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Daily and Nondaily Oral Preexposure Prophylaxis in Men and Transgender Women Who Have Sex With Men: The Human Immunodeficiency Virus Prevention Trials Network 067/ADAPT Study

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Background. Nondaily dosing of oral preexposure prophylaxis (PrEP) may provide equivalent coverage of sex events compared with daily dosing.

Methods. At-risk men and transgender women who have sex with men were randomly assigned to 1 of 3 dosing regimens: 1 tablet daily, 1 tablet twice weekly with a postsex dose (time-driven), or 1 tablet before and after sex (event-driven), and were followed for coverage of sex events with pre- and postsex dosing measured by weekly self-report, drug concentrations, and electronic drug monitoring.

Results. From July 2012 to May 2014, 357 participants were randomized. In Bangkok, the coverage of sex events was 85% for the daily arm compared with 84% for the time-driven arm ($P = .79$) and 74% for the event-driven arm ($P = .02$). In Harlem, coverage was 66%, 47% ($P = .01$), and 52% ($P = .01$) for these groups. In Bangkok, PrEP medication concentrations in blood were consistent with use of ≥2 tablets per week in >95% of visits when sex was reported in the prior week, while in Harlem, such medication concentrations occurred in 48.5% in the daily arm, 30.9% in the time-driven arm, and 16.7% in the event-driven arm ($P < .0001$). Creatinine elevations were more common in the daily arm ($P = .050$), although they were not dose limiting.

Conclusions. Daily dosing recommendations increased coverage and protective drug concentrations in the Harlem cohort, while daily and nondaily regimens led to comparably favorable outcomes in Bangkok, where participants had higher levels of education and employment.

Clinical Trials Registration. NCT01327651.

Keywords. HIV; prevention; preexposure prophylaxis; men who have sex with men; transgender women.

Daily dosing of preexposure prophylaxis (PrEP) is recommended by the US Food and Drug Administration and the Centers for Disease Control and Prevention [1], whereas the European AIDS Clinical Society recommends either daily dosing or dosing before and after sex [2]. The Ipergay trial demonstrated effectiveness of "on demand" dosing, involving a double emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) dose 2–24 hours before sex and an additional FTC/TDF dose on each of the 2 days following sex [3], confirming findings from animal models [4]. The Iniciativa Profilaxis Pre-exposición (iPrEx) open-label extension found no new infections among men with drug concentrations indicating the use of ≥4 tablets of FTC/TDF per week as well as an 81% reduction in human immunodeficiency virus (HIV) incidence associated with average use of 2–3 tablets per week [5].

Adherence to event-driven dosing recommendations has been mixed. Such dosing was associated with lower PrEP adherence in 2 small blinded and placebo-controlled PrEP trials conducted in Africa [6, 7]. The use of blinding and a placebo may have undermined PrEP use in these trials. Furthermore, different measurements provided highly divergent estimates of adherence, which highlighted the methodological challenges arising when assessing event-driven PrEP dosing.

The HIV Prevention Trials Network (HPTN) study 067, the Alternative Dosing to Augment PrEP Pill Taking (ADAPT) study, randomly assigned participants to daily or nondaily dosing of

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open-label oral FTC/TDF. The aim was to assess the likelihood that sex events would be covered by pre- and postexposure antiretroviral dosing with daily or nondaily regimens that were effective in animal models [4] and the likelihood of achieving drug concentrations that provide substantial reductions in HIV incidence among men and transgender women who have sex with men [5].

METHODS

Study Design

The HPTN 067 study was a phase 2, randomized, open-label, pharmacokinetic, and behavioral equivalence study of daily vs nondaily oral FTC/TDF PrEP. The study enrolled men and transgender women who have sex with men at a community clinic and clinical research site in Bangkok, Thailand, and a clinical research site in Harlem in New York City. Women were enrolled at a study site in Cape Town, South Africa, as reported separately [8]. Ethics committee approvals were obtained from all applicable authorities (see Supplementary Materials). The protocol was registered at ClinicalTrials.gov (identifier NCT01327651; https://www.hptn.org/research/studies/82).

Participants

Participants were eligible based on the following criteria: male sex assigned at birth, HIV-antibody negative, at least 18 years old, normal renal function (estimated creatinine clearance >70 mL/minute), hepatitis B surface antigen negative, literate in English or Thai, able to provide written informed consent, and reported anal or neovaginal sex with a man in the past 6 months, and have at least 1 of the following self-reported risk factors for HIV acquisition in the past 6 months: sex with >1 man or transgender woman; history of an acute sexually transmitted infection; sex in an exchange for money, goods, or favors; or intercourse without a condom with an HIV-infected partner or partner of unknown HIV infection status (see Supplementary Materials for eligibility related to hepatitis B immunity).

Visits and Medication Dispensation

Study visits were divided into phases for screening, directly observed dosing, self-administered dosing, and post-PrEP use. Visits were scheduled at screening; enrollment (the beginning of directly observed dosing); weeks 1, 2, 3, and 4 (the end of directly observed dosing); weeks 5 and 6 (randomization and the beginning of self-administered dosing); weeks 10, 14, 18, 22, 26, and 30 (end of self-administered dosing); and week 34. To facilitate interpretation of drug concentration results during the study, participants received once per week directly observed dosing of 1 tablet of oral FTC/TDF at enrollment and at weeks 1, 2, 3, and 4. At week 6, participants were randomized and were dispensed 30 tablets of oral FTC/TDF and provided counseling specific to their randomization group (see Supplementary Materials). Every 4 weeks during the self-administered phase, an additional 30 tablets of FTC/TDF were dispensed.

