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Research

Acceptability and tolerability of and adherence to HIV preexposure prophylaxis among Toronto gay and bisexual men: a pilot study

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Abstract

Background: Preexposure prophylaxis is efficacious at preventing HIV infection, but concerns persist about adherence and sexually transmitted infections (STIs). We assessed preexposure prophylaxis acceptability, adherence and clinical outcomes in a pilot demonstration project.

Methods: HIV-uninfected adult gay and bisexual men who scored 10 or higher on a validated HIV risk score (HIV Incidence Risk Index for MSM) and reported condomless receptive anal sex were sequentially enrolled into a 1-year open-label single-arm pilot study of daily oral therapy with tenofovir disoproxil fumarate/emtricitabine in Toronto. The primary outcome was acceptability of preexposure prophylaxis. Secondary outcomes were preexposure prophylaxis adherence (4-d recall, pill count and dried blood spot analysis), HIV seroconversion, STIs and adverse events.

Results: Of the 86 men screened, 52 were enrolled. Participants were mostly young (median age 33 yr [interquartile range (IQR) 28–37 yr) white (38 [73%]) gay (49 [94%]) men. Preexposure prophylaxis acceptability was high: all participants reported their experience as "good" or "very good." The median adherence rate was high, at 100% (IQR 95%–100%) by self-report and 96.9% (IQR 93.4%–98.4%) by pill count. Dried blood spot analysis suggested that doses were taken 4–7 days/week at 88.7% (173/195) of month 3–12 visits. No cases of HIV seroconversion occurred, but 25 participants (48%) experienced at least 1 bacterial STI, with incidence rates per 100 person-years of 32.8, 32.8, 8.2 and 8.2 for chlamydia, gonorrhea, syphilis and lymphogranuloma venereum, respectively. No adverse events led to discontinuation of prophylaxis, but the estimated glomerular filtration rate declined by 0.22 mL/min per month.

Interpretation: Preexposure prophylaxis was associated with high adherence and acceptability and no HIV infections in this study. Frequent STIs and clinically unapparent toxic renal effects reinforce the need for ongoing vigilance. **Trial registration:** ClinicalTrials.gov, no. NCT02149888

A disproportionate burden of HIV infections in Canada occurs among gay, bisexual and other men who have sex with men, who account for 49.7% of prevalent infections and have a 131-fold higher risk of incident HIV than other Canadian men.[1] Preexposure prophylaxis with daily oral tenofovir disoproxil fumarate/emtricitabine therapy is a biomedical HIV prevention approach that has been shown to be safe and efficacious in reducing HIV acquisition in randomized trials.[2–5] As the results of these studies became available, interest increasingly turned to conducting "demonstration projects" or clinical trials addressing implementation outcomes such as adherence and real-world effectiveness.[6–8] However, in surveys we conducted among stakeholders across Canada,[9–13] respondents expressed concerns about the potential for suboptimal adherence, sexually transmitted infections (STIs) and toxic drug effects. Furthermore, there was uncertainty about the acceptability of preexposure prophylaxis, fuelled in part by reports of slow uptake in other settings.[14,15]

To address these concerns and inform broader rollout in Canada, we conducted a pilot demonstration project among gay, bisexual and other men who have sex with men in Toronto. Our primary objective was to assess the acceptability of preexposure prophylaxis at the community and individual levels, by quantifying both the volume of referrals to the study and participants' satisfaction. As secondary outcomes, we also quantified adherence, HIV seroconversion, bacterial STIs and adverse events.

Competing interests: In the past 2 years, Darrell Tan's institution has received research support for investigator-initiated research studies from Gilead Sciences and ViiV Healthcare, and Darrell Tan has been a site principal investigator for clinical trials sponsored by GlaxoSmithKline. Janet Raboud is a coinvestigator on several projects with in-kind contributions or research support from Merck & Co. and Gilead Sciences. No other competing interests were declared.

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Methods

Study design

PREPARATORY-5 was a 1-arm, open-label pilot demonstration project of daily preexposure prophylaxis among high-risk Toronto gay, bisexual and other men who have sex with men (NCT02149888). Study staff dispensed tenofovir disoproxil fumarate/emtricitabine (300/200 mg), 1 tablet administered orally once daily over 1 year, during quarterly follow-up visits at St. Michael's Hospital, a tertiary academic hospital.

