Bangkok Metropolitan Administration

Thailand Ministry of Public Health

The Bangkok Tenofovir Study

An HIV pre-exposure prophylaxis trial among people who inject drugs

A collaborative project involving: The Bangkok Metropolitan Administration, the US Centers for Disease Control and Prevention, and the Thailand Ministry of Public Health

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of HIV/AIDS Prevention

BTS Study Design

- Phase 3, randomized, double-blind, placebo-controlled, endpoint-driven trial
- Enrolled 2413 HIV-uninfected PWIDs
- Randomized 1:1 to receive tenofovir or placebo
- Followed until endpoint target (40 incident HIV infections) reached
- Participants chose either daily DOT or monthly visits without DOT and could switch at monthly visits
- Annual DSMB safety reviews
- One interim efficacy review

Oversight

- BMA and MOPH Ethical Review Committees and CDC IRB approved protocol, consent, and other trial materials
- CROs provided oversight and assured GCP compliance
- Independent Data and Safety Monitoring Board conducted annual safety reviews and an interim efficacy analysis

Recruitment

- Posters and brochures describing study posted in drug-treatment clinics
- Staff available at clinics to discuss the study with people interested in joining the trial
- Provided presentations about the study at IDU drop-in centers
- Potential participants received an explanation of study objectives and design, eligibility criteria, and study activities and procedures

Services offered to volunteers

- HIV testing monthly
- Risk reduction education and counseling
- Methadone maintenance treatment
- Matrix model methamphetamine treatment
- Free condoms and counseling
- Free contraception and counseling
- Social services and primary medical care
- Bleach to clean injection equipment

Activities to Involve Community

- Focus group discussions
- Outreach to organizations working with PWID and communities at risk of HIV/ AIDS
- Community Relations Committee (CRC) formed

Focus Group Discussions

- 6 focus groups conducted, July-Aug 2004
  - 4 with IDUs (n=31)
  - 2 with staff (n=15); MD, RNs, social workers, counselors
- Examples of discussion findings
  - Participants agreed with conduct of Tenofovir trial among PWID
  - Study information clear but not exhaustive
  - Need more information about why tenofovir selected
  - Questions about risks and benefits of participation
  - Concerns about tenofovir side-effects and access to HIV treatment and care

Outreach to Organizations

- Reached out to local Community Based Organizations, Government and Non-Government Organizations, 2004
  - Met with representatives from over 16 CBOs, GOs, and NGOs
    - Distributed draft protocol, consent forms, education materials
    - Discussed and asked for comments on all documents and materials
    - Discussed potential implementation of tenofovir as HIV prevention tool
  - PWID drop-in sites
    - Met with community representatives at 3 drop-in sights to discuss potential trial
- Comments informed development of protocol, consent form and consent process, and education materials

