Oral Examination: A Simple Tool to Identify HIV-Infected Patients in Need of Starting Antiretroviral Therapy

AS Batavia[1], R Secours[2], P Espinosa[3], MA Jean Juste[2], P Severe[2], JW Pape[1,2], DW Fitzgerald[1]

[1]Weill Cornell Medical College, New York, NY, [2]Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), Port-au-Prince, Haiti, [3]University of California San Francisco School of Dentistry, San Francisco, CA

Introduction

Globally, there are 34.3 million HIV-infected people, most are in resource-limited settings. Haiti, the Western Hemisphere's poorest country, has the highest HIV prevalence in the Caribbean (2.1%).

The oral exam is inexpensive to perform and can provide valuable information about HIV progression. For example, candidiasis is associated with low CD4 T cell counts, Kaposi Sarcoma (KS) is AIDS-defining, and there is speculation that oral warts may be part of the immune reconstitution inflammatory syndrome (IRIS).

Early initiation of antiretroviral therapy (ART) may mitigate chronic inflammation, which is thought to be the major driving force in AIDS pathogenesis.

Purpose

HIV-related oral lesions have diverse etiologies ranging from microbial to malignant to idiopathic. It is important to describe how the timing of ART initiation, and by extension the immune landscape of the host, affect the incidence of these lesions. This information will enhance the utility of the oral examination in an era when our approach to treatment is rapidly changing.

To our knowledge, this is the first prospective study comparing the incidence of HIV-related oral lesions in subjects randomized to early versus delayed ART initiation.

Methods

- Prospective study of HIV-infected ART-naïve non-pregnant adults conducted at the GHESKIO Center in Port-au-Prince, Haiti [NCT00120510].
- 816 subjects were randomized to early (CD4 T cell count ≤ 350 cells/mm^3) vs. delayed (CD4 T cell count ≤ 200 cells/mm^3) ART initiation.
- The study protocol required all subjects to undergo a comprehensive physical examination, including evaluation of the oral cavity, at enrollment and then every three months for the duration of the study.
- Standardized case definitions established by the Oral HIV/AIDS Research Alliance of the AIDS Clinical Trials Group were used. Only incident diagnoses between enrollment (8/05– 6/08) and 5/1/09 were considered for analysis.
- All analysis was performed using Stata 13 software (StataCorp LP, Texas)

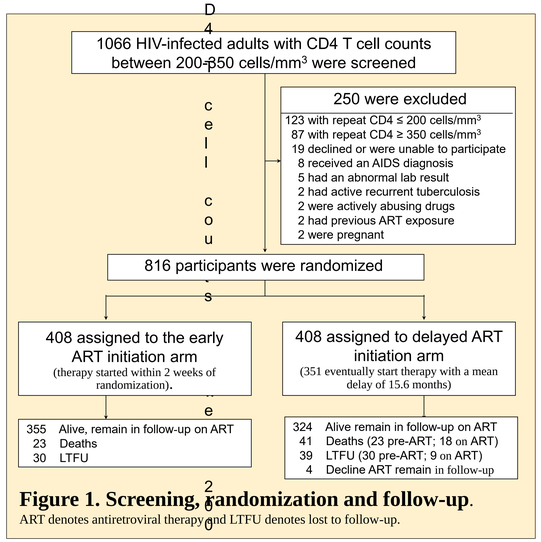


Figure 1. Screening, randomization and follow-up.
ART denotes antiretroviral therapy and LTFU denotes lost to follow-up.

Results

	Delayed ART Initiation (N=408)	Early ART Initiation (N=408)
Median age (IQR)	40 (32-47)	40 (34-46)
Female (%)	229 (56)	241 (59)
HIV Clinical Stage (%)		
Stage 1	126 (31)	135 (33)
Stage 2	219 (54)	199 (49)
Stage 3	63 (15)	74 (18)
Median CD4T cell count, cells/mm^3 (IQR)	282 (250-310)	280 (250-305)

Table 1. Baseline characteristics
IQR denotes interquartile range

Oral diagnosis (%)	Delayed ART Initiation (N=408)	Early ART Initiation (N=408)	P-value
Any oral candidiasis	106 (26.0)	26 (6.4)	**<0.001**
Oral hairy leukoplakia	9 (2.2)	1 (0.2)	**0.021**
Oral warts	15 (3.7)	9 (2.2)	0.214
HPV-related malignancy	0 (0)	0 (0)	---
Herpes labialis	19 (4.7)	10 (2.5)	0.089
Recurrent herpes labialis	8 (2.0)	4 (1.0)	>0.950
Recurrent apthous ulcer	3 (0.7)	4 (1.0)	0.261
Kaposi sarcoma	4 (1.0)	1 (0.2)	0.373
Total	164 (40.2)	55 (13.5)	**<0.001**

Table 2. Frequency of incident cases of HIV-related oral diagnoses (intention to treat analysis)

- Per protocol analysis revealed that 75% of all oral warts were diagnosed after ART initiation (N=18, p-value <0.001). The median time from ART initiation to diagnosis of oral warts was 177 days (IQR: 143-282 days)
- In subjects with recurrent herpes labialis, the per person number of episodes (median 2.5 and 2 for the delayed and early arm respectively) was not statistically significant between arms (p > 0.95)
- All diagnoses of KS prompted either ART initiation or switch to a second-line regimen.

Conclusions

- Subjects were 4.31 times more likely to receive an HIV-related oral diagnosis in the delayed arm (CI: 3.05- 6.10; p-value <0.0001).
- The most common diagnoses were oral candidiasis (N=132, 32.4%), herpes labialis (N=29, 7.2%) and oral warts (N=24, 5.9%).
- Subjects were 5.15 times times more likely to receive a diagnosis of oral candidiasis in the delayed arm (CI: 3.27- 8.13; p-value <0.0001).
- Per protocol analysis of the incidence of oral warts was suggestive of an IRIS-related phenomena, but more research is needed.
- Interestingly, no HPV-related oral malignancies were noted in our cohort.
- KS was AIDS-defining and prompted a change in clinical management in 1.2% of subjects.

Acknowledgements

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Correspondence: **Ashita S. Batavia, MD**; Weill Cornell Center for Global Health, 402 E. 67th, 2nd Floor, New York, NY 10065; e-mail: asb2009@nyp.org; Tel: 646-962-8140

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