

Research letters

Effect of highly active antiretroviral therapy on frequency of oral warts

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To investigate changes in the pattern of oral disease associated with highly active antiretroviral therapy (HAART), we assessed the frequency of these lesions in our clinic over 9 years. We retrospectively studied 1280 patients seen between July, 1990, and June, 1999, and related oral findings to medication use, immune function, and viral load. We found significant decreases in oral candidosis, hairy leucoplakia, and Kaposi's sarcoma over time, but no change in the occurrence of aphthous ulcers. There was an increase in salivary-gland disease and a striking increase in warts: three-fold for patients on antiretroviral therapy and six-fold for those on HAART ($p=0.01$). This pattern of oral disease in a referral clinic suggests that an increase in oral warts could be occurring as a complication of HAART.

Oral lesions are important features of HIV infection.¹ The introduction of highly active antiretroviral therapy (HAART) has been accompanied by reports of a reduction in the frequency of many of the secondary events caused by HIV infection,² including some oral lesions.³ We sought to investigate the changing pattern of oral lesions associated with HIV infection and HAART among patients in our referral clinic.

All 1280 HIV-positive individuals seen between July 1, 1990, and June 30, 1999, were retrospectively studied. Since individuals could have been seen more than once, we randomly chose one visit per 12 months or 3 years for each individual, and looked at oral lesions diagnosed and medications being used at that visit. In our analysis of CD4-cell count and viral load, we used the measurement taken closest to the visit. For the analysis of oral lesions, we divided the study into nine 12-month periods: July 1, 1990, to June 30, 1991; July 1, 1991, to June 30, 1992, &c, and used a two-sided Cochran-Armitage test of trend to calculate whether the occurrence of an oral lesion was changing over time. Immune status over time was studied with the Kruskal-Wallis test. We examined data on oral candidosis (including the pseudomembranous form [thrush], the

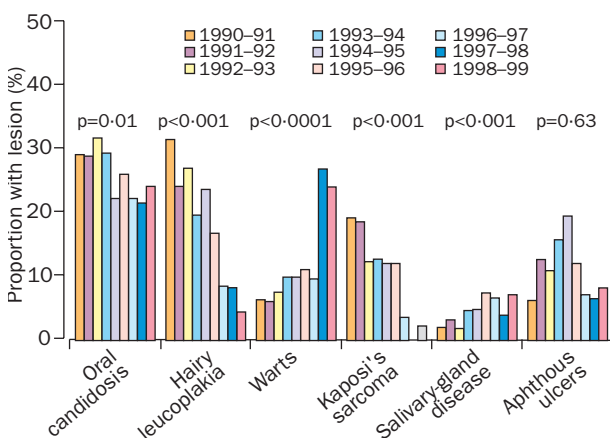


Figure 1: Changes in prevalence of oral lesions

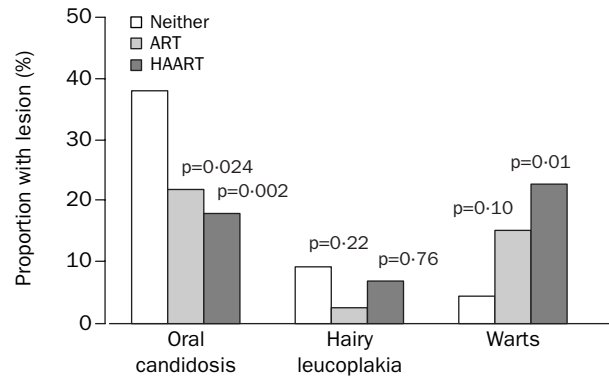


Figure 2: Oral lesions and use of antiretroviral therapy, 1996–99. p values adjusted for CD4 count and viral load. ART=antiretroviral therapy without protease inhibitors. HAART=highly active antiretroviral therapy (with protease inhibitors).

erythematous form, and angular cheilitis), hairy leucoplakia, oral warts, aphthous ulcers, salivary-gland disease, and Kaposi's sarcoma.⁴ We then focused on three key oral lesions—oral candidosis, hairy leucoplakia, and oral warts—and studied their relation with antiretroviral therapy, with or without use of protease inhibitors, adjusting for CD4 count and viral load. Treatment that included one or more antiretroviral agents including non-nucleosides, but excluding protease inhibitors, was defined simply as antiretroviral therapy (ART), and treatment that included one or more antiretroviral agents plus protease inhibitors was defined as HAART. We calculated odds ratios and 95% CI, adjusted for CD4-cell count and viral load, using logistic-regression models.

Over the nine 12-month periods, the occurrence of oral candidosis, hairy leucoplakia, and Kaposi's sarcoma decreased substantially, whereas the frequency of aphthous ulcers did not change. There was an increase in the occurrence of salivary-gland disease and a striking increase in the rate of warts (figure 1). CD4-cell counts increased over time in individuals with warts: the median CD4 count was 96 cells/ μ L in 1990–91 and 350 cells/ μ L in 1998–99 ($p=0.01$). No significant changes in CD4-cell counts occurred in patients with oral candidosis or hairy leucoplakia. HIV RNA viral load did not change during 1996–99 for individuals with oral candidosis, hairy leucoplakia, or warts. During 1990–93 (ie, before protease inhibitors were introduced), oral candidosis, hairy leucoplakia, and warts were not associated with use of ART, after adjusting for CD4-cell count. However, during 1996–99 (after the introduction of protease inhibitors), the prevalence of oral candidosis was lower in patients on ART and HAART than in those on neither medication (figure 2). After adjusting for CD4-cell count and HIV viral load, the odds of having oral candidosis were lower in individuals on ART (odds ratio 0.32 [95% CI 0.12–0.86], $p=0.02$) and in those on HAART (0.28 [0.12–0.63], $p=0.002$) than in