Monitoring of PrEP Use and Sex

All participants received a real-time electronic drug monitoring (EDM) device (WisePill) at enrollment. Weekly phone-based or in-person interviews at the study site (at the choice of the participant) were conducted using real-time EDM data to determine if an electronically recorded "opening" event was reflective of an ingested dose (vs curiosity opening, pocket dose, or refill of device) and for correction of date and time for doses removed and taken at a later time; after collecting dose date and time information, sexual events over the past week were documented for date and time, as well as type of sex, condom use, and partners. Interviewers were not part of the clinical care team and did not feed back information to team members and were trained in neutral interviewing [9]. The results of the EDM-guided weekly interviews formed the basis for assessing coverage of sex events with pre- and postexposure dosing and adherence (see Supplementary Materials). Participants were offered vitamin tablets during the 6-week directly observed therapy phase (to become familiar with the device). Long-term adherence to PrEP was evaluated using blood concentrations of tenofovir diphosphate (TFV-DP) in dried blood spots [5, 10] or peripheral blood mononuclear cells [11] (see Supplementary Materials). Tablet sharing was investigated by a computer-assisted self-interview conducted 12 and 24 weeks after randomization.

Primary Outcomes

The primary outcome was coverage of anal and neovaginal intercourse events with pre- and postexposure dosing of PrEP defined as at least 1 tablet reported taken within 96 hours (4 days) prior to intercourse and another tablet reported taken within 24 hours after intercourse. Drug concentrations during weeks when sex was reported should reflect use of at least 2 PrEP tablets if the sex event was covered with pre- and postsex dosing according to the regimens recommended in the protocol. This amount of oral FTC/TDF PrEP use protected nonhuman primates [4] and reduced HIV incidence in men who have sex with men (MSM) by 76% [11]. See the Supplementary Materials for definitions of outcomes.

Statistical Analysis

Quantitative measures are summarized using medians and interquartile ranges; categorical measures are summarized with proportions. In the primary analysis of coverage, the unit of analysis is the sex act (covered or not covered). A logistic regression for dependent data [12] with robust variance and clustering on participant was used to compare coverage between the daily arm and each intermittent arm (P values for a standard inequality test are given and we comment on noninferiority as needed). A similar approach (with the follow-up visit as the unit of analysis) was used to compare the prevalence of neurological and gastroenterological side effects between arms. The number

