Prevalence of oral HPV among people living with HIV (PLHIV) in Pune, India

Article *in* F1000Research · March 2023

DOI: 10.12688/f1000research.127474.1

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BRIEF REPORT

Prevalence of oral HPV among people living with HIV (PLHIV) in Pune, India [version 1; peer review: awaiting peer review]

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v1 **First published:** 14 Mar 2023, **12**:285
https://doi.org/10.12688/f1000research.127474.1
Latest published: 14 Mar 2023, **12**:285
https://doi.org/10.12688/f1000research.127474.1

Abstract

Background: People living with HIV (PLHIV) are at an increased risk of human papillomavirus (HPV)-related head and neck cancers (HNCs). However, there is little data on the prevalence of oral HPV among PLHIV in India, limiting the planning of oral HPV preventive strategies.
Methods: We used cross-sectional data from an oral cancer screening study conducted at the antiretroviral therapy (ART) centre of Byramjee-Jeejeebhoy Government Medical College-Sassoon General Hospitals (BJGMC-SGH). PLHIV ≥21 years of age with no prior history of HNCs were enrolled. We determined the prevalence of high-risk oncogenic HPV (hrHPV) and low-risk non-oncogenic HPV (lrHPV) using real-time PCR and Next-Generation Sequencing. We used multinomial logistic regression to determine the prevalence ratios (PRs) of different sociodemographic, clinical, and behavioural predictors with hrHPV and lrHPV. Multivariable models were adjusted for age, sex, CD4 count and duration on ART.
Results: Of the 582 PLHIV enrolled, the median age was 40 years (IQR: 34–46) and 54% were male. More than a fourth (25.8%) had multiple sexual partners and 11% had given oral sex. Median CD4 counts were 510 cells/mm^3 (IQR: 338–700). The prevalence of hrHPV was 4.5% and lrHPV was 3.4%. Of those with hrHPV, 77% had HPV16. There were no significant associations with any predictors for both lrHPV and hrHPV in adjusted analyses.
Conclusions: We found the prevalence of any oral HPV (hrHPV and lrHPV) to be 7.9% among PLHIV in India. Larger studies are required to better understand risk factors for oral HPV among Indian PLHIV.

Open Peer Review

Approval Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

Keywords
oral HPV, HIV, India

This article is included in the Global Public Health gateway.

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Author roles: Marbaniang I: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Writing – Original Draft Preparation, Writing – Review & Editing; **Joshi S**: Conceptualization, Investigation, Resources, Supervision, Writing – Review & Editing; **Borse R**: Conceptualization, Investigation, Supervision, Writing – Review & Editing; **Khaire S**: Investigation, Methodology, Writing – Review & Editing; **Thakur R**: Investigation, Writing – Review & Editing; **Deshpande P**: Investigation, Methodology, Writing – Review & Editing; **Kulkarni V**: Investigation, Methodology, Writing – Review & Editing; **Chavan A**: Formal Analysis, Writing – Review & Editing; **Nimkar S**: Investigation, Project Administration, Writing – Review & Editing; **Mave V**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center, as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA; U01AI069907) and the NIH-funded Johns Hopkins Baltimore-Washington-India Clinical Trials Unit for NIAID Networks (UM1AI069465). The content and views expressed are those of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Marbaniang I, Joshi S, Borse R *et al.* **Prevalence of oral HPV among people living with HIV (PLHIV) in Pune, India [version 1; peer review: awaiting peer review]** F1000Research 2023, **12**:285 https://doi.org/10.12688/f1000research.127474.1

First published: 14 Mar 2023, **12**:285 https://doi.org/10.12688/f1000research.127474.1

Introduction

People living with HIV (PLHIV) have a 2–3 times higher odds of oral human papillomavirus (HPV) prevalence compared to HIV-uninfected individuals.[1] This is estimated to increase their risk of HPV-associated head and neck cancers (HNCs) 1.2–2.1 times relative to HIV-uninfected individuals.[2] However, estimates of oral HPV prevalence among PLHIV are mostly derived from high income countries (HICs) and data from low- and middle-income countries (LMICs) remain scarce, despite the burden of HIV in LMICs being considerably higher than HICs.[3]