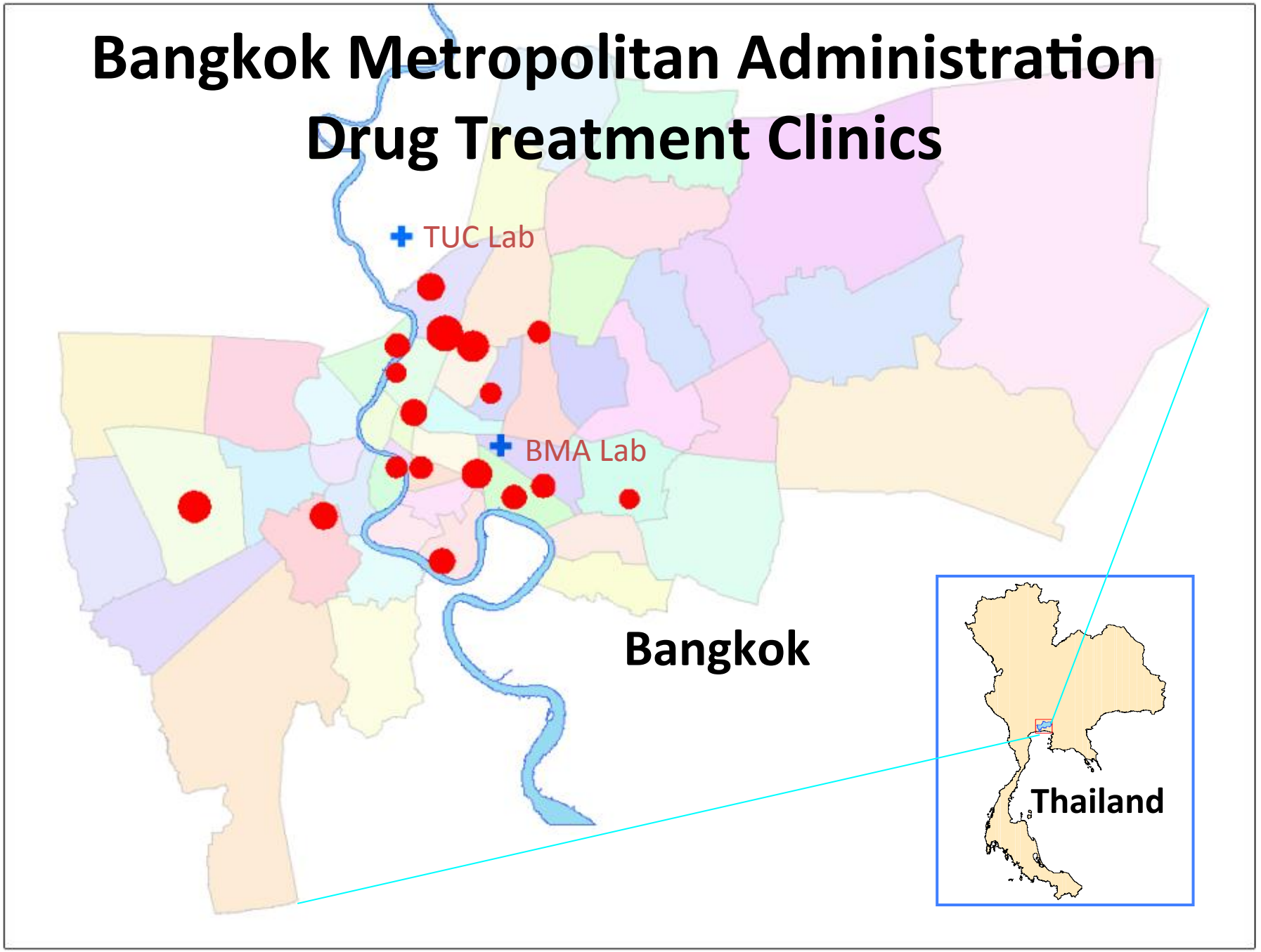
Community Relations Committee

- CRC Membership
  - at least one PWID from each of the 17 BMA clinics
  - HIV infected and uninfected, male and female
  - Family members
  - Community leaders
- CRC meets every 2 months with investigators
- CRC members have raised concerns about study procedures, confidentiality, police harassment, incarceration, tenofovir side-effects, medical care, trial compensation, and post-trial access to tenofovir
- Research staff have clarified misinformation about the BTS protocol and study activities

Conclusion

- A variety of methods have been used to involve communities in the Bangkok Tenofovir Study
- Community involvement has
  - Informed the development of the protocol, consent forms and consent process, education materials
  - Prompted the research team to
    - Reassess and define participant access to medical care
    - Develop detailed graphic representations of trial procedures for use during enrollment
    - highlight community concerns with law-enforcement and public health authorities
  - Provided forum to correct misinformation about trial