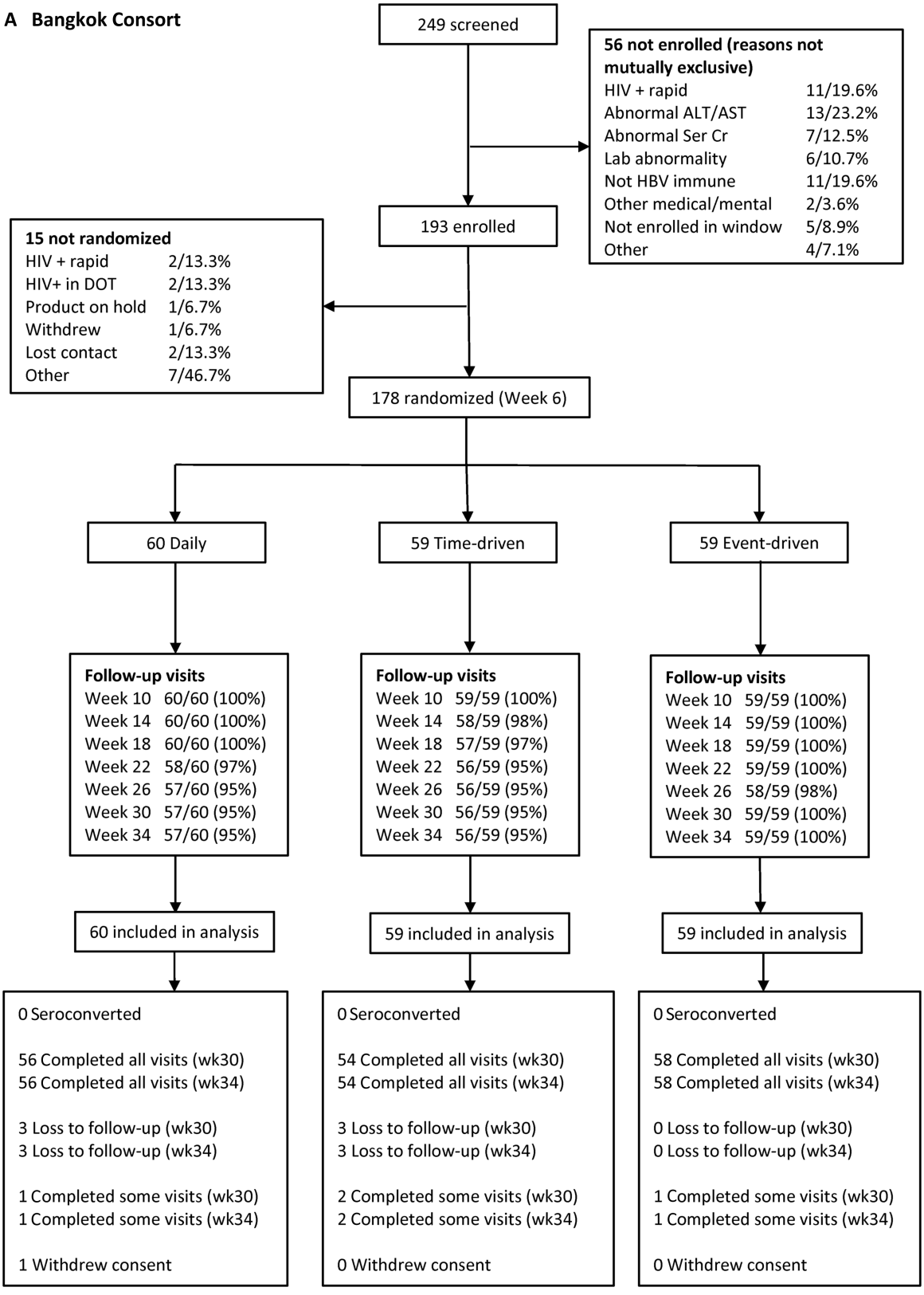

Figure 1. Consort diagrams for the HIV Prevention Trials Network (HPTN) 067 ADAPT study in Bangkok, Thailand (*A*) and Harlem, New York (*B*). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DOT, directly observed therapy; HBV, hepatitis B virus; HIV, human immunodeficiency virus; Ser Cr, serum creatinine.

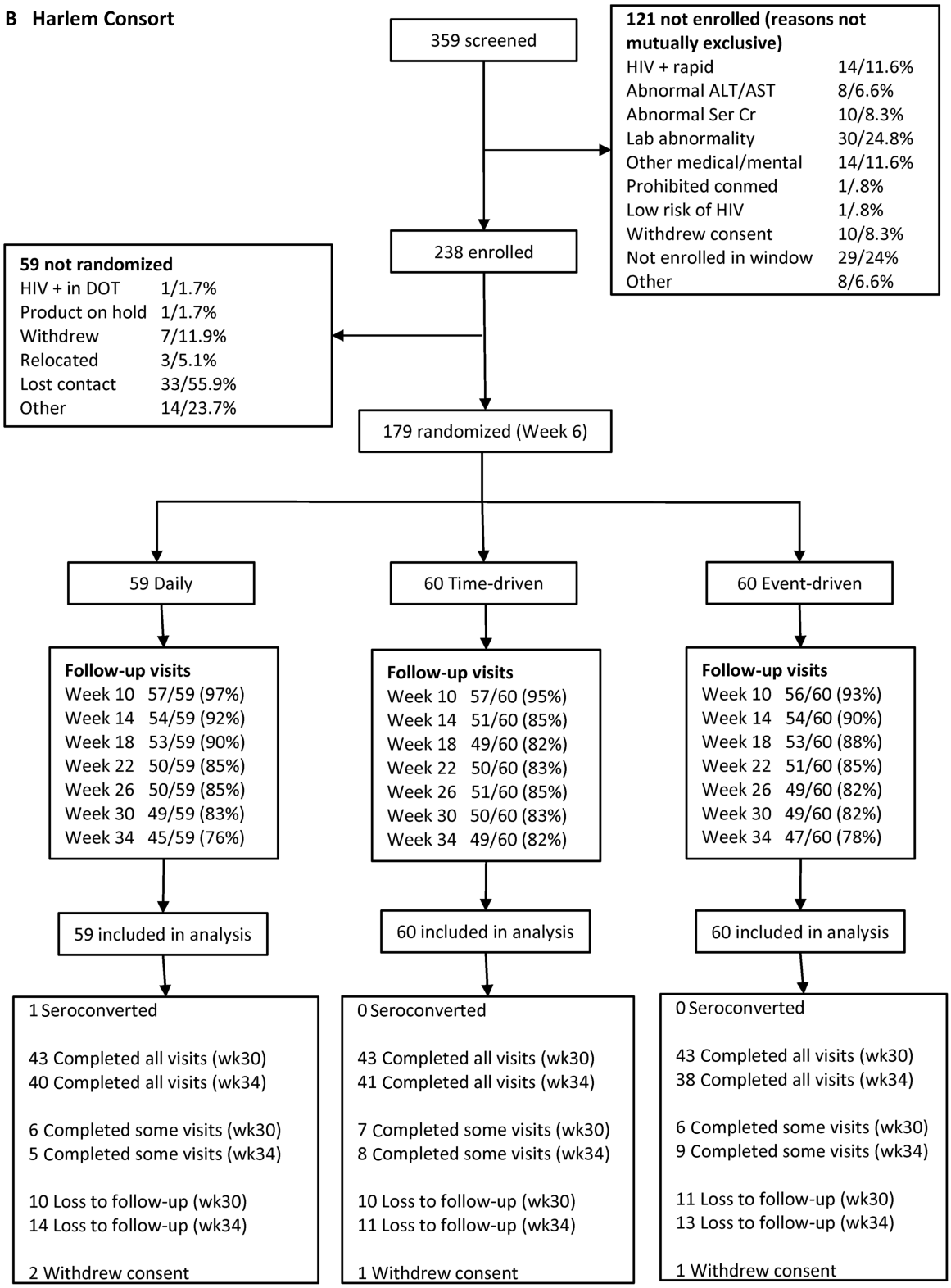

Figure 1. Continued

of pills used and the number of pills required to achieve full adherence to the recommended regimens were compared using a log regression with offset equal to the log of the duration of follow-up and a robust variance. All analyses were intent to treat. Individuals were dropped from analyses following HIV seroconversion.

