

What is the risk of HIV resistance when PrEP is started during Acute HIV infection?



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Conflicts of Interest

- No conflicts of interest to disclose

Quick Primer on PrEP (Pre-exposure prophylaxis)

- **Only 1 PrEP drug regimen currently approved* for use**
 - TDF/FTC 300/200 mg taken once daily
 - > 99% effective if taken with good adherence
 - 4 pills/wk > 90% efficacy in MSM

*Other regimens endorsed or with evidence for efficacy (but with little or no data on risk for resistance):

- TDF/3TC 300/300mg endorsed by WHO
- On-demand PrEP (2 pills before sex and then every 24 hours for 2 days)
- TAF/FTC 25/200 mg taken once daily

3 ways in which a PrEP user could end up with drug-resistant HIV

1. Transmission of resistant HIV from the donor.
2. Transmission of non-resistant HIV during a period of poor PrEP adherence (< 4 pills/wk) and subsequent emergence of HIV resistance
3. Transmission of non-resistant HIV before PrEP, starting PrEP during AHI, before screening antibody tests are reactive, then emergence of resistance mutations.

Transmission of resistant HIV virus while on PrEP with good adherence is a very rare event (n=6)

Location	Time Between PrEP Initiation and HIV Diagnosis (months)	Major Resistance Mutations	Inferred Resistance	Likely Cause of PrEP Failure (per study authors)
Toronto	24	NRTI (M41L, D67G, T69D, K70R, M184V, Y215E); NNRTI (Y181C); PI (L10I); INSTI (H51Y, E92Q)	FTC resistance TDF low-level resistance	Transmitted FTC/TDF resistance
New York City	5	NRTI (K65R, M184V) NNRTI (K103S, E138Q, Y188L)	FTC/TDF resistance	Transmitted FTC/TDF resistance
Amsterdam	8	None	None	High inoculum effect with multiple exposures and concomitant lymphogranuloma infection
Charlotte, NC	14	NRTI (M184V, K70T, K65R) NNRTI (K103N)	FTC/TDF resistance	Transmitted FTC/TDF resistance or HIV acquisition during period of low adherence
Pattaya	2	NRTI (M184V) NNRTI (A98G, K103N)	FTC resistance	Transmitted FTC or HIV acquisition very proximate to PrEP initiation
San Francisco	13	NRTI (L74V, M184V) NNRTI (L100I, K103N)	FTC resistance	Unknown

Knox DC, et al. *N Engl J Med*. 2017;376:501-502.

Markowitz M, et al. *JAIDS*. 2017;76:e104-e106.

Hoorneborg E, et al. *Lancet HIV*. 2017;4:e522-e528.

Thaden JT, et al. *AIDS*. 2018;32:F1-F4.