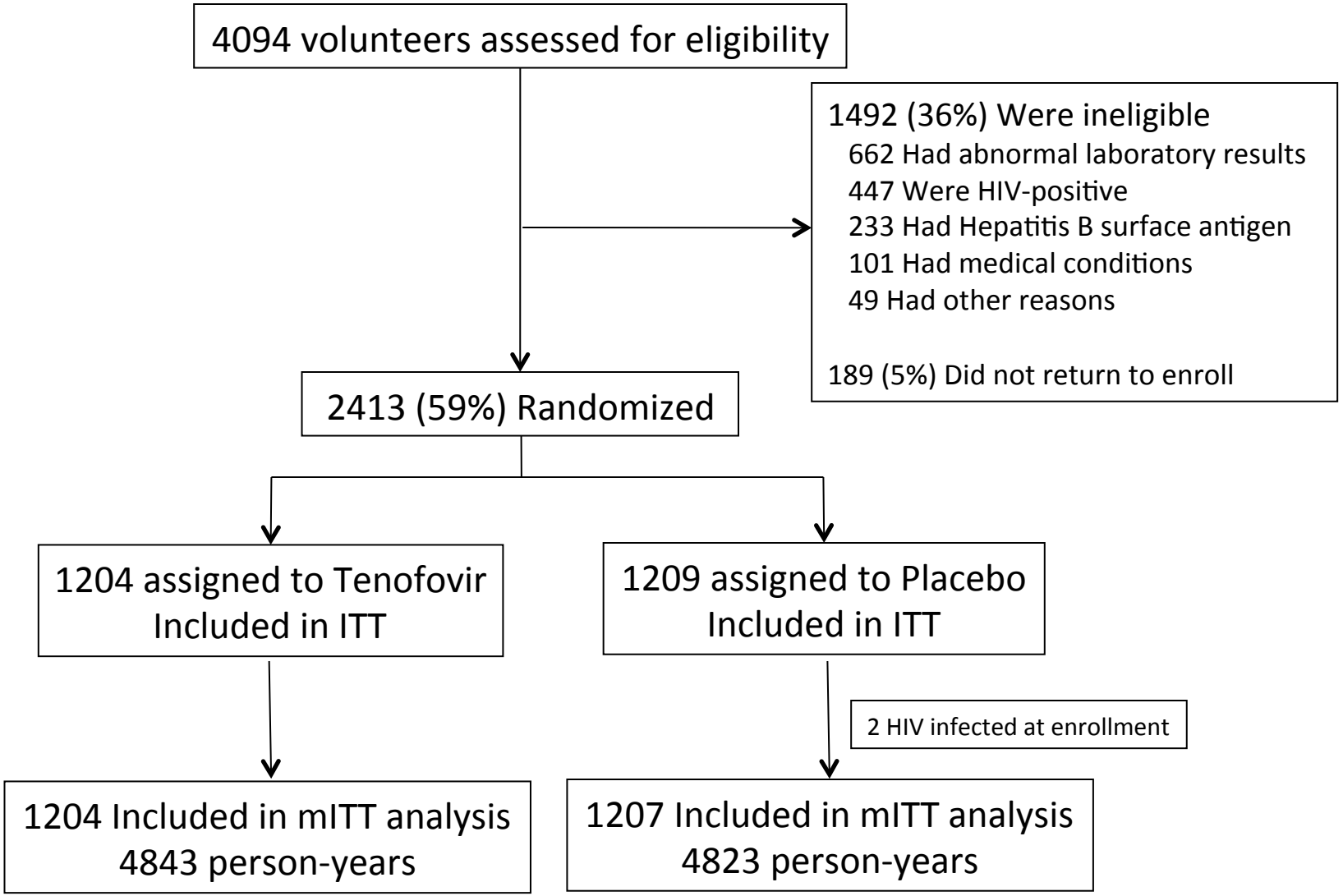
Bangkok Metropolitan Administration
Drug Treatment Clinics



Participant Activities

Visit	Activities
Monthly visits	• Pill count with study drug diary • Assessed for adverse events • Adherence and risk reduction counseling • Received pre- and post-test HIV counseling • Oral HIV test • Women: urine pregnancy test
3 Monthly	• All monthly activities, plus: • Risk behavior assessed using ACASI • Blood collected for safety and HIV testing
Daily visits (DOT)	• Staff watch volunteer take study drug initial diary