RESULTS

Study Participants

From 4 July 2012 to 6 May 2014, 608 people were screened, 431 were enrolled, and 357 (83%) were randomized and included in the analysis (Figure 1A and 1B). One randomized participant in Bangkok was excluded from the analysis, as instructed by the local institutional review board, due to a protocol deviation. Retention through the end of the self-administered dosing phase (week 30) was 97% at the Bangkok site and 83% at the Harlem site. Overall, among people randomized, 350 identified as a man, 5 identified as a transgender woman, and 2 identified as gender queer (Table 1). Participants in Bangkok were more likely than those in Harlem to have at least secondary education ($P < .0001$) and be fully employed ($P < .0001$). Among the 179 participants in Harlem, race/ethnicity was self-reported in nonexclusive categories: 126 (70%) were black, 23 (13%) were white, 5 (3%) were Asian, 5 (3%) were Native American, 44 (25%) were Hispanic, and 37 (21%) were other.

Coverage and PrEP Use

Overall, 357 people reported 7734 sex events during the 24-week self-administered phase (average 0.9 sex events per person per week). In Bangkok, coverage of sex events was 85% (1266/1485) for the daily arm compared with 84% (1129/1337) for the time-driven arm ($P = .79$ vs daily), and 74% (749/1018) for the event-driven arm ($P = .02$ vs daily) (Figure 2A). In Harlem, coverage was 66% (718/1081) for the daily arm compared with 47% (615/1311) for the time-driven arm ($P = .01$ vs daily) and 52% (786/1502) for the event-driven arm ($P = .01$ vs daily) (Figure 2B). Among people with partial coverage, the postsex dose was more commonly missed than the presex dose at both sites (Figure 2). Coverage did not change over time in any arm at either site ($P = .98$ for Bangkok, $P = .20$ for Harlem; Figure 3). The results were not different when coverage of sex events without a condom was considered.

In Bangkok, TFV-DP concentrations in peripheral blood mononuclear cells suggested use of ≥2 tablets on visits when sex was reported in the prior week among 97.6% in the daily arm, 98.7% in the time-driven arm ($P = .60$ vs daily), and 95.7% in the event-driven arm ($P = .51$ vs daily) (Table 2). In Harlem, TFV-DP concentrations in dried blood spots suggested use of ≥2 tablets on visits when sex was reported in the prior week among 48.5% in the daily arm, 30.9% in the time-driven arm ($P = .11$ vs daily), and 16.7% in the event-driven arm ($P = .004$

Table 1. Baseline Characteristics Among Participants Randomized in the HIV Prevention Trials Network (HPTN) 067 Study, Bangkok, Thailand (n = 178) and Harlem, New York (n = 179)

	Bangkok			Harlem		
Characteristic	Daily	Time-Driven	Event-Driven	Daily	Time-Driven	Event-Driven
Age, y						
18–24	8 (13.3)	12 (20.3)	8 (13.5)	19 (32.2)	17 (28.3)	17 (28.3)
25–29	13 (21.7)	19 (32.2)	16 (27.1)	13 (22.0)	11 (18.4)	8 (13.4)
30–39	36 (60.0)	23 (39.0)	28 (47.5)	11 (18.7)	12 (20.0)	14 (23.3)
≥40	3 (5.0)	5 (8.5)	7 (11.9)	16 (27.1)	20 (33.3)	21 (35.0)
Self-identified gender						
Man	59 (98.3)	58 (98.3)	59 (100)	57 (96.6)	59 (98.3)	58 (96.6)
Transgender woman	1 (1.7)	1 (1.7)	0 (0)	2 (3.4)	0 (0)	1 (1.7)
Gender queer	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (1.7)
Schooling						
Less than secondary	0 (0)	1 (1.7)	1 (1.7)	16 (27.1)	18 (30.0)	7 (11.7)
Completed secondary	1 (1.7)	7 (11.9)	1 (1.7)	10 (17.0)	19 (31.7)	33 (55.0)
More than secondary	59 (98.3)	51 (86.4)	57 (96.6)	33 (55.9)	23 (38.3)	20 (33.3)
Employment						
None	8 (13.3)	9 (15.2)	3 (5.1)	40 (67.8)	39 (65.0)	44 (73.3)
Part-time	2 (3.3)	5 (8.5)	3 (5.1)	6 (10.2)	14 (23.3)	10 (16.7)
Full-time	50 (83.4)	45 (76.3)	53 (89.8)	13 (22.0)	7 (11.7)	6 (10.0)
Sex partners (past 3 mo)						
0–1	17 (28.3)	16 (27.1)	10 (17.0)	3 (5.1)	4 (6.7)	4 (6.7)
2–4	19 (31.7)	24 (40.7)	29 (49.2)	30 (50.8)	21 (35.0)	26 (43.3)
5–9	16 (26.7)	6 (10.2)	11 (18.6)	8 (13.6)	18 (30.0)	18 (30.0)
≥10	8 (13.3)	13 (22.0)	9 (15.2)	17 (28.8)	15 (25.0)	12 (20.0)
Missing	0 (0)	0 (0)	0 (0)	1 (1.7)	2 (3.3)	0 (0)
Anal intercourse without a condom						
No	38 (63.3)	33 (55.9)	42 (71.2)	12 (20.3)	20 (33.3)	10 (16.7)
Yes	22 (36.7)	26 (44.1)	17 (28.8)	47 (79.7)	40 (66.7)	50 (83.3)

Data are presented as No. (%).

