HIV moments and pre-exposure prophylaxis

The PROUD study (Jan 2, p 53)[1] recently reported confirmatory evidence that oral tenofovir disoproxil fumarate–emtricitabine pre-exposure prophylaxis (PrEP) protects men who have sex with men against HIV acquisition. The study showed unexpectedly high HIV incidence (9·0 infections per 100 person-years) in men who asked for PrEP and who were asked to defer. The HIV incidence in this group was three times what was expected on the basis of epidemic trends. This finding is consistent with our observations that people at higher risk for HIV infection were more likely to seek PrEP services, stay in care, and be adherent.[2]

There is other evidence that PrEP might be a strong attractor for people who are entering into a season of high exposure to HIV. The prevalence of acute HIV infection in the iPrEx trial,[3] defined as detection of nucleic acids before seroconversion, was 0·001 during follow-up of the placebo group that had an annual HIV seroincidence of 3·9 per 100 person-years;[4] this finding is consistent with the known duration of the viraemic seronegative window period. At enrolment, the prevalence of acute infection was 3·8 times greater, suggesting that the incidence might have been 14·8 per 100 person-years at the time PrEP was being sought. Such high-risk moments could explain the high prevalence of acute infection at baseline in iPrEx and the high incidence of HIV in participants asked to defer PrEP in PROUD.

Extreme temporal variation in HIV risk is also consistent with patterns of sexual behaviour over time. For example, of 83 iPrEx participants in the placebo group who subsequently became HIV infected, 72 (87%) reported receptive anal intercourse without a condom when they first sought PrEP, whereas such behaviour was reported in only 208 (34%) of 609 visits therafter (figure). 5–15% reported no sex at all during any given quarter. The people reporting no sex or safer sex changed over time: only six (7%) of 83 seroconversions occurred in people reporting receptive anal intercourse without a condom every quarter. Identification of high-risk people might be less helpful than identification of high-risk moments, and the situations that cause them, such as leaving home, becoming an adult, coming out as a man who has sex with men, immigrating to a new city, ending a relationship, and others.

People who are passing through HIV risk moments seem to be inclined to seek PrEP. As consumer demand for PrEP rises from the front lines of the epidemic,[5,6] people will come forward at times of recent or frequent HIV exposure, thereby presenting powerful opportunities for PrEP, post-exposure prophylaxis, and early treatment. Any request for these services should prompt an urgent and thorough response.

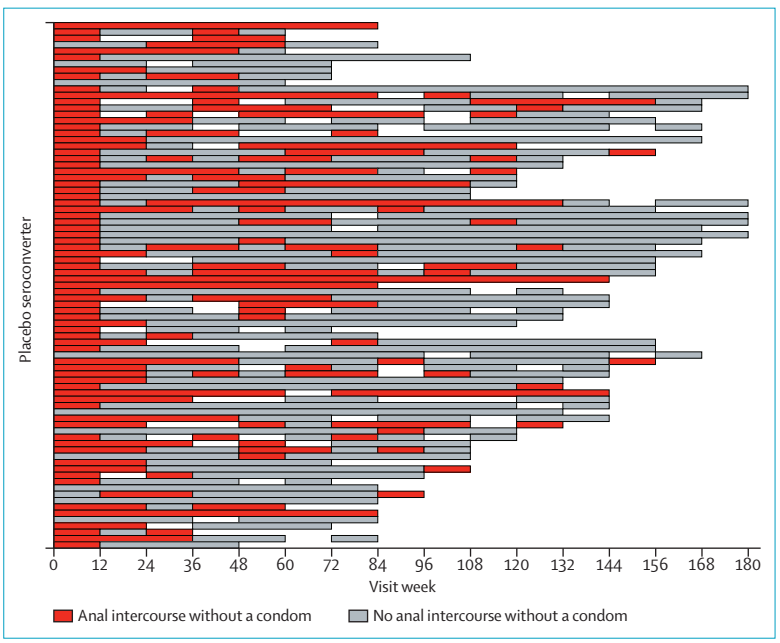

Figure: **Temporal variation in sexual practices involving HIV risk**
Each row represents one person who seroconverted in the placebo group of the iPrEx trial of pre-exposure prophylaxis in men who have sex with men and transgender women. Non-condom receptive anal intercourse was reported most frequently at enrolment, and sporadically thereafter.

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Gilead Sciences donated study medication to the US National Institutes of Health who sponsored the iPrEx trial. RMG reports non-financial support from Gilead Sciences and grants from GlaxoSmithKline, outside the submitted work. DVG reports grants from the National Institutes of Health, during the conduct of the study. DVG is on a monitoring board for ViiV, which makes a candidate product for pre-exposure prophylaxis.

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1 McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016; **387:** 53–60.
2 Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; **14:** 820–29.
3 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.
4 Marcus JL, Glidden DV, Mayer KH, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. *PLoS One* 2013; **8:** e81997.
5 Grant R, Hecht J, Raymond H, et al. Scale-up of pre-exposure prophylaxis in San Francisco to impact HIV incidence. CROI; Seattle, WA; Feb 23–26, 2015. 25.