Participant Flow



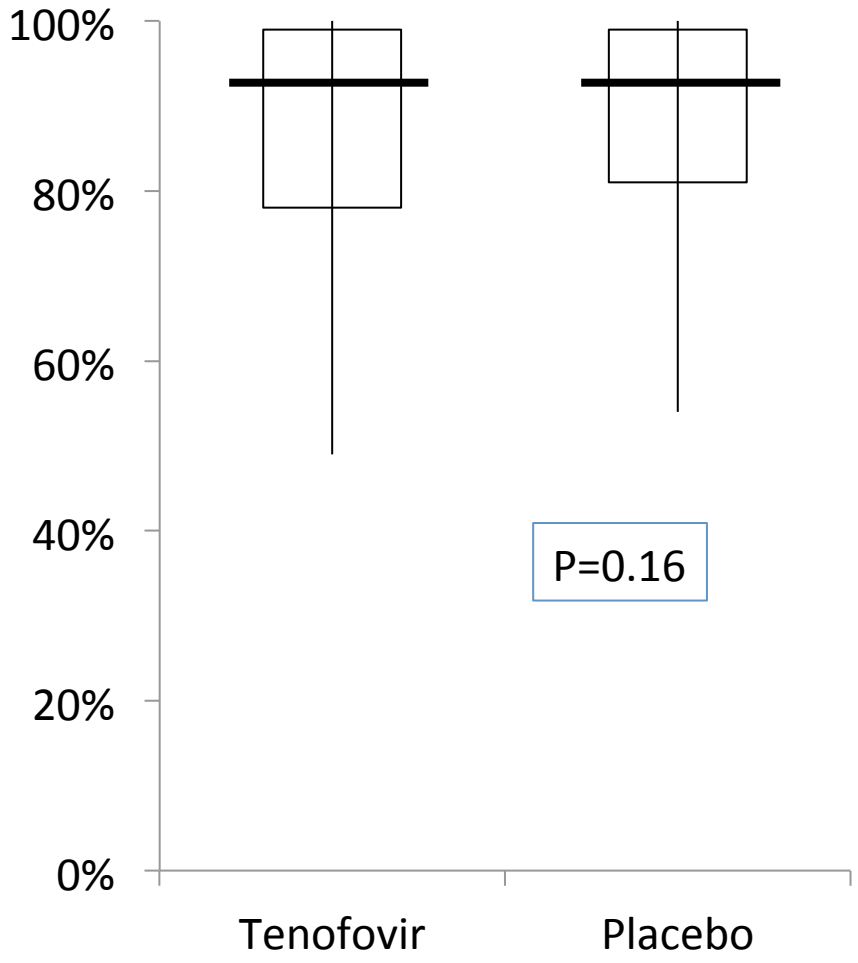
Enrollment and Follow-up

- Enrolled 2413 participants
- Most common reasons couldn't enroll: lab abnormalities and HIV infection
- Median age 31, 80% were male, and 48% had a primary school education or less
- Randomization distributed participants evenly by sex, age, education, and risks behaviors
- 355 (15%) lost, most in the first year, similar in both groups
- 107 deaths, similar number and causes in both groups

Risk Behavior

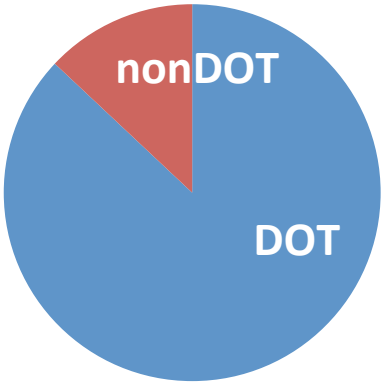
- Risk behavior similar among tenofovir and placebo recipients
- Risk behavior (injecting, sharing, sex with more than one partner) declined significantly during follow-up
- Using a proportional hazards model to evaluate demographic and risks reported the visit of 1st positive HIV test as predictors of HIV infection
- Age (20-29 years), sharing needles, and incarceration significantly associated with HIV
- Sex not a risk factor for HIV infection