We conceived the trial as a pilot study because we planned to use the findings to inform the design of future studies. In accordance with a previously published taxonomy of reasons for conducting pilot studies,[16] our study objectives corresponded to both process and scientific reasons. Our specific process-related objectives were to determine the rate of referrals for preexposure prophylaxis from community organizations as well as preexposure prophylaxis acceptability to inform potential recruitment rates for future trials. As scientific objectives, we sought to quantify key outcomes such as adherence and STIs to inform the sample size calculations for such studies.

Participants

We recruited participants through self-referral and provider referral between Oct. 16 and Dec. 30, 2014, as previously described.[17] English-speaking men aged 18 years or more were eligible if they reported having sex with men, tested nonreactive on a fourth-generation HIV test (Architect antigen/antibody combo assay, Abbott Laboratories), had a creatinine clearance rate of 60 mL/min or greater by the Modified Diet in Renal Disease formula, reported condomless receptive anal sex over the preceding 6 months and scored 10 or higher on the HIV Incidence Risk Index for MSM, a recommended cut-off value for identifying candidates for preexposure prophylaxis.[18]

Exclusion criteria included symptoms or signs of HIV seroconversion, use of pre- or postexposure prophylaxis within the preceding 3 months, concomitant therapy with nephrotoxic or immunomodulatory drugs, hepatitis B surface antigen positivity, high risk of osteoporosis, enrolment in another HIV prevention trial or perceived inability to adhere to the study protocol. The last criterion refers to situations in which the potential participant and the study staff together determine that the study visits required by the study protocol are not feasible for the person owing to frequency, timing and/or time commitment. Eligibility criteria were assessed via standardized interviews and blood tests done during screening.

Study procedures

Eligible men attended a baseline visit within 2 weeks and follow-up visits at months 1, 3, 6, 9 and 12 thereafter. Each visit included assessment for adverse events, Insti HIV rapid antibody testing (bioLytical Laboratories), fourth-generation HIV testing, complete blood count, determination of creatinine and phosphate levels, serologic testing for syphilis, pill count, dried blood spot collection for measurement of intraerythrocytic tenofovir disphosphate levels[19] and drug dispensing. At all visits except month 1, participants also underwent urinalysis and screening for gonorrhea and chlamydia infections by means of urine nucleic acid amplification testing, and pharyngeal and rectal swabs were collected for culture. Data on STIs diagnosed at other facilities were collected by history. Every visit included personalized counselling on adherence with preexposure prophylaxis and sexual risk reduction. Electronic questionnaires assessed preexposure prophylaxis acceptability and adherence (Adult AIDS Clinical Trials Group Adherence Questionnaire[20]). Participants received $25 compensation per visit. Each participant was also asked to attend a single adherence-support session with an experienced counsellor housed at a partner community-based organization, where one-on-one counselling was provided based on a published adherence-support intervention.[21]

Sample size considerations

The target sample size was 50 participants, based primarily on feasibility considerations. This sample size permitted estimation of the proportion of participants reporting high acceptability, anticipated at 80%–90%, with reasonable precision (within 10%).

Outcome measures and statistical analysis

We summarized demographic and clinical characteristics of participants using descriptive statistics. To assess community-level interest in preexposure prophylaxis, we quantified the number of individual referrals received per unit time. To assess individual-level acceptability, we calculated each participant's response to the question "Overall, how would you rate your experience on PrEP [preexposure prophylaxis]?", averaged over all available study visits, on a Likert scale ranging from 1 ("very bad") to 5 ("very good").

We quantified adherence using self-report, pill count and intraerythocytic tenofovir diphosphate levels in dried blood spots.[22] We used self-report data to calculate the proportion of doses taken over the preceding 4 days and pill count data to estimate the total number of doses taken between successive study visits. We used dried blood spot data to classify the results into 4 categories: dosing 7 days/week, 4–6 days/week, 2–3 days/week or less than 2 days/week, corresponding to HIV risk reduction values of 100%, 100% (95% confidence interval [CI] 86% to 100%), 84% (95% CI –24% to 99%) and 44% (95% CI –31% to 77%), respectively.[23] At the time that this study was designed, the relation between adherence and effectiveness of preexposure prophylaxis had not been formally quantified, which precluded specification of an evidence-based threshold for adherence a priori.