Globally, India has the third highest number of PLHIV (approximately 2.3 million).[4] Only one study from the country has previously reported on oral HPV prevalence among PLHIV, restricted to a key population, men who have sex with men (MSM).[5] To develop comprehensive strategies for oral HPV prevention that are geographically relevant for PLHIV, it is also important to report on the prevalence of oral HPV among PLHIV that are not key populations. In this manuscript, we estimate the prevalence of oral HPV and assess associated factors among PLHIV in Pune, India.

Methods

Ethics

The Ethics Committee of Byramjee Jeejeebhoy Government Medical College – Sassoon General Hospitals (BJGMC-SGH) (Date of approval: 19 September 2016) and the Institutional Review Board of Johns Hopkins University (IRB00118708, Date of approval: 13 December 2016) approved the study. It should be noted that the Ethics Committee of BJGMC does not issue ethical approval numbers, nor does it have an Ethics Number itself.

Study population

We used data from a parent oral cancer screening study conducted between June 2017 and June 2019 at Byramjee Jeejeebhoy Government Medical College – Sassoon General Hospitals (BJGMC-SGH), a tertiary health care centre in Pune, India.[6] The parent study enrolled 1,234 participants, including 633 HIV-uninfected individuals and 601 PLHIV. For this analysis, data from HIV-uninfected participants and PLHIV with missing data for oral HPV (n=19) were excluded. Details of the study including enrolment procedures are provided elsewhere.[6] This analysis included data of PLHIV≥21 years of age attending the ART centre for care, with no prior history of HNCs who provided a 30 seconds oral rinse and gargle sample, and written informed consent.

Sociodemographic (age, biological sex), behavioural factors (smoking, smokeless tobacco (SLT) and alcohol use), sexual history (men who have sex with men (MSM), oral sex, lifetime sexual partners), clinical history (CD4 counts, duration on antiretroviral therapy, suspected oral potentially malignant disorder (OPMD), HPV results including genotype) data were extracted from the database of the parent study.[6] These data were collected by trained non-medical health care professionals of the study team in the parent study.

Assuming that the prevalence of oral HPV was 24%, consistent with the previous study that reported on oral HPV prevalence among Indian MSM living with HIV,[5] our sample size of 582 was >95% powered at an alpha of 0.05.

Laboratory methods

The parent study[6] used polymerase chain reaction (PCR) and next-generation sequencing (NGS) to obtain the prevalence of oral HPV. PCR and NGS were performed at a private laboratory (GenePath Diagnostics, Pune). These procedures are described below.

Reagents

Platinum Taq DNA polymerase (Invitrogen, Cat No. 10966034), HotStarTaq DNA polymerase (Qiagen, Cat No. 203205), dNTP (deoxyribonucleotide triphosphate) 25 micromolar (mM) (Lucigen, Cat No. D59104) were used. [Note - Invitrogen PCR buffer and $MgCl_2$ are provided by Invitrogen along with Platinum Taq DNA polymerase].

Thermal cycling conditions, primers used and model of PCR machine

A nested PCR approach targeting the L1 gene was used. The outer PCR was carried out using an equimolar mixture of each PGMY09 and PGMY11 primer pool[7] at a concentration of 80 nanomolar (nM) each, which generated a 450 base pairs (bp) product. This product was used as a template for the inner PCR. The inner PCR was carried out using custom tagged GP5+ and GP6+ primers[7] at a final concentration 200 nM each, which generated a 150 bp product. The tagged inner PCR products were used for library generation where specific barcodes were incorporated for each sample. The library was sequenced on an Illumina MiSeq or a NextSeq next generation sequencer in a shared run using the Illumina V2 2*250 (MiSeq) or Mid-output 2*150 (NextSeq) paired-end sequencing by synthesis chemistry. The resulting .fastq raw

read files were aligned against HPV DNA database using in-house bioinformatics pipeline and read counts generated were analysed for presence/absence and type of HPV DNA in each sample.