Overall adherence by treatment group



Percentiles	Tenofovir adherence	Placebo adherence
90%	99.8%	99.8%
75%	98.6%	98.8%
Median	94.0%	94.3%
25%	77.6%	81.1%
10%	49.2%	53.7%

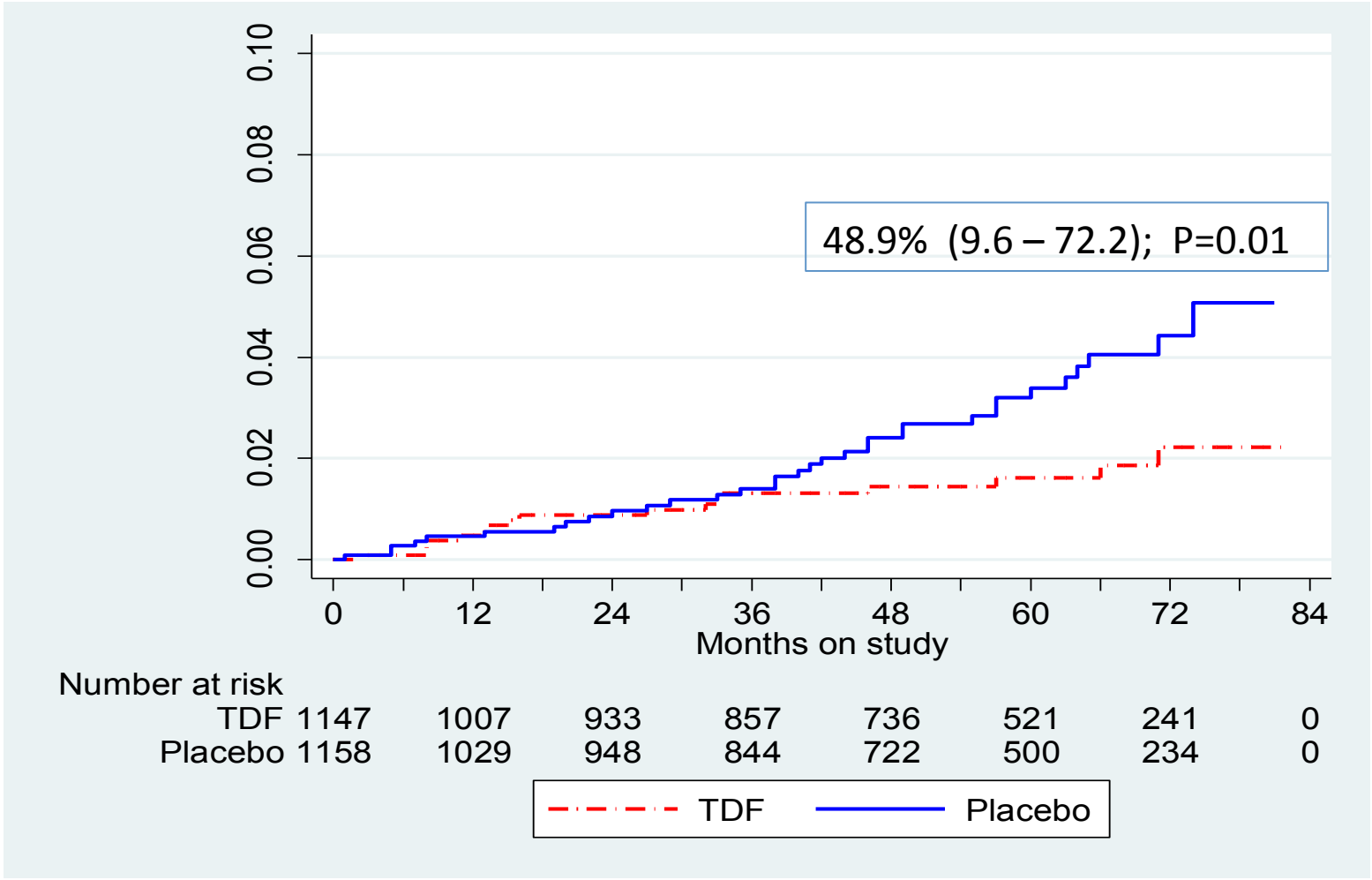
Overall, participants in DOT follow-up 87% of days on study