We tabulated incident STIs, converted into incidence rates per 100 person-years of follow-up. We classified clinical adverse events according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events,[24] severity and investigator-assessed probability of association with the study drug. We calculated the creatinine clearance rate at each visit using the Modified Diet in Renal Disease equation and modelled the effect of time on estimated glomerular filtration rate using a linear mixed model with a random intercept and a fixed effect of continuous time. Sexual behaviour data

were collected but were not a protocol-defined secondary objective; they will be the subject of a separate publication.

We did not impute missing data because we achieved 93.8% of planned follow-up. Analyses were conducted with SAS version 9.4 (SAS Institute) and R version 3.4.1 (R Foundation for Statistical Computing).

Ethics approval

Ethics approval was provided by the research ethics boards of St. Michael's Hospital, Ryerson University, the University Health Network and the University of Toronto. All participants provided written informed consent before any study activities.

Results

Participant flow and recruitment

Our process-related evaluations showed that, during the 75-day recruitment period, community-based organizations referred 115 people, and our electronic advertisements generated 1518 click-throughs. These referrals generated 165 unique inquiries about trial participation (2.2/d) from the community.

Of the 86 men screened for participation, 52 were eligible and were enrolled (Figure 1). Those deemed ineligible were not significantly different from enrolled participants with respect to referral source (self- v. community-referred), age, ethnicity, sexual orientation, income and education (data not shown). Of the 52 participants enrolled, 43 (83%) were retained for the full year, and 1, 2 and 6 participants left the study early, after their month 3, 6 and 9 visits respectively, producing 48.75 person-years of follow-up overall. Baseline characteristics were similar for the 43 retained participants (Table 1) and the 9 who left

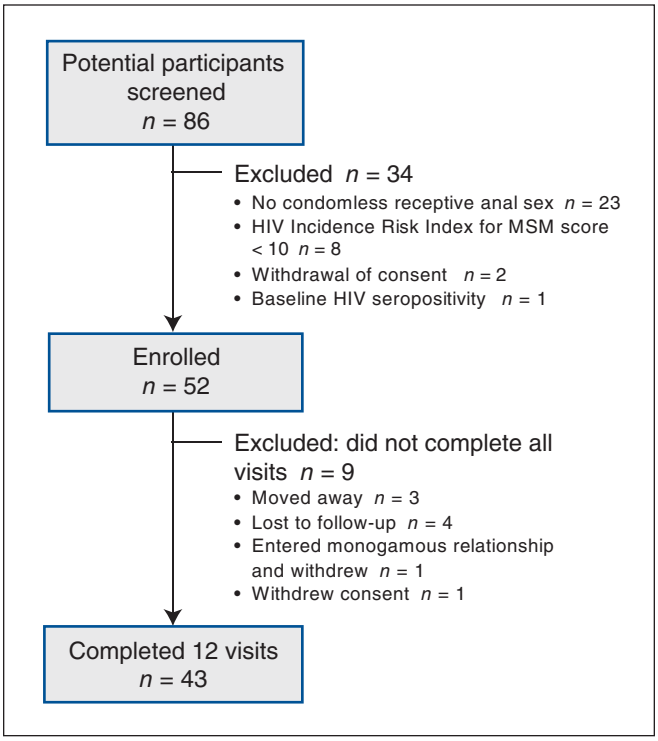

Figure 1: Flow diagram showing participant selection.