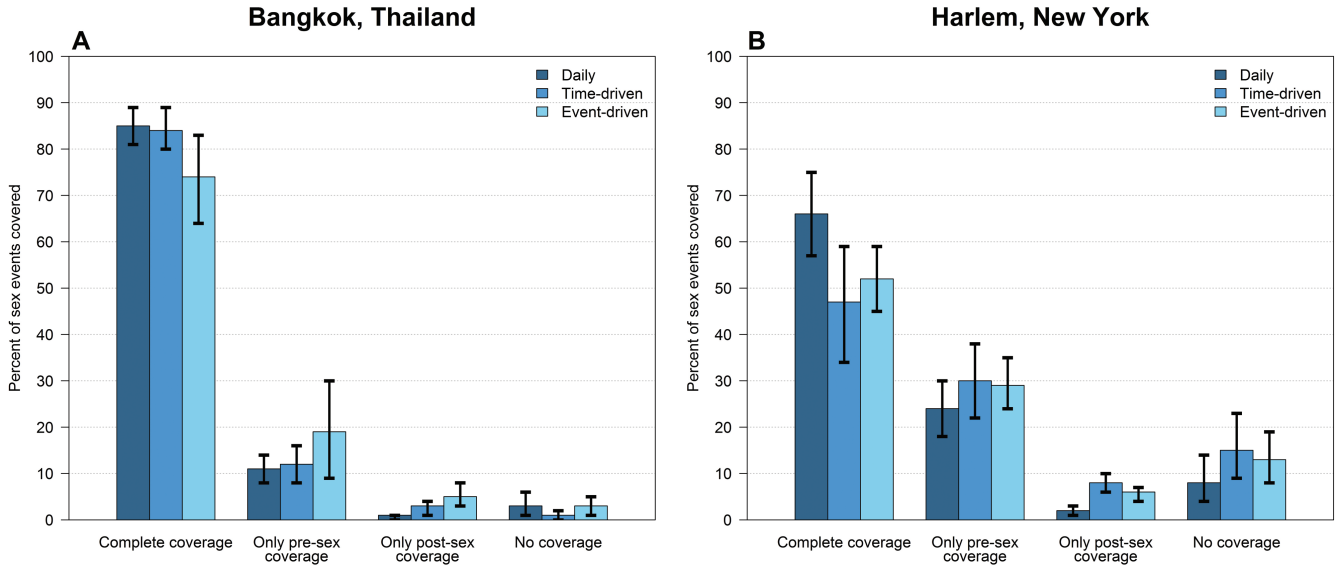

Figure 2. Coverage of sex events with pre- and postsex preexposure prophylaxis dosing in the HIV Prevention Trials Network (HPTN) 067 study, Bangkok, Thailand (*A*) and Harlem, New York (*B*). Error bars represent the 95% confidence interval of the estimate of coverage, based on bootstrap analysis.

vs daily) (Table 2). Proportions taking ≥2 tablets on weeks when sex was reported did not change over time ($P > .14$ for all randomization groups).

Numbers of PrEP Tablets Required for Adherence and Numbers Used

Daily dosing was associated with more than twice as many tablets required for adherence to the recommended regimen ("Tablets Recommended" in Table 2) and larger numbers of tablets actually used compared to both nondaily dosing regimens. Median drug concentrations in the daily arms were nearly double the concentrations of those in the time-driven and event-driven arms when sex was reported in the prior week ($P < .0001$ for Bangkok, $P = .0064$ for Harlem; Table 2).

Adherence

In Bangkok, adherence to the recommended regimen in the daily and time-driven arms were comparable (85.4% vs 79.4%; $P = .42$), whereas adherence in the event-driven arm was less (65.1%;