The outer PCR was carried out at 20 microlitre (µl) reaction volume, with 1X Invitrogen PCR buffer, 4 mM MgCl2, 0.2 mM dNTP and a blend of two polymerases, 0.5U of Platinum Taq DNA polymerase (Invitrogen) and 0.5U of HotStarTaq DNA polymerase (Qiagen). The outer PCR was carried out on Veriti 96-well thermal cycler (Applied Biosystems) with initial incubation at 37°C, initial denaturation at 95°C for 15 min, followed by 35 cycles of denaturation at 95°C for 20 sec, annealing at 56.5°C for 30 sec, extension at 72°C for 1 min. The amplified outer PCR products were diluted 100 times with ultrapure nuclease free PCR grade water and used as a template for inner PCR.

For the inner PCR, custom tagged GP5+ and GP6+ primers[7] were used at a final concentration of 200 nM each. The inner PCR was carried out at 20 µl reaction volume with 1X Invitrogen PCR buffer, 4 mM $MgCl_2$, 0.2 mM dNTP, 0.5 mg/ml BSA, and a blend of two polymerases, 0.5U of Platinum Taq DNA polymerase (Invitrogen) and 0.5U of HotStarTaq DNA polymerase (Qiagen). The inner PCR was carried out on Veriti 96-well thermal cycler (Applied Biosystems) with initial incubation at 37°C, initial denaturation at 95°C for 15 min, followed by eight cycles of denaturation at 95°C for 20 sec, ramp up annealing from 40°C to 72°C for 30 sec, extension at 72°C for 30 sec, followed by 27 cycles of denaturation at 95°C for 20 sec and extension at 72°C for 1 min.

Statistical analyses

PCR (and NGS) results were treated as the outcome, classified into three groups: 1) no HPV; 2) high risk or oncogenic HPV (hrHPV *i.e.*, if they belonged to any of the following genotypes HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, HPV68)[8]; and 3) low risk HPV (6/11, 7, 13, 27, 32/42, 34, 43/91, 44, 53, 62, 71, 72, 73, 81, 82, 83, 84, 86/87, 89/102, 90/106, 107, 114, and 120).[8]

Medians and proportions across the outcome were compared using Kruskal Wallis and Fisher's exact tests, respectively, for different sociodemographic, behavioural, sexual history and clinical predictors (Table 1). We used multinomial logistic regression to obtain prevalence ratios (PRs) comparing lrHPV and hrHPV groups (comparison groups) against the no HPV group (reference group) for different predictors. Multivariable models were adjusted for variables chosen *a priori* as predictors of oral HPV and that had a minimum of five participants when cross tabulated against the outcome. These were age, sex, CD4 counts and duration on ART.

We performed three sensitivity analyses, comparing primary results with: 1) Findings in which CD4 counts were categorized into <200 and ≥200 cells/mm; 2) Findings from models in which PRs were obtained for a binary outcome *i.e.*, no HPV and any HPV (collapsing hrHPV and lrHPV into a single group); 3) Findings from regression models in which imputations using chained equations for those with missing HPV were performed.

Statistical significance was set to a two-sided p-value of 0.05. All analyses were performed in Stata 17.0 (RRID: SCR_012763) (free alternative, RStudio).

Results

A total of 582 PLHIV were enrolled. The median age was 40 years (IQR: 34–46), 46.4% (n=270) were biologically female, 18.2% (n=106) had smoked, 41.1% (n=239) had used smokeless tobacco (SLT) and 35.2% (n=205) had consumed alcohol. Approximately 2.5% (n=14) self-identified as MSM, 10.5% (n=61) had given oral sex and 25.8% (n=150) had multiple sexual partners, in their lifetime. Median time updated CD4 counts were 510 cells/mm^3 (IQR: 338–700) and median duration on ART was eight years (IQR: 4–12). None of the participants were vaccinated against HPV.