Table 1: Participant sociodemographic and behaviour characteristics

Characteristic	No. (%) of participants* n = 52
Age, yr, median (IQR)	33 (28–37)
Race	
White	38 (73)
Asian	4 (8)
Latino	3 (6)
Middle Eastern	3 (6)
Other†	4 (8)
Sexual orientation	
Gay	49 (94)
Bisexual‡	3 (6)
Education	
High school or some postsecondary	14 (27)
Undergraduate	23 (44)
Graduate	15 (29)
Annual income, $	
≤ 20 000	9 (17)
20 001–40 000	11 (21)
40 001–60 000	14 (27)
60 001–80 000	7 (13)
80 001–100 000	5 (10)
> 100 000	6 (12)
No. of prescription medications, median (IQR)	0 (0–1)
No. of supplements, median (IQR)	1 (0–3)
Current smoker	13 (25)
Previous sexually transmitted infection diagnosis	
Gonorrhea	21 (40)
Chlamydia	24 (46)
Syphilis	10 (19)
Any bacterial sexually transmitted infection	36 (69)
Baseline HIV Incidence Risk Index for MSM score, median (IQR)	29 (22.5–33.0)
Recreational drug use in prior 3 mo	
Amphetamines (crystal)	9 (17)
"Poppers"	36 (69)
Baseline sexual behaviours in prior 6 mo, median (IQR)	
No. of partners	18 (12–30.5)
No. of HIV-positive partners	1 (0–3)
Condomless receptive anal sex, no. of times	5 (2–15)
Condomless receptive anal sex with HIV-positive partner, no. of times	0 (0–0)
Condomless insertive anal sex, no. of times	5 (2–12.5)
Condomless insertive anal sex with HIV-positive partner, no. of times	0 (0–3)

Note: IQR = interquartile range.
*Except where noted otherwise.
†Includes participants who identified as mixed (n = 2), black (n = 1) or First Nations (n = 1).
‡Includes 1 participant who identified as pansexual.

early (data not shown). Study visits were conducted between Nov. 10, 2014, and June 28, 2016.

Baseline characteristics

Most of the participants identified as gay (49 [94%]) white (38 [73%]) men with an undergraduate degree or higher (38 [73%]). The median age was 33 (interquartile range [IQR] 28–37) years (Table 1). The median number of prescription medications taken was 0 (IQR 0–1), but the median number of supplements taken was 1 (IQR 0–3). Most participants (36 [69%]) had a prior history of 1 or more bacterial STIs. The median number of sexual partners over the preceding 6 months was 18 (IQR 12–30.5), and the median number of condomless receptive and insertive anal sex acts was 5 (2–15) and 5 (2–12.5), respectively.

Outcomes

Additional process-related evaluations showed that individual-level preexposure prophylaxis acceptability was high. After we averaged data for each participant over all follow-up visits for which responses were available (5, 4 or 3 visits for 81%, 12% and 8% of participants, respectively), 100% of participants rated their experience with preexposure prophylaxis as 4 ("good") or 5 ("very good"), and the median overall response was 4.8 (IQR 4.4–5.0).

Overall adherence to preexposure prophylaxis was high, whether assessed by self-report, pill count or dried blood spot analysis (Table 2). The median adherence rate was 100% (IQR 95%–100%) by self-report and 96.9% (IQR 93.4%–98.4%) by pill count. Intraerythrocytic tenofovir diphosphate levels were consistent with dosing on 7 days, 4–6 days, 2–3 days and less than 2 days per week, at 50.6%, 36.8%, 9.7% and 2.8% of all study visits, respectively. After we removed month 1 data, since tenofovir diphosphate may not have reached steady state inside erythrocytes at this point,[22] these figures increased to 58.5%, 30.3%, 8.7% and 2.6%, respectively.

There were no cases of HIV seroconversion. However, the burden of bacterial STIs was high, with 40 confirmed infections occurring in 25 participants (48%) (Table 3). Fifteen [60%]) of these 25 men had a prior history of an STI. In addition, there were 6 episodes of nonspecific urethritis treated empirically at other facilities, for which gonorrhea and chlamydia testing reportedly gave negative results.

Adverse events

Of the 185 adverse events overall (Table 4), 37 (20%) were at least possibly related to the study drug, but all were mild (30 [81%]) or moderate (7 [19%]) in severity, and none led to discontinuation of prophylaxis. The most common adverse events at least possibly related to study drug were nausea, diarrhea and headache, occurring in 11 (21%), 6 (12%) and 6 (12%) participants, respectively. The only serious adverse event was hospital admission for severe but self-limited infectious colitis, for which no specific cause was identified. The other 2 adverse events graded as severe included 1 episode each of lymphogranuloma venereum and stress. All 3 severe adverse events were deemed unrelated to the study drug.

We observed 1 grade 2 and 3 grade 1 instances of creatinine level elevation, all of which resolved spontaneously without the need to interrupt the study drug. The creatinine clearance rate appeared to change by –0.22 (95% CI –0.45 to 0.01) mL/min per month of follow-up in a generalized linear mixed model, but this change was of borderline statistical significance ($p = 0.06$).