Efficacy results

	Infections/ person-years	Incidence/100 pys (95% CI)	Efficacy (95% CI)	P-value
ITT				
Tenofovir (n=1204)	17/4843	0.35 (0.21 – 0.56)	51.8 (15.3 – 73.7)	0.01
Placebo (n=1209)	35/4823	0.73 (0.51 – 1.01)		
mITT				
Tenofovir (n=1204)	17/4843	0.35/100 (0.21 – 0.56)	48.9 (9.6 – 72.2)	0.01
Placebo (n=1207)	33/4823	0.68/100 (0.47 – 0.96)		
All (n=2411)	50/9665	0.52/100 (0.38 – 0.68)		

Modified Intention-To-Treat Analysis
Kaplan-Meier estimates of time to HIV infection



Secondary Efficacy Analyses
Adherence-defined per-protocol analysis

- Adherent defined: DOT participant taking study drug ≥71% of days with no more than 2 consecutive day off study drug
- 48 seroconverters eligible, reference efficacy estimate 45.7% (95% CI, 3.1-70.6; p=0.04)
- 17 met the adherent definition
  - 5 tenofovir/12 placebo = 55.9% (-25.1 - 84.5; p=0.12)
  - 2 of 5 undetectable tenofovir; removing these 73.5% (16.6 – 94.0; p=0.03)

Unmatched case-control study limited to tenofovir recipients

	HIV infected	HIV uninfected	Total
Tenofovir detected	5 (39%)	93 (67%)	98
Tenofovir not detected	8	45	53
Total	13	138	151

- The odds of HIV infection were 3-times lower (OR 0.30; 95% CI, 0.09 to 0.98; p=0.04) among participants with detectable tenofovir levels, compared to those with undetectable tenofovir
- Represents a reduction in risk of 70% (95% CI, 2.3 to 90.6)