The prevalence of hrHPV was 4.5% (n=26) and lrHPV was 3.4% (n=20). Of those with hrHPV, 76.9% (n=20) had HPV16. Approximately 40% of those with hrHPV (n=8) and 50% (n=10) of those with lrHPV had never smoked, used SLT or consumed alcohol. The distribution of hrHPV was HPV16: n=20, HPV18: n=2, HPV35: n=1, HPV66: n=2 and HPV68: n=1; and that of lrHPV was HPV7: n=1, HPV13: n=1, HPV27: n=1, HPV32: n=1, HPV42: n=1, HPV44: n=3, HPV72: n=3, HPV81: n=1, HPV84: n=1, HPV90: n=1, HPV107: n=4, HPV120: n=2 (Table 1).

The prevalence of hrHPV and lrHPV were not statistically significantly different (*i.e.*, p>0.05) by age, biological sex, tobacco and alcohol use habits, and sexual and clinical history.

In the univariate analysis, relative to the no HPV group, a unit increase in age was associated with 5% increase in the prevalence of lrHPV (PR: 1.05; 95% CI: 1.01, 1.10). There were no predictors significantly associated with hrHPV in univariate analysis. When adjusted for age, sex, time updated CD4 counts and ART duration, no predictors were significantly associated with either lrLPV or hrHPV (Table 1).

Table 1. Characteristics of PLHIV in Pune, India, and associations with oral hrHPV and lrHPV prevalence.

Characteristics	Total N (%, IQR)	hrHPV* N (%, IQR)	lrHPV* N (%, IQR)	No HPV* N (%, IQR)	PR (95% CI) Ref (No HPV) Comp (hrHPV)	PR (95% CI) Ref (No HPV) Comp (lrHPV)	aPR (95% CI) Ref (No HPV) Comp (hrHPV)	aPR (95% CI) Ref (No HPV) Comp (lrHPV)
Total N	582	26 (4.5)	20 (3.4)	536 (92.1)	-	-	-	-
Median age in years (IQR)	40 (34 – 46)	38.5 (31 – 48)	43.5 (40 – 47.5)	40 (34 – 46)	0.99 (0.95, 1.04)	1.05 (1.01, 1.10)	0.99 (0.95, 1.04)	1.04 (1.00, 1.09)
Biological sex								
Male	312 (53.6)	14 (53.8)	15 (75.0)	283 (52.8)	Ref	Ref	Ref	Ref
Female	270 (46.4)	12 (46.2)	5 (25.0)	253 (47.2)	0.96 (0.44, 2.11)	0.37 (0.13, 1.04)	0.97 (0.43, 2.21)	0.50 (0.17, 1.45)
Ever smoked								
No	475 (81.8)	20 (76.9)	14 (70.0)	441 (82.4)	Ref	Ref	-	-
Yes	106 (18.2)	6 (23.1)	6 (30.0)	94 (17.6)	1.41 (0.55, 3.60)	2.01 (0.75, 5.37)		
Ever consumed alcohol								
No	377 (64.8)	18 (69.2)	10 (50.0)	349 (65.1)	Ref	Ref	-	-
Yes	205 (35.2)	8 (30.8)	10 (50.0)	187 (34.9)	0.83 (0.35, 1.94)	1.87 (0.76, 4.56)		
Ever used SLT[a]								
No	343 (58.9)	19 (73.1)	13 (65.0)	311 (58.0)	Ref	Ref	-	-
Yes	239 (41.1)	7 (26.9)	7 (35.0)	225 (42.0)	0.51 (0.21, 1.23)	0.74 (0.29, 1.89)		
Ever smoked, used SLT or consumed alcohol								
No	281 (48.3)	16 (61.5)	10 (50.0)	349 (65.1)	Ref	Ref	-	-
Yes	301 (51.7)	10 (38.5)	10 (50.0)	187 (34.9)	0.83 (0.35, 1.94)	1.87 (0.76,4.56)		
Ever given oral sex								
No	521 (89.5)	24 (92.3)	16 (80.0)	481 (89.7)	Ref	Ref	-	-
Yes	61 (10.5)	2 (7.7)	4 (20.0)	55 (10.3)	0.73 (0.17, 3.17)	2.19 (0.71, 6.77)		
Lifetime multiple sexual partners								
No	431 (74.2)	22 (84.6)	12 (60.0)	397 (74.2)	Ref	Ref	-	-
Yes	150 (25.8)	4 (15.4)	8 (40.0)	138 (25.8)	0.52 (0.18, 1.54)	1.92 (0.77, 4.79)		
Self identifies as MSM [b]								
No	568 (97.6)	26 (100.0)	20.0 (100.0)	522 (97.4)	-	-	-	-
Yes	14 (2.4)	0 (0)	0 (0)	14 (2.61)				