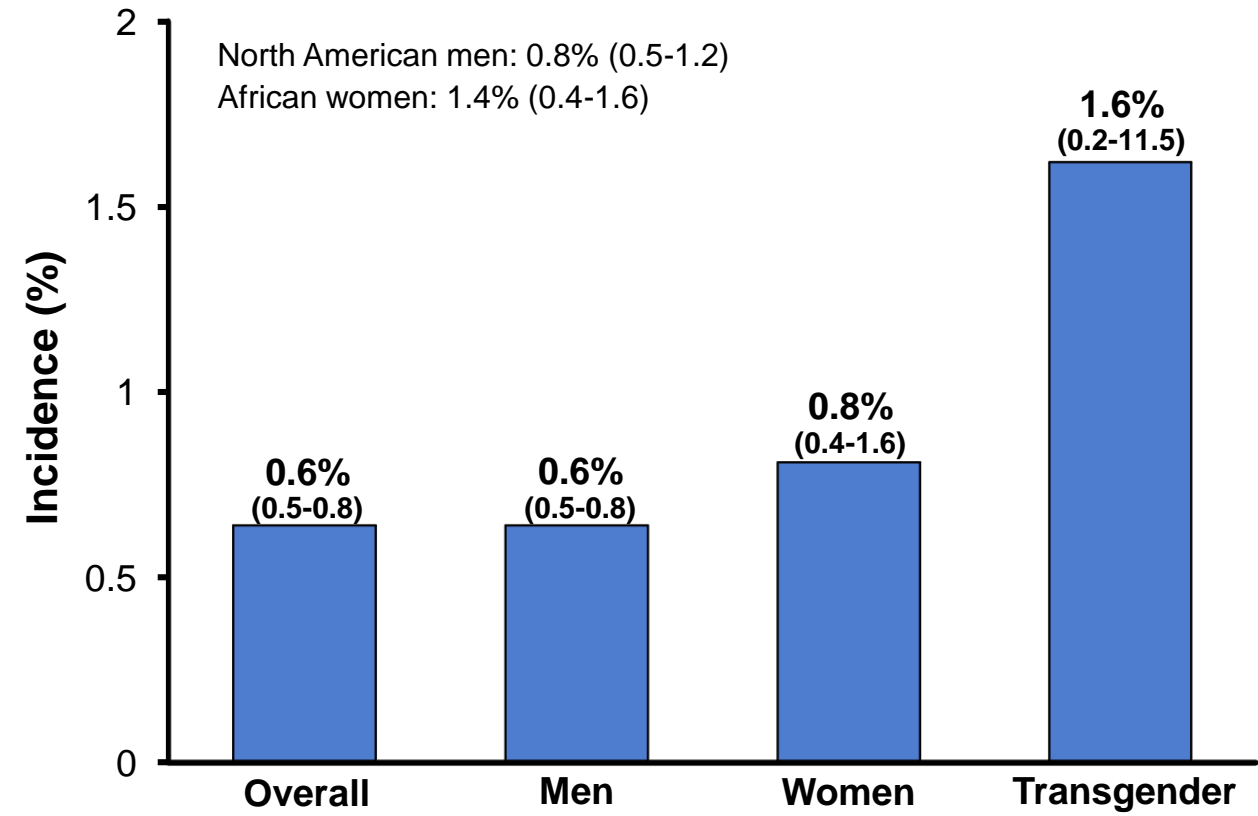
Colby DJ, et al. *Clin Infect Dis*. 2018;67:962-964.

Cohen SE, et al. *Lancet HIV*. 2018;Nov 29. [Epub ahead of print].

On PrEP: HIV Incidence <1%/Year

- 10,609 PrEP users in 46 demonstration projects (9,936 PY)
- Incidence of HIV infections (n=91)
 - Occurred >30 days after last PrEP dose (n=27)
- HIV infections while potentially exposed to PrEP (n=64)