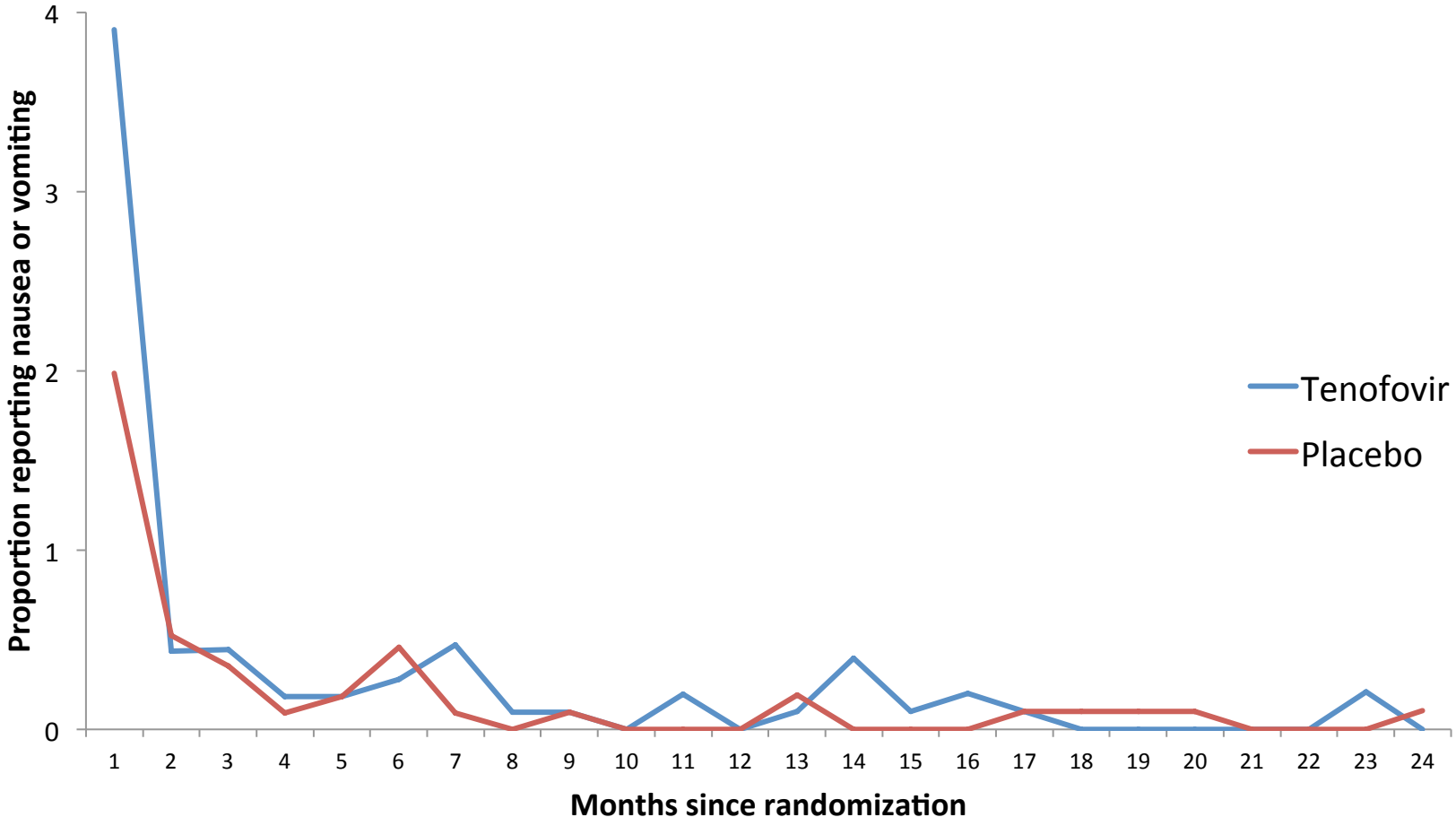
Genotyping and Resistance

- Plasma collected the visit study drug stopped used to test for antiretroviral resistance mutations using Trugene assay and OpenGene software
- HIV viruses from 49 of the 52 HIV-infected participants were successfully amplified:
  - 43 (88%) were CRF01_AE
  - 5 (10%) were subtype B'
  - 1 (2%) was CRF01_AE/subtype B' strain
- No resistance mutations associated with tenofovir (K65R, K70E) were detected.

Adverse Events

	Tenofovir (n=1204)		Placebo (n=1209)		
Adverse Event	**no. of participants (%)**	**no. of events**	**no. of participants (%)**	**no. of events**	**† p value**
Any adverse event	1098 (91.2)	10965	1083 (89.6)	11550	0.455
Any serious adverse event	227 (18.9)	340	246 (20.3)	375	0.352
Death	49 (4.1)	49	58 (4.8)	58	0.369
Any grade 3 or 4 event	156 (13.0)	414	160 (13.2)	389	0.886
Grade 3 event	147 (12.2)	350	142 (11.7)	331	0.716
Grade 4 event	28 (2.3)	64	31 (2.6)	58	0.689
Abdominal pain	135 (11.2)	213	146 (12.1)	214	0.484
Nausea/vomit	**96 (8.0)**	**113**	**59 (4.9)**	**71**	**0.002**
Anorexia	76 (6.3)	94	77 (6.4)	92	0.915
Weight loss	121 (10.0)	140	122 (10.1)	135	0.987
Rash	91 (7.6)	148	105 (8.7)	145	0.271
Fracture	94 (7.8)	169	73 (6.0)	153	0.086
Diarrhea	211 (17.5)	302	206 (17.0)	312	0.885