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Table 1. *Continued*

Characteristics	Total N (%, IQR)	hrHPV* N (%, IQR)	lrHPV* N (%, IQR)	No HPV* N (%, IQR)	PR (95% CI) Ref (No HPV) Comp (hrHPV)	PR (95% CI) Ref (No HPV) Comp (lrHPV)	aPR (95% CI) Ref (No HPV) Comp (hrHPV)	aPR (95% CI) Ref (No HPV) Comp (lrHPV)
Median time- updated CD4 counts (cells/mm^3)[c]	510 (338 – 700)	475 (242 – 651)	467 (311 – 611)	512 (349 – 708)	0.97 (0.90, 1.05)	0.93 (0.85, 1.02)	0.97 (0.90, 1.05)	0.96 (0.87, 1.05)
Median duration on ART (in years)[d]	8 (4-12)	8.5 (2 – 16)	6.5 (4 – 9.5)	8 (4-12)	1.03 (0.97, 1.09)	0.95 (0.87, 1.03)	1.05 (0.65, 1.72)	0.68 (0.38, 1.23)
Suspected OPMD[e]								
No	470 (80.8)	22 (84.6)	18 (90.0)	430 (80.2)	Ref	Ref	-	-
Yes	112 (19.2)	4 (15.4)	2 (10.0)	106 (19.8)	0.74 (0.25, 2.18)	0.45 (0.10, 1.97)		

PLHIV: people living with HIV; HPV: human papillomavirus; hrHPV: high risk HPV; lrHPV: low risk HPV; PR: prevalence ratio; aPR: adjusted prevalence ratio with adjustments for age, biological sex, time updated CD4 counts and duration on ART; Ref: reference group; Comp: comparison group.
hrHPV: HPV16: n=20, HPV18: n=2, HPV35: n=1, HPV66: n=2 and HPV68: n=1; **lrHPV:** HPV7: n=1, HPV13: n=1, HPV27: n=1, HPV32: n=1, HPV42: n=1, HPV44: n=3, HPV72: n=3, HPV81: n=1, HPV84: n=1, HPV90: n=1, HPV107: n=4, HPV120: n=2.
Missing values for predictors: Ever smoked (n=1), CD4 counts (n=8), lifetime multiple sexual partners (n=1).
*There are no significant differences between the medians or proportions across no HPV, hrHPV (high risk HPV) and lrHPV (low risk HPV) groups (p-value associated with Kruskal- Wallis and Fisher's exact test >0.10 for all characteristics.
[a]**SLT:** Smokeless tobacco, which are forms of tobacco that are not burned. Locally available forms available: khaini (tobacco + slaked lime); gutka (tobacco + areca nut + slaked lime); mishri (roasted powdered tobacco); paan (tobacco + areca nut + slaked lime + condiments, wrapped in a betel leaf); paan masala; snuff.
[b]**MSM:** Men who have sex with men.
[c]**ART:** Antiretroviral therapy.
[d]Regression estimates are interpreted with respect to an increase in 50 CD4 cell counts; CD4 count values were missing for 8 participants.
[e]**OPMD:** Oral potentially malignant disorder.