Interpretation

In this pilot demonstration project, we observed high acceptability of preexposure prophylaxis at the community and individual levels, excellent adherence, a favourable adverse event profile and no cases of seroconversion over 48.75 person-years of follow-up. The high adherence is important because adherence is the key predictor of preexposure prophylaxis effectiveness.[2,23,25] However, STIs were common, as seen elsewhere,[26,27] and the creatinine clearance rate appeared to decline by 0.22 mL/min per month. Our process-related findings confirm the feasibility of preexposure prophylaxis in this population, and our scientific findings highlight the need for ongoing attention to STIs and clinically unapparent toxic

Table 2: Adherence by measurement technique

		% of doses taken, median (IQR)		Tenofovir disoproxil fumarate/emtricitabine level, fmol/punch*; no. (%) of participants				
Month	No. of participants	Self-reported 4-d recall	Pill count	Median (IQR)	≤ 349	350–699	700–1249	≥ 1250
1	52	100 (100–100)	100 (96.4–100)	930 (746.5–1199)	2 (4)	7 (13)	32 (62)	11 (21)
3	52	100 (100–100)	98.7 (93.7–100)	1341 (1062–1555.5)	0 (0)	4 (8)	18 (35)	30 (58)
6	51	100 (100–100)	98.9 (92.9–100)	1432 (1068–1847)	0 (0)	4 (8)	15 (29)	32 (63)
9	48	100 (100–100)	98.9 (95.0–100)	1392.5 (1141–1662.5)	1 (2)	3 (6)	11 (23)	33 (69)
12	42	100 (95.0–100)	98.0 (90.1–100)	1191.5 (777–1527)	2 (5)	6 (14)	15 (36)	19 (45)

Note: IQR = interquartile range.
*Levels of 349 fmol/punch or less, 350–699 fmol/punch, 700–1249 fmol/punch and 1250 fmol/punch or greater correspond to preexposure prophylaxis dosing on less than 2, 2–3, 4–6 and 7 days per week, respectively.[24]

Table 3: Incident sexually transmitted infections

Infection	No. of cases	Incidence per 100 person-years of follow-up (95% CI)
Gonorrhea	16	32.8 (19.4 to 52.2)
Urethral	5	
Pharyngeal	2	
Rectal	6	
Multiple sites	3	
Chlamydia	16	32.8 (19.4 to 52.2)
Urethral	7	
Pharyngeal	1	
Rectal	8	
Lymphogranuloma venereum (rectal)	4	8.2 (2.6 to 19.8)
Syphilis	4	8.2 (2.6 to 19.8)

Note: CI = confidence interval.

Table 4: Adverse events

Adverse event	No. (%) of participants *n* = 52	No. (%) of events *n* = 185
Any	47 (90)	–
Grade 1 (mild)	34 (65)	144 (77.8)
Grade 2 (moderate)	10 (19)	38 (20.5)
Grade 3 (severe)	3 (6)	3 (1.6)
Any serious	1 (2)	1 (0.5)
By relation to study drug		
Possibly	14 (27)	26 (14.0)
Probably	9 (17)	11 (5.9)
At least possibly related to study drug		
Nausea	11 (21)	12 (6.5)
Diarrhea	6 (12)	6 (3.2)
Headache	6 (12)	6 (3.2)
Fatigue	5 (10)	5 (2.7)
Bloating	2 (4)	2 (1.1)
Vivid dreams	2 (4)	2 (1.1)
Anorexia	1 (2)	1 (0.5)
Difficulty sleeping	1 (2)	1 (0.5)
Flatulence	1 (2)	1 (0.5)
Itching	1 (2)	1 (0.5)

drug effects. Our results are broadly consistent with those of other studies,[28] and our estimates regarding referral rates, adherence and STIs will be helpful in the design of future studies.

Our inclusion criteria were selected to include gay, bisexual and other men who have sex with men at very high risk for HIV. Specifically, all participants reported condomless receptive anal sex within the preceding 6 months and scored high on a validated risk score (HIV Incidence Risk Index for MSM).[18] The sample thus represents a population that should be prioritized for the rollout of preexposure prophylaxis in order to maximize both its public health impact and its cost-effectiveness.