Nausea and/or vomiting



Adverse Events

	Tenofovir (n=1204)		Placebo (n=1209)		
Adverse Event	**no. of participants (%)**	**no. of events**	**no. of participants (%)**	**no. of events**	**†p value**
Renal disease	13 (1.1)	18	11 (0.9)	15	0.687
Elevated creatinine: grade 1	37 (3.1)	114	28 (2.3)	33	0.268
Elevated creatinine: grade 2	2 (0.2)	3	0 (0)	0	0.249
Elevated creatinine: grade 3 or 4	3 (0.2)	4	3 (0.2)	3	0.996
Decreased phosphorus: grade 1	193 (16)	334	171 (14.1)	276	0.201
Decreased phosphorus: grade 2 or 3	80 (6.6)	118	73 (6)	97	0.573
Elevated AST: grade 1 or 2	580 (48.2)	3430	545 (45.1)	3108	0.067
Elevated AST: grade 3 or 4	80 (6.6)	214	102 (8.4)	234	0.084
Elevated ALT: grade 1 or 2	**635 (52.7)**	**3823**	**587 (48.6)**	**3556**	**0.003**
Elevated ALT: grade 3 or 4	71 (5.9)	121	73 (6)	144	0.836
Elevated amylase: grade 1 or 2	637 (52.9)	4831	628 (51.9)	4497	0.656
Elevated amylase: grade 3 or 4	77 (6.4)	184	76 (6.3)	126	0.921

†P-values obtained from analysis of first events using the Poisson model with robust standard error.

Conclusions

- We provide the first evidence that daily oral tenofovir, when used in combination with other HIV prevention strategies, reduces the risk of HIV infection among people who inject drugs
- Once-daily oral tenofovir decreased the risk of HIV infection 49% among PWIDs when provided with a package of HIV prevention services at drug treatment clinics in Bangkok
- The protective efficacy increased with improved adherence
- Consistent with other PREP studies, we did not identify any significant safety concerns associated with daily use of tenofovir
- Participant reports of injecting and sharing declined during follow-up and may be due to HIV preventive services provided as part of the study
- We now have evidence that PREP can prevent both sexual and parenteral transmission of HIV

Interim Guidance* For PrEP Use

<table>
<tr><th></th><th>MSM</th><th>HRH</th><th>IDU</th></tr>
<tr><td rowspan="2">Detecting Very High Risk of Acquiring HIV Infection</td><td colspan="2">HIV+ sexual partner
STI history
High number of sex partners
History of inconsistent or no condom use
Commercial sex work</td><td>HIV+ injecting partner
Sharing injection equipment
Injecting > once daily
Injecting cocaine
Injecting methamphetamine</td></tr>
<tr><td></td><td>In high prevalence area or network</td><td></td></tr>
<tr><td>Clinically Eligible</td><td colspan="3">Documented negative HIV test before prescribing PrEP
No signs/symptoms of acute HIV infection
Normal renal function, no contraindicated medications
Documented hepatitis B virus infection/vaccination status</td></tr>
<tr><td>Prescription</td><td colspan="3">Daily, continuing, oral doses of TDF/FTC (Truvada®), ≤ 90 day supply</td></tr>
<tr><td rowspan="2">Other services</td><td colspan="3">Follow-up visits at least every 3 months to provide:
HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment
At 3 months and every 6 months after, assess renal function
Every 6 months test for bacterial STIs</td></tr>
<tr><td>Do oral/rectal STI testing</td><td>Assess pregnancy intent
Every 3 months do pregnancy test</td><td>Access to clean needles/syringes and drug treatment services</td></tr>
</table>

***Main points only. See source documents**:

- CDC. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR.* 2011;60(3):65-68.
- CDC. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. *MMWR.* 2012;61(31):586-590.
- CDC. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users. MMWR. 2013;62(23):463-465.

Recommended HIV prevention services for injection drug users (IDU) prescribed PrEP*

Provide access to:

- Substance abuse treatment and relapse prevention services, including medication-assisted therapy
- New, sterile needles and to clean drug preparation equipment, as available and consistent with local laws and regulations
- Condoms and support for their consistent and correct use
- Sexual health services including STD diagnosis and treatment and family planning services
- Any indicated social services
- Any indicated mental health services
- Integrated health services for any other conditions (e.g., TB, hepatitis, pregnancy)

***Main points only. See also**:
Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons who Use Drugs Illicitly: Summary Guidance from CDC and US Department of Health and Human Services. MMWR 2012;61(5):1-43