individuals on neither. There was no association between hairy leucoplakia and ART or HAART. During 1996–99, the prevalence of oral warts was higher in patients on ART and HAART. 5% of patients on neither medication had warts, compared with 15% of those on ART alone and 23% of those on HAART. When adjusted for CD4 count and viral load, the odds of having warts for those on ART alone showed a non-significant association (3.90 [0.77–19.70], $p=0.10$), but for those on HAART there was a highly significant association (6.80 [1.49–30.80], $p=0.01$) compared with individuals on neither treatment.

The reduction in oral infections associated with HAART is not surprising and confirms other preliminary studies. The observed increase in salivary-gland disease is also to be expected: this disorder is regarded as part of the CD8-cell diffuse infiltrative lymphocytosis syndrome, which has previously been associated with improved prognosis. However, the results suggest that HAART might cause an increase in oral warts. The changes in the pattern of oral disease we describe here may or may not reflect actual changes in prevalence or incidence of those lesions in the HIV-infected population. Our cases are referred from a variety of clinics for a range of reasons. Nevertheless, the increase in the occurrence of oral warts, and its apparent association with both ART and protease inhibitors, is somewhat unexpected, although a link has been suggested previously.⁵ Some other opportunistic infections, notably tuberculosis and cytomegalovirus retinitis, can also recur among patients receiving HAART as HIV viral loads fall and CD4-cell counts improve. The reconstitution of the immune system might be functionally incomplete and its effectiveness might therefore vary with regard to different potentially pathogenic micro-organisms. This situation could lead to the development of oral warts, and perhaps skin warts, in the context of an overall reduction in opportunistic infections. The oral warts we see in HIV-positive individuals, including those on HAART, present substantial management challenges. The warts are often extensive and progressive and recur after removal. So far, no effective cure has been established. Thus they cause substantial discomfort and aesthetic problems.

We thank Evangeline Leash for editing the paper and Joan Hilton and Caroline Shiboski for helpful comments.

The study was supported by NIH/NIDCR PO 1 DE 07946, and the UCSF AIDS Clinical Research Center (which is itself funded by the California Universitywide AIDS Research Program).

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Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia

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Acute hepatitis with lactic acidosis is a life-threatening but reversible toxic effect on mitochondria of HIV-1 nucleoside-analogue treatment. We report fatal portal hypertension, liver failure, and persistent mitochondrial dysfunction in a man aged 65 years with HIV-1 infection who had recovered from nucleoside-analogue-induced acute hepatitis and lactic acidemia more than 18 months previously. We believe that symptomfree patients who receive nucleoside-analogue therapy should have hepatic function constantly monitored, especially those with past or present lactic acidemia.

Acute hepatitis with lactic acidosis is a toxic effect of HIV-1 nucleoside analogues on mitochondria. 80% of patients with lactate greater than 10 mmol/L die. The longterm outcome of those who survive is unknown, but all reports have shown full recovery.

A man aged 65 years with symptomless HIV-1 infection since 1989 had received zidovudine from 1992 to 1994, but no other antiretroviral therapy. In August, 1997, we restarted him on antiretroviral therapy with 40 mg stavudine and 200 mg didanosine both twice daily. His liver enzymes and serum albumin were normal. 14 months later, in May, 1998, his CD4 lymphocyte count was 350 cells per μL and plasma HIV-1 RNA load less than 400 copies/mL.¹ He had a 1-year history of 14 kg weight loss, and 3 months of fatigue, abdominal distension, nausea, and dyspnoea. We noted pronounced peripheral lipotrophy, tender hepatomegaly, gross ascites, and dependent oedema, but no jaundice, encephalopathy, or features of chronic liver disease.

Laboratory investigations showed lactic acidemia (arterial pH 7.4, venous lactate 7.0 mmol/L [normal range 0.5–2.0]), bicarbonate 20 mmol/L (normal range 24–30), albumin 27 g/L (35–48), alanine aminotransferase 181 IU/L (<35), and prothrombin time of 19 s (<13). Computed tomography and doppler ultrasonography showed ascites and liver of normal size with diffuse steatosis but no focal mass, biliary abnormality, or portal hypertension. The patient did not drink alcohol, was not previously obese, had no history of liver disease, had normal serum ferritin and $\alpha 1$ antitrypsin concentrations, and was seronegative for viral hepatitis A, B, and C. We did not detect serum hepatitis B DNA, hepatitis C RNA, antinuclear antibodies, or hepatic autoantibodies to smooth muscle and mitochondria. We did not do a liver biopsy because vitamin K treatment for his coagulation disorder was not successful. Ascitic fluid was free of cells.

We stopped antiretroviral therapy, and clinical and biochemical values returned to normal ranges within 3–5 months. Treatment of ascites with 40 mg furosemide daily and 50 mg spironolactone twice daily was given for a further 9 months. The patient regained only 8 kg. Between February, 1999, and January, 2000, he was well, had normal metabolic values, received no medication, and restarted full-time work.

In March, 2000, the patient complained of 3 months of progressive dependent oedema. He also had mild ascites, confusion, apraxia, asterixis, and 4 cm non-tender splenomegaly. The liver edge was not palpable. Lactate