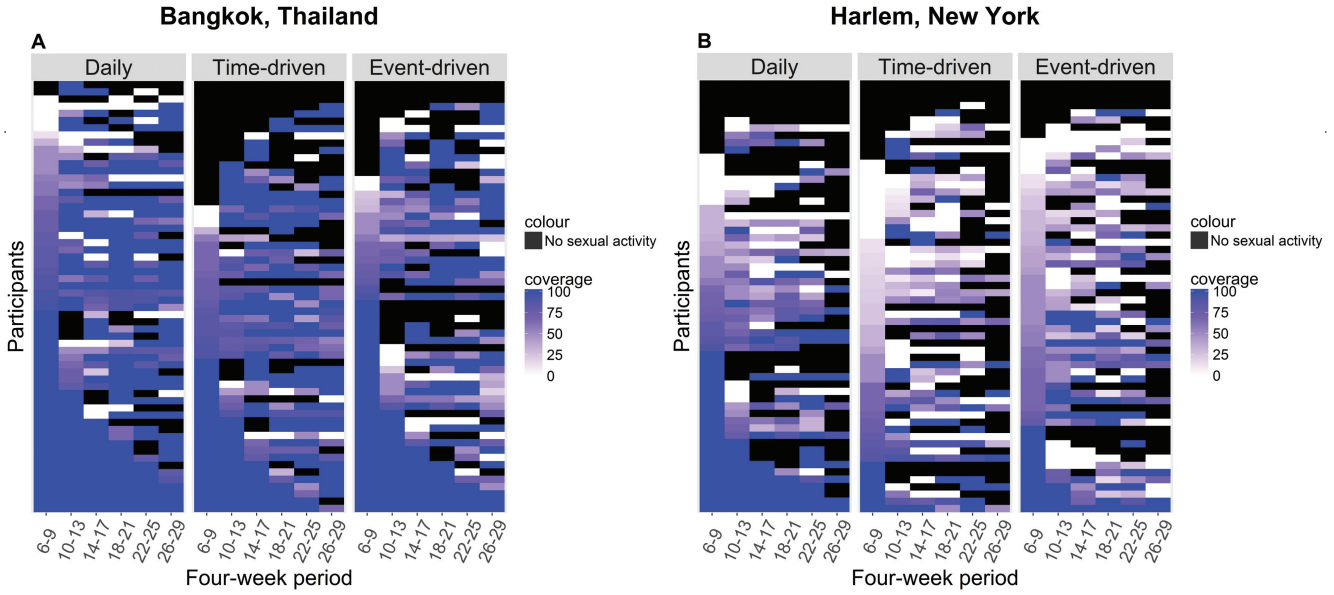

Figure 3. Coverage of sex events with pre- and postsex dosing, the primary outcome, by study site in Bangkok, Thailand (*A*) and in Harlem, New York (*B*), showing 4-week period and recommended regimen. Each row represents a different participant. Dark blue represents complete coverage of sex events with pre- and postsex dosing. Lighter blue shades indicate partial coverage. White represents periods where there was no coverage with pre- or postsex dosing. Black periods reflect periods where there was no sexual intercourse reported or data regarding preexposure prophylaxis use or sexual activity was missing.

$P < .0001$ vs daily). In Bangkok, ≥90% adherence was evident in 29 of 60 (48.3%) participants in the daily arm vs 14 of 59 (23.7%) in the time-driven arm vs 4 of 59 (6.8%) in the event-driven arm. In Harlem, adherence in the daily arm was higher than the time-driven arm (65.1% vs 46.5%; $P < .0001$) and the event-driven arm (41.3%; $P < .0001$ vs daily). In Harlem, ≥90% adherence was evident in 15 of 59 (25.4%) in the daily arm, none of the participants in the time-driven arm, and 1 of 59 (1.7%) in the event-driven arm.

In Bangkok, sharing tablets with other trial participants who needed them was reported during 6% of interviews in the event driven arm and not in other groups. Receiving tablets from other participants because of need was reported in 3% of interviews in the daily arm and not in other groups. In Harlem, tablet sharing was reported during 1%–4% of interviews in all groups.

Self-reported Switching of Regimens

Participants were instructed to follow their specific regimen (see Supplementary Materials), although each participant received enough tablets to adopt an alternative strategy in practice. Computer-assisted self-interviews about regimen switching indicated that the following proportions of participants in Bangkok and Harlem intentionally switched regimens during the self-administered phase of the study: 12% and 10%, respectively, of the daily arm, 0 and 4%, respectively, of the time-driven arm, and 10% and 20%, respectively, of the event-driven arm after excluding missing responses (Bangkok, $P = .015$; Harlem, $P = .037$; overall $P = .0010$). The adopted regimen varied among people who switched.

Table 2. Tablet Use and Side Effects in the HIV Prevention Trials Network (HPTN) 067 Study by Site and Arm, Bangkok, Thailand (n = 178) and Harlem, New York (n = 179)

	Bangkok				Harlem			
Characteristic	Daily	Time-Driven	Event-Driven	*P* Value	Daily	Time-Driven	Event-Driven	*P* Value
No.	60	59	59	…	59	60	60	…
Tablets required for full coverage	1746	1573	1268	.90	1244	1390	1582	.55
Total tablets used (% of daily)	8285	3713 (44.8%)	2157 (26.0%)	<.0001	5507	2468 (44.8%)	2356 (42.8%)	<.0001
Tablets recommended (% of daily)	9420	4121 (43.7%)	1928 (20.5%)	<.0001	8222	3674 (44.7%)	2572 (31.3%)	<.0001
Recommended tablets used (% of daily)	8047	3272 (40.7%)	1255 (15.6%)	<.0001	5351	1708 (31.9%)	1063 (19.9%)	<.0001
Adherence (tablets used / recommended)	85.4%	79.4%	65.1%	<.0001	65.1%	46.5%	41.3%	<.0001
Adherence category (% of group)				<.0001				<.0001
0	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	1 (1.7%)	
1%–49%	4 (6.7%)	2 (3.4%)	9 (15.2%)		20 (33.9%)	36 (60.0%)	40 (66.6%)	
50%–89%	27 (45.0%)	43 (72.9%)	45 (76.3%)		24 (40.7%)	22 (36.7%)	15 (25.0%)	
90%–99%	25 (41.6%)	13 (22.0%)	2 (3.4%)		14 (23.7%)	0 (0%)	0 (0%)	
100%	4 (6.7%)	1 (1.7%)	2 (3.4%)		1 (1.7%)	0 (0%)	1 (1.7%)	
No sex	0 (0%)	0 (0%)	1 (1.7%)		0 (0%)	0 (0%)	0 (0%)	
No interview data	0 (0%)	0 (0%)	0 (0%)		0 (0%)	2 (3.3%)	3 (5.0%)	
TFV-DP concentration on weeks when sex is reported[a]								
Median	84.3	36.9	29.9	<.0001	316.0	122.5	84.9	.0064
IQR	(64.3–127.0)	(22.9–83.0)	(18.8–46.4)		(0–942.0)	(41.8–409.0)	(0–202.0)	
Visits with TFV-DP concentrations indicating ≥2 tablets[b] taken per week on weeks when sex is reported.				.52				.014
Week 10	31/31 (100%)	29/29 (100%)	30/30 (100%)		13/23 (56.5%)	8/23 (34.8%)	5/27 (18.5%)	
Week 18	28/29 (96.6%)	30/30 (100%)	24/26 (92.3%)		11/27 (40.7%)	10/27 (37.0%)	3/21 (14.3%)	
Week 30	22/23 (95.7%)	18/19 (94.7%)	13/14 (92.9%)		9/18 (50.0%)	3/18 (16.7%)	3/18 (16.7%)	
Overall	81/83 (97.6%)	77/78 (98.7%)	67/70 (95.7%)		33/68 (48.5%)	21/68 (30.9%)	11/66 (16.7%)	
Neurologic side effect, % of visits	14.2%	14.3%	13.3%	.94	6.1%	3.3%	4.5%	.32
Gastrointestinal side effects, % of visits	13.1%	8.5%	10.5%	.38	8.0%	5.8%	7.1%	.75

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; TFV-DP, tenofovir diphosphate.