6 Bush S, Ng L, Magnuson D, Piontkowsky D, Mera Giler R. Significant uptake of truvada for pre-exposure prophylaxis (PrEP) utilization in the US in late 2014–1Q 2015. IAPAC Treatment, Prevention, and Adherence Conference; Miami, FL; June 28–30, 2015. 74.

Authors' reply

This online publication has been corrected. The corrected version first appeared at thelancet.com on April 11, 2016

Robert Grant and David Glidden present interesting data from the iPrEx trial.[1] By contrast with their findings, the PROUD study[2] did not show a major reduction over time in risky sexual behaviour. The figure shows the number of different partners with whom participants reported receptive anal sex without a condom in the 90 days before visits at enrolment, and at 12 months and 24 months. In both the immediate and deferred PrEP groups, about 80% of participants reported one or more partners at 12 months and at 24 months (not necessarily the same individuals). Thus for most men it was appropriate to continue prescribing PrEP, suggesting that subpopulations might exist who need the drug for a longer time than suggested by the iPrEx data. We note the iPrEx analysis is limited to seroconverters who, by definition, were at especially high risk of HIV infection; the PROUD analysis[2] excludes men who stopped attending clinic and who might have been at lower risk. These factors could partly account for the difference between the findings of these two analyses.

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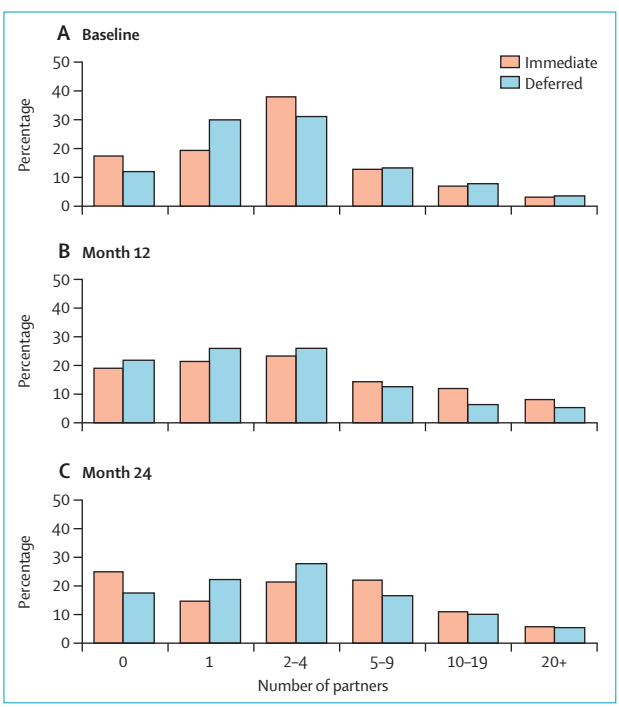

Figure: **Number of partners with whom participants reported receptive anal sex without a condom in previous 90 days**
Based on 515 values at baseline, 406 values at 12 months, and 244 values at 24 months. Further data will become available at 24 months with continued follow-up.

Nonetheless, we agree with Grant's and Glidden's key point about individual variation in the risk of acquiring HIV infection, including periods of no or low risk. In view of this, we were surprised that they did not mention the IPERGAY study,[3] which reported that intermittent PrEP (two tablets before sex and a further two tablets after sex) was highly effective. This is arguably a more logical and cost-effective approach than daily dosing for individuals who "[pass] through HIV risk moments" rather than being at continuous substantial risk. PrEP guidelines for the men who have sex with men population at risk of HIV are not uniform at present: US guidelines recommend daily dosing only,[4] whereas the European AIDS Clinical Society recommend either daily or intermittent dosing.[5] Further evaluation is needed to determine the optimum way to promote and deliver PrEP in different populations, taking account of the wide range of behaviours and the need to tailor regimens to individual circumstances.

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1 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.
2 McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016; **387:** 53–60.
3 Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373:** 2237–46.
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Refusal to provide health care to people with HIV in France

Refusals to provide care to people with HIV have been reported in the USA,[1] the UK,[2] and elsewhere in Europe,[3] but their frequency remains poorly documented. In 2015, the French parliament examined a law that includes an article on non-discrimination in access to health care and the possibility of doing tests to determine the extent and nature of the discrimination. During the legislative debates, AIDES did a situation testing survey[4] to ascertain the frequency and nature of refusals to provide dental and gynaecological care to people with HIV.

The situation testing survey was done by telephone in 440 dental and 116 gynaecology offices randomly selected in 20 French cities, chosen on the basis of their HIV incidence and medical density for these two specialties. The replies to two callers requesting an appointment for the same reason (scaling or a vaginal smear), both with the same sociodemographic characteristics and the same health insurance status, differing only in their HIV serological status, were compared. Negative responses were categorised as outright refusals (explicit refusals to grant an appointment), disguised refusals (arguments aimed at discouraging the caller from making an appointment), and discriminatory remarks with no refusal to provide care.