Because our study lacked a comparison group, it was not possible to determine to what extent preexposure prophylaxis was causally related to the high burden of STIs observed. Previous studies have given mixed findings on this topic. A meta-analysis summarizing cohorts of men using versus not using preexposure prophylaxis showed incidence rate ratios of 25.3, 11.2 and 44.6 for gonorrhea, chlamydia and syphilis, respectively.[29] However, since these infections are also an important marker of HIV risk, these results are heavily confounded by indication; high incidence could alternatively signify that programs have been successful at identifying those in greatest need. That 69% of our study participants had a prior bacterial STI at study entry supports this notion. High rates could also be partly attributable to increased screening. The PROUD (Pre-exposure Prophylaxis to Prevent the Acquisition of HIV-1 Infection) study showed that, after adjustment for the frequency of testing, the odds of any bacterial STI was similar to that for control participants (odds ratio 1.07, 95% CI 0.78 to 1.46).[27] Additional control strategies for STIs are urgently needed.[30]

Although concern about side effects has been reported as the most common reason for not wanting to use preexposure prophylaxis in acceptability studies,[9,31] adverse events in our cohort were minimal and were generally restricted to mild gastrointestinal symptoms that resolved spontaneously. These findings are consistent with a systematic review of preexposure prophylaxis clinical trials, in which the risk of adverse events was similar to that with placebo (relative risk 1.01, 95% CI 0.99 to 1.03).[32] However, we did observe clinically unapparent declines in the creatinine clearance rate, at –0.22 mL/min per month, or –2.64 mL/min per year. This is greater than the age-related decline in glomerular filtration rate observed in healthy adults, estimated at roughly 0.75–0.97 mL/min per year.[33,34] Our findings are consistent with those from randomized trials, in which preexposure prophylaxis has been associated with decreases in estimated glomerular filtration rate that were roughly 1 mL/min per year greater than seen with placebo.[35–39] Importantly, such changes in renal function are felt to be reversible.[40]

Limitations

Our pilot study has limitations that warrant consideration. First, it was not comparative, and our sample size was modest. However, our purpose was to conduct descriptive analyses only, to inform the design of future studies by addressing specific process-related and scientific objectives. Second, at the time that this study was designed, the relation between preexposure prophylaxis adherence and effectiveness among gay, bisexual and other men who have sex with men had not been formally quantified, which precluded us from specifying an

evidence-based threshold for adherence a priori. Nevertheless, we found generally favourable adherence results, for several potential reasons. Most participants were already taking at least 1 supplement at study entry, which suggests experience with regular pill-taking and high health-seeking behaviour, and our adherence-support intervention may have further bolstered adherence. Third, we included only English-speaking participants. Fourth, 34 of the 86 men screened were ineligible for the study, mostly because of not recently having had condomless receptive anal sex, which raises the possibility of selection bias. However, the demographic characteristics of included and excluded people were similar, such that our findings are reflective of men at high risk who met our eligibility criteria. Finally, because we recruited participants in a context where preexposure prophylaxis was not widely available, our participants could be considered "early adopters"[41] and thus may not represent the broader population of at-risk gay, bisexual and other men who have sex with men in Canada. Health Canada granted regulatory approval for preexposure prophylaxis only in February 2016, and public reimbursement became available in Ontario only in September 2017.

Conclusion

Preexposure prophylaxis was associated with high adherence and acceptability and no cases of seroconversion in this study. Our findings support the broader rollout of preexposure prophylaxis for at-risk gay, bisexual and other men who have sex with men in this Canada and in similar industrialized settings. However, changes in sexual behaviour, frequent STIs and clinically unapparent effects on renal function reinforce the need for ongoing vigilance. Furthermore, these data were collected during 2014–2016, and outcomes related to preexposure prophylaxis may continue to evolve. It will be important to continually monitor outcomes as public drug coverage and community uptake increase and as clinical practice guidelines[42] lead to greater prescribing. As such, the results of our pilot study have been used to perform sample size calculations for the Ontario PrEP Cohort Study, which will monitor these and related outcomes across the province in the coming years and may similarly inform the design of interventional studies in the future.

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