[a]TFV-DP in peripheral blood mononuclear cells (PBMCs) was analyzed for Bangkok, and dried blood spots (DBSs) for Harlem.

[b]For Bangkok, TFV-DP in PBMCs >5.2 fmol/10^6 cells is considered as participants taken ≥2 tablets per week; For Harlem, TFV-DP in DBSs ≥326 fmol/punch is considered as participants taken ≥2 tablets per week.

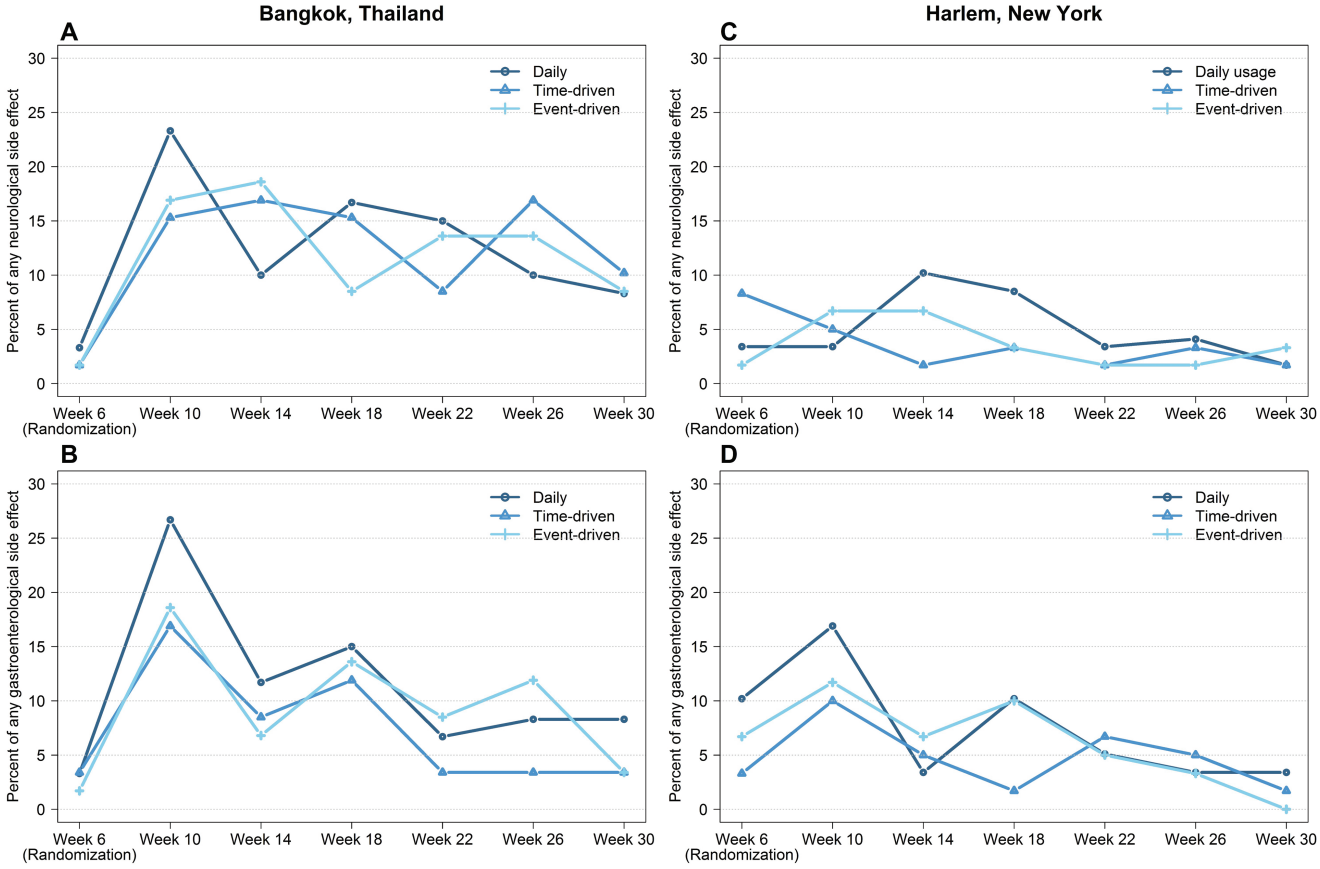

Figure 4. Side effects in the HIV Prevention Trials Network (HPTN) 067 study by randomization group in Bangkok, Thailand (*A* and *B*) and Harlem, New York (*C* and *D*). Neurological side effects include dizziness and headache (*A* and *C*). Gastrointestinal side effects include nausea, vomiting, and abdominal cramping (*B* and *D*).

HIV Infections

Four HIV seroconversions occurred during the study; 3 before randomization and 1 after randomization as reported previously [13]. The postrandomization seroconversion occurred after randomization to the daily arm, yet drug concentrations indicated use of <1 tablet per week at seroconversion.

