes according to their risk of causing or exacerbating oral disease? Is this mediated by IRIS or via wider ART-associated co-morbidities such as liver and renal dysfunction, hypertension, hyperlipidemia, diabetes and disturbed bone homeostasis? Original presentation by Marilena Komesu (Brasil).
2. What are the particular effects of ART on maxillofacial bones and teeth? How does this influence progression of periodontal diseases, risk of osteonecrosis and dental caries? Original presentation by Lance Vernon (USA).
3. What oral soft tissue conditions are caused or exacerbated by ART? How can these risks be minimised and how should the conditions be managed? Original presentation by Raj Nair (Australia).
4. Do HIV-infected patients have a higher risk of developing oral and/or oropharyngeal cancer? What are the Mechanisms? (Distinguish between the common cancers of ageing in people living with HIV/AIDS (PLWHA) enjoying increased lifespans, and the associated lifestyle risk factors, versus biological synergisms with HIV). What are future research needs? Original presentation by Newell Johnson (Australia/France).
5. What is known about reservoirs of HIV RNA and DNA in different anatomical compartments: CNS; lymph nodes; MALT; bone marrow, thymus; spleen and genital fluids? With a focus on Waldeyer's ring, what is the risk of shedding competent virus into oral fluids and what are the implications for transmission? Original presentation by Pradeep Jayashantha (Sri Lanka).
6. Changing concepts of cure: Eradication of HIV versus Functional Cures/ Remission. How does the [uneven] availability of ART increase or ameliorate inequalities in oral health around the world? How can such inequalities be addressed? Original presentation by Midion Chidzonga (Zimbabwe).

Focused Research Questions from Workshop A1

1. What are the biological mechanisms and immunological determinants of dental caries, xerostomia and periodontal disease and traditional HIV-related oral manifestations? Can large-scale longitudinal (within subject, pre-post ART) study designs or translational studies tease out the differential contributions of HIV and ART on oral conditions in PLWHA?
2. How can oral health providers better address global inequalities? How can dentists be “first responders”—i.e., help detect HIV+ persons earlier and advocate for optimal treatment of all health of all HIV+ individuals?
3. On successful ART, where are the major reservoirs of HIV RNA/DNA located in the head and neck region? Is HIV DNA or RNA detected in saliva/oral mouth rinse fluid and it is potentially infectious? On ART, why are herpesviruses suppressed, but not human papilloma viruses (HPV)? What can be done to reduce the risk of HPV-related head and neck cancers?
4. Do pathologies associated with HIV (kidney/renal dysfunction, metabolic syndrome, immune activation) affect oral health? Does nadir CD4 count influence long-term tooth loss?