 - Occurred <3 months of starting PrEP (n=17)
 - May reflect HIV infection prior to PrEP
- HIV incidence in demonstration projects compared favorably to active PrEP arm incidence of pivotal trials with oral PrEP
 - iPrEx: 2.0%
 - Partners PrEP: 0.5%

HIV Incidence on FTC/TDF



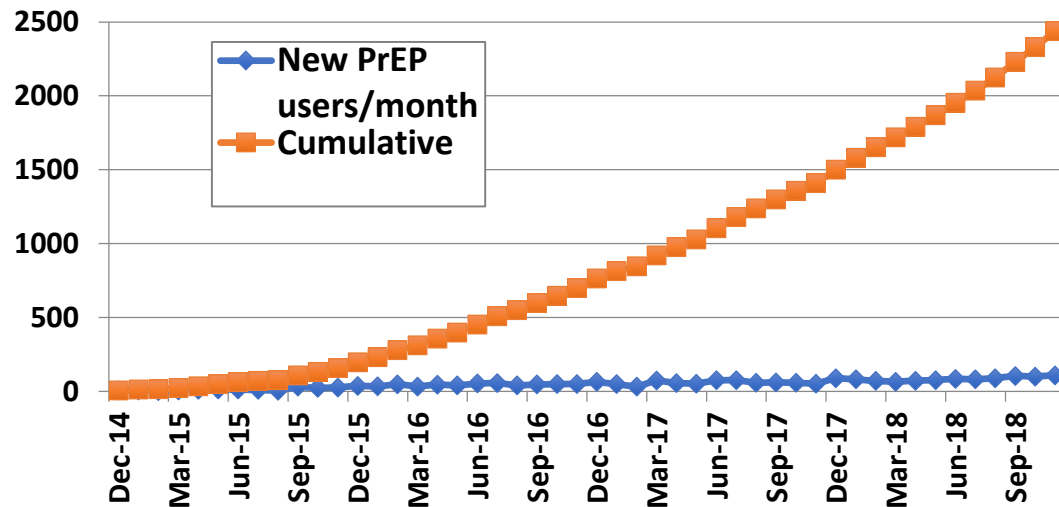
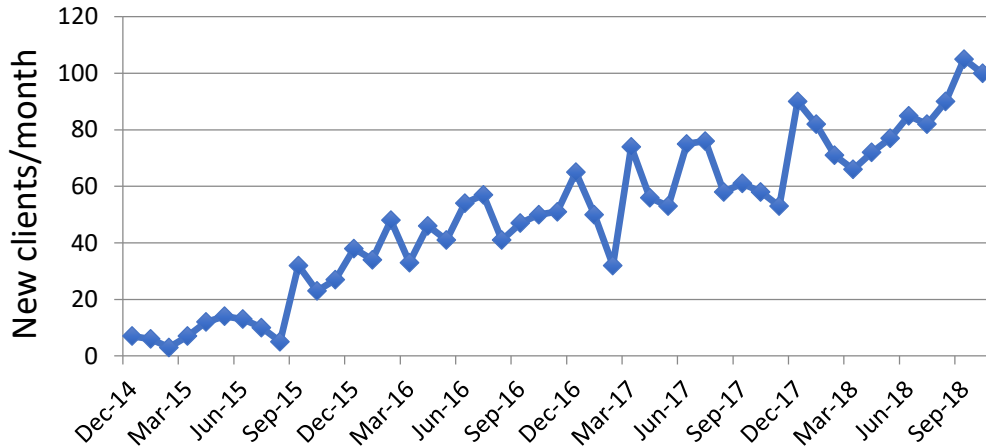
Numbers in parentheses are 95% CI.