Safety and Tolerability

There were no significant differences in side effects by randomization group at Bangkok and Harlem related to the neurological system ($P = .94$ and $P = .32$, respectively) or gastroenterological system ($P = .38$ and $P = .75$, respectively; Table 2; Figure 4). However, there were trends toward greater side effects in the daily arm at week 10 (4 weeks after randomization) at both study sites (Figure 4). Gastrointestinal side effects became less frequent after week 10 ($P < .0001$ at both sites) and neurological side effects became less frequent in Bangkok ($P < .017$) and did not change in Harlem ($P = .091$). Creatinine elevations (whether confirmed or not) occurred among 16 of 178 (9.0%) participants in Bangkok (10, 2, and 4 in the daily, time-driven, and event-driven arms, respectively, $P = .050$) and 1 of 179 (0.5%) in Harlem in the daily arm; all were grade 1 except for 1 participant in Bangkok in the daily arm who had a grade 2 elevation. Overall, 10 of 357 (2.8%) participants temporarily or permanently discontinued PrEP due to side effects (6/178 [3.3%] in Bangkok and 4/179 [2.2%] in Harlem). Of these, 5 were in the daily arm, 4 were in the time-driven arm, and 1 was in the event-driven arm. No bone fractures were reported among participants in Bangkok and 2 fractures were reported in 2 participants in Harlem, both related to trauma.

DISCUSSION

The overall feasibility of nondaily PrEP in this study differed by study site: Nondaily dosing appeared to be feasible among men and transgender women who have sex with men in Bangkok, as was also seen in the Ipergay trial [3], whereas participants in Harlem who received a recommendation for daily dosing did substantially better in terms of coverage, adherence, and drug concentrations compared with those in Harlem who received recommendations for nondaily regimens. In contrast with MSM in Bangkok, MSM in Harlem were more similar to women in Cape Town [8], where recommendations for daily dosing also led to higher levels of coverage of sex acts.

A separate analysis of primary outcomes by site was planned based on the premise that social and cultural factors could impact behavioral outcomes, including PrEP use before and

after sexual intercourse. The overall levels of retention in the study, PrEP coverage of sex events, adherence, and drug concentrations were all higher in Bangkok relative to Harlem. The participants at the Bangkok site had more years of schooling and greater employment, which may have facilitated participation in this research study. In addition, the Bangkok site provides longitudinal clinical services to large numbers of gay and bisexual men and transgender women, whereas the Harlem site is a dedicated clinical trials facility. Research settings that also provide clinical services to nonresearch clients may attract more-adherent participants or may foster greater adherence; high PrEP adherence has been observed in the context of clinical services and demonstration projects [5, 14–17]. Increased PrEP use in Bangkok may also reflect greater familiarity with PrEP among clients, more health literacy generally, more identification with gay communities, less stigma, more trust in medical services, and less access to PrEP outside the study.

Nondaily PrEP use in HPTN 067 did not decrease neurological or gastrological side effects; these symptoms are primarily reported in the first weeks of use [18, 19] and may reflect a startup syndrome rather than accumulated dose effect. Creatinine elevations occurred more frequently in Bangkok than Harlem, especially in the daily arm, likely reflecting greater PrEP use or smaller body size. The creatinine elevations were mild, nonprogressive, and did not require stopping study medication (defined per protocol as estimated creatinine clearance ≤50 mL/minute or serum creatinine ≥1.5 times the upper limit of normal). FTC/TDF PrEP decreases bone mineral density in a dose-dependent manner [20], although PrEP trials have not demonstrated an impact on bone fractures. Bone mineral density was not evaluated in this trial.

A limitation of this study is that it was conducted before the results of the Ipergay study were available. Reflecting the information available at the time, participants were informed that the efficacy of daily oral PrEP was known, whereas nondaily regimens were considered experimental, which may have undermined adherence to these regimens. Qualitative information collected during this study indicated that belief in PrEP efficacy was a powerful facilitator of adherence [21]. Providing information about the safety and efficacy of nondaily PrEP for MSM from the Ipergay study [3] may increase uptake and adherence to nondaily regimens. Another limitation is that participants were randomly assigned to the treatment arms, rather than choosing the regimen based on their frequency of sex, ability to plan for sex, and personal preference. Regimen switching was reported by a substantial minority of participants, especially from randomization to the daily and event-driven arms. This may reflect individual preferences or changes in sexual practices, which are known to change with time [22, 23]. Other limitations of the study are that the EDM device was bulky and occasionally lost (especially in Harlem), study procedures were burdensome, and visits were frequent, all of which created inconvenience that can be expected to undermine PrEP use. The duration of self-administered therapy was too short to evaluate nonpersistence of PrEP use. Too few transgender women were enrolled to allow any conclusions about their experience with daily vs nondaily regimens.

PrEP has an important role in containing the spread of HIV, as reflected in the new World Health Organization recommendation that PrEP should be offered to people at substantial risk [24]. PrEP use expanded 3-fold in the United States in 2014 [25, 26] and has been approved for support by public programs in multiple countries. Guiding people on how and when to start and stop PrEP as sexual practices and relationships change is an emerging challenge, which may be addressed with event-driven dosing for some people. For others in this study, a recommendation for daily PrEP dosing led to protective PrEP drug concentrations among the majority of men and transgender women who have sex with men in 2 markedly different settings. How well services can be adapted to diverse settings and changing sexual practices is a critical determinant of the dissemination of innovations, including PrEP, and their impact on HIV transmission.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID), the National Institutes of Health (NIH), or the US Centers for Disease Control and Prevention.

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