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SHORT COMMUNICATION

Pregnancy and HIV transmission among HIV-discordant couples in a clinical trial in Kisumu, Kenya

SG Brubaker,[1] EA Bukusi,[2] J Odoyo,[2] J Achando,[2] A Okumu[2] and CR Cohen[1]

[1]*Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA, USA and* [2]*Centre for Microbiology Research, Kenya Medical Research Institute, Kisumu, Kenya*

Objectives

A large proportion of new HIV infections in sub-Saharan Africa occur in stable HIV-discordant partnerships. In some couples, the strong desire to conceive a child may lead to risky behaviour despite knowledge of discordant serostatus. Our objective was to compare HIV transmission between discordant couples who did and did not conceive during participation in a clinical trial.

Methods

Five hundred and thirty-two HIV-discordant couples were followed for up to 2 years in Kisumu, Kenya as part of the Partners in Prevention HSV/HIV Transmission Study. Quarterly HIV-1 antibody and urine pregnancy test results were analysed.

Results

Forty-one HIV-1 seroconversions occurred over 888 person-years of follow-up, resulting in an annual incidence of 4.6/100 person-years. Twenty seroconversions occurred among 186 HIV-1-uninfected individuals in partnerships in which pregnancy occurred (10.8% of HIV-1-negative partners in this group seroconverted), in comparison to 21 seroconversions among 353 uninfected individuals in partnerships in which pregnancy did not occur (5.9% of HIV-1-negative partners seroconverted), resulting in a relative risk of 1.8 [95% confidence interval (CI) 1.01–3.26; $P<0.05$].

Conclusions

Pregnancy was associated with an increased risk of HIV seroconversion in discordant couples. These data suggest that the intention to conceive among HIV discordant couples may be contributing to the epidemic.

Keywords: heterosexual HIV transmission, HIV-discordant couples, pregnancy, reproductive health

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Introduction

There are an estimated 33 million people in the world infected with HIV, 60% of whom reside in sub-Saharan Africa [1]. Emerging data indicate that a large proportion of new infections in this region occur in stable HIV-discordant relationships [2,3]. Prevention efforts in this population have focused on couples-based HIV testing to equip partners with knowledge of their serostatus in order to motivate behaviour change [4]. However, discordant couples studies in Rwanda and Zambia have shown that, while condom use did increase among HIV-discordant couples after HIV testing, 20–43% of sex acts among these couples remained unprotected [5,6]. Our hypothesis is that the desire to have children is one of the motivations for the high-risk behaviour among some HIV-discordant couples.

Total fertility rates (TFRs) are trending downward worldwide but still remain high in sub-Saharan Africa, with an average of 5.6 births per woman [7]. In Kenya, the TFR declined from 8.1 in 1977 to 4.7 in 1998 [8]. However, this downward trend slowed dramatically over the next 10 years, and the TFR in 2008 was 4.6, minimally changed from 1998 [9]. Multiple analyses have focused on this phenomenon in Kenya and have examined how the HIV epidemic may affect fertility rates [8,10,11]. The relationship between HIV infection and fertility is complex. They share a common antecedent, i.e. sexual intercourse, which can induce a relationship between the two. In addition, HIV infection can have opposing effects on fertility; fertility

Correspondence: Dr Sara G. Brubaker, 50 Beale Street, Suite 1200, San Francisco, CA 94105, USA. Tel: + 1 415 321 9690; fax: + 1 415 597 9300; e-mail: sara.brubaker@ucsf.edu

rates can decline as a result of lower fecundity caused by comorbidities associated with HIV disease, or rise as a result of shorter breastfeeding duration, the desire to replace lost children, or the attempt to ensure ideal family size in the setting of higher infant mortality caused by HIV [10,11].

Multiple studies have evaluated the stated fertility desires of HIV-infected individuals in sub-Saharan Africa. The results have been mixed. Four quantitative studies, two in Uganda, one in Kenya and one in Malawi, showed that a smaller proportion of HIV-infected individuals report a desire for children than HIV-uninfected individuals [12–15]. However, studies in Rwanda, Zambia and Zimbabwe have shown that the diagnosis of HIV does not have a marked effect on reproductive behaviours [5,16,17]. Additionally, cross-sectional surveys in South Africa and Nigeria found that a significant proportion of HIV-infected men and women (29% and 63%, respectively) surveyed expressed a desire to have children [18,19]. A literature review of factors influencing fertility desires and intentions among people living with HIV/AIDS concluded that the desire for children is associated with young age, having few children, and having access to antiretroviral therapy (ART) [20], which suggests that the variation in the observed rates of desired fertility may be attributable to differing demographics of the populations surveyed. Qualitative studies on this topic, including one performed in Kenya in 2009, revealed that the desire for children among people living with HIV is motivated by societal expectations, a strong personal wish to experience parenthood, and the belief that children signify hope and a reason for living [21–23]. A qualitative study of serodiscordant couples in