PrEP Use in 46 Demonstration Projects: Adherence and Resistance

- Data on adherence and resistance available among 49 who seroconverted while on PrEP
- Most HIV infections occurred in absence of sufficient PrEP use
 - 98% were taking < 4 PrEP doses/week
 - 94% were taking < 2 PrEP doses/week
- Emergent resistance
 - Emtricitabine: 17%
 - Tenofovir DF: 2% (n=1)

PrEP at the Thai Red Cross Anonymous Clinic

PrEP-15 at TRCAC



PrEP-15 at the Thai Red Cross

- Unsubsidized PrEP service available to all individuals at-risk for HIV since December 2014
- Same-day PrEP after screening for HIV (4th gen Ag/Ab test), creatinine, HBsAg
- Total cost = 15 THB/day (HK\$4/day)
- All HIV negative specimens screened for acute HIV infection (AHI) by pooled NAAT (Aptima, qualitative HIV RNA) within 24-48 hrs (research funding)
- Through October 2018:
 - 2,442 new PrEP clients
 - 93% male, 83% MSM
 - Median age 32 (range 17-78)

AHI at PrEP initiation in PrEP-15

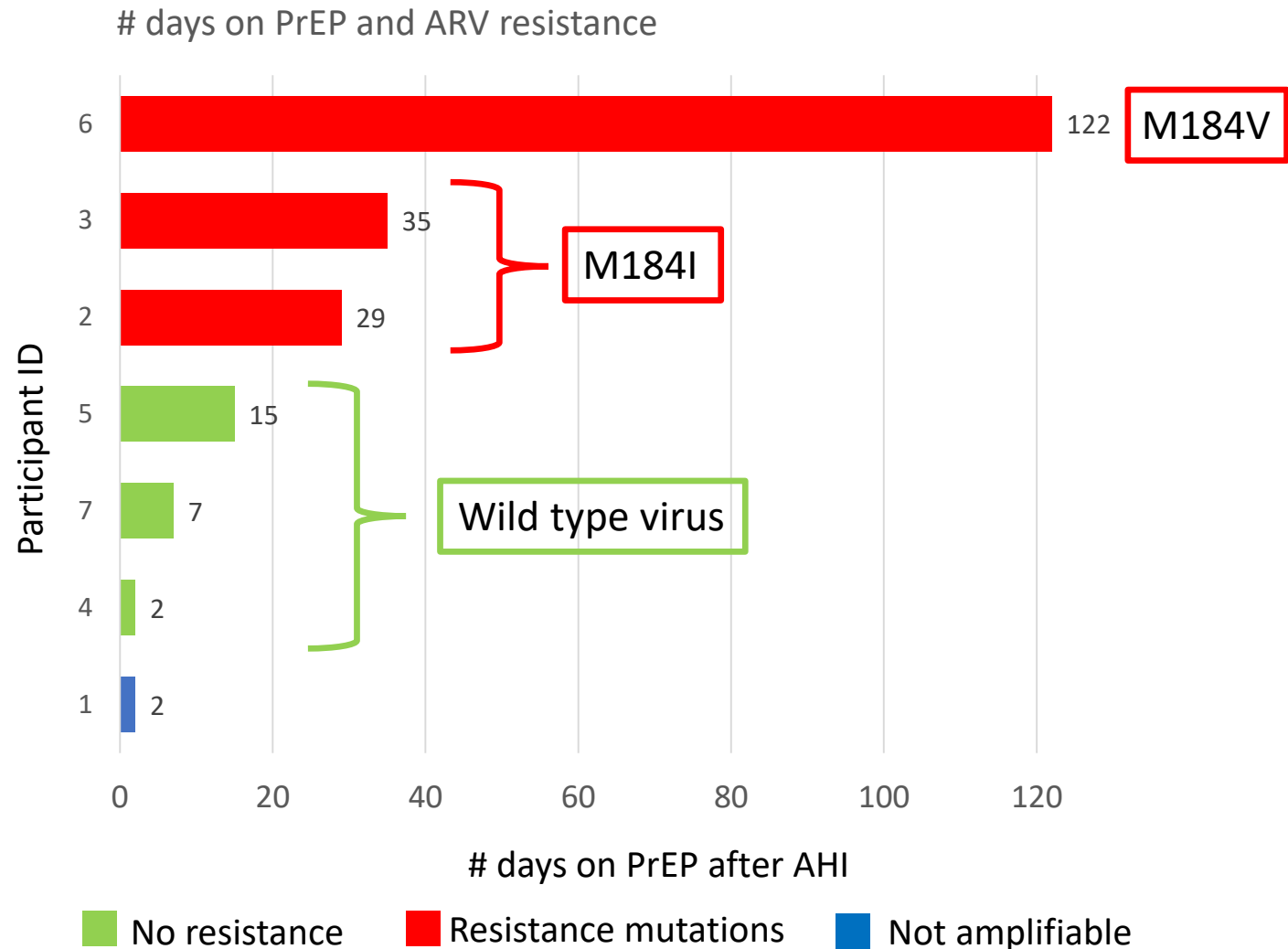
- 7 of 2,442 PrEP clients (~ 1/350) had AHI at PrEP initiation (HIV antibody non-reactive, positive HIV-RNA)
 - 5/7 identified by detection of qualitative HIV RNA pooled Aptima
 - 2/7 were identified by reactive HIV antibody test at the first PrEP follow-up visit after 1 month
 - Pooled NAAT (10-15 specimens/pool) testing was negative before PrEP in both cases
 - Quantitative HIV-RNA on stored specimens from before PrEP was 58 and 86 copies/mL

HIV resistance

- 6/7 cases had genotype resistance test results
- **3/6 had FTC resistance (M184I, M184V)**
 - PrEP use 29-122 days
- **0/6 had TDF resistance**
 - 1/6 cases had NNRTI mutation (E138A)
 - 0/6 cases had PI mutations

Comparison to AHI cohort in Bangkok¹:

- 0/229 (0%) FTC resistance
- 1/229 (0.4%) TDF resistance



Conclusions

- 1/350 at-risk clients starting PrEP at the TRCAC have AHI
- Pooled Aptima (NAAT) testing can detect AHI, may give false-negative results when HIV RNA < 100 cps/mL
- The risk for emergence of resistance mutations to FTC increases with time on PrEP
 - \leq 15 days: no resistance noted
 - > 4 weeks on PrEP: high risk for resistance to FTC/3TC
- The risk for TDF resistance is low when PrEP is used for 5 weeks or less.

Recommendations

How to start ARV when HIV is acquired during PrEP use in LMIC?

1. Ask about adherence: if PrEP not taken, then very low risk for resistance
2. If PrEP was taken, do a resistance test
3. Choose initial ARV based on risk for resistance and availability of drugs:
 - If PrEP used for < 2-4 weeks, then resistance unlikely
 - If PrEP used for > 2-4 weeks, then higher risk for resistance:
 - Avoid drugs with low barrier to resistance (EFV)
 - If INSTI not available: (AZT or TDF)/XTC/PI/r
 - If INSTI available: TDF/XTC/DTG or ABC/3TC/DTG

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