Sensitivity analyses findings were consistent with results presented in Table 1. However, when CD4 counts were categorized into <200 and ≥200 cells/mm^3, participants with <200 cells/mm^3 had a 3.14- (95% CI: 1.20, 8.22) and 3.12- (95% CI: 1.19, 8.20) fold higher prevalence of hrHPV in univariate and multivariable analyses, respectively, but associations with lrHPV were non-significant. We do not present these as primary findings because there were no female participants with CD4 counts <200 cells/mm^3 in the hrHPV group and multivariable results are likely an extrapolation by the model.

Discussion

Using oral rinse samples, we found the overall prevalence of any HPV to be 7.6%, lrHPV to be 3.4% and hrHPV to be 4.5% among PLHIV. To our knowledge this is the first study from India to report on oral HPV among PLHIV that are not exclusively MSM and the largest study from the country to date to report on the prevalence of oral HPV.[9,10]

We found combined oral HPV (*i.e.*, any oral HPV: lrHPV and hrHPV) and hrHPV (only) prevalence to be lower than what has been reported among studies in PLHIV from the United States.[1] However, the sample size of the present study is larger than most of these studies. Compared to the study conducted among MSM living with HIV in India, our overall prevalence of any oral HPV was lower (7.6% *versus* 23.7%), hrHPV prevalence was higher (4.5% *versus* 2.4%) and hrHPV was almost exclusively HPV16 (77% *versus* 0%).[5] These findings indicate the heterogeneity of oral HPV prevalence and genotypes among different subgroups of PLHIV in India and the need for larger studies to better characterize oral HPV in them.

Most previous studies in India have only reported on oral HPV among HIV-uninfected individuals with HNCs. The prevalence of oral HPV in these studies varies between 0–79%, with HPV16 being the most common genotype.[9,10] More than three-fourths of those with hrHPV in our study had HPV16. Further, 40% of those with hrHPV reported to have never smoked, used SLT or consumed alcohol, which are traditional risk factors for HNCs. Oral HPV screening is not routinely performed as part of HIV care at present. Given the strong association between HPV16 and HNCs,[1] and the increased vulnerability of PLHIV for HNCs,[1] oral HPV assessment for PLHIV must be considered.

We found no association with CD4 counts in our primary analysis. This may be due to the high median CD4 counts of the study population. Immunosuppression is an important risk factor for oral HPV,[1,8] and our sensitivity analysis indicates that those with CD4 counts <200 cells/mm^3 may be more likely to have prevalent hrHPV. A previous publication from our site showed that a large proportion of PLHIV consistently presented with CD4 counts <200 cells/mm^3 over a 12-year period (2005–2017).[11] This underlines the need to facilitate earlier engagement of PLHIV in HIV care, to reduce their risk of oral HPV acquisition.

There are several limitations in our study that merit discussion. We did not measure HIV viral loads and are unable to comment on the association between viral suppression and oral HPV prevalence. We did not find associations between oral HPV with either multiple sexual partners or oral sex. This is likely due to participants underreporting these behaviours, driven by social desirability. We are committed to improving on this aspect and have organized a series of workshops for sexual history assessment. While this is the largest study till date to report on oral HPV from India, we were not powered to detect significant associations especially in multivariable models. Our findings may also not be generalizable to other PLHIV living elsewhere in India.

PLHIV are a vulnerable group for HPV-associated HNCs and those living in LMICs may be particularly at risk because oral HPV screening is not routinely performed as part of HIV care. We reiterate the need for larger studies to better understand oral HPV prevalence and associated risk factors among PLHIV in India, simultaneously with the scaling-up of oral HPV screening measures among them.

Data availability

Underlying data

Data cannot be shared publicly because it comes from people living with HIV in India, many of whom have not disclosed their HIV status except to their HIV health care provider and spouses. Data are available from the Ethics Committee - Byramjee Jeejeebhoy Medical College & Sassoon General Hospitals, Pune, India (contact via email @bjmcecirb@gmail.com) for researchers who meet the criteria for access to confidential data.

Acknowledgements

We would like to thank the non-medical health care workers involved: Suhasini Surwase, Archana Pawar and Kanta Zarekar; the data entry operator: Rohini Kamble; all the ART staff and the study participants without whom this work would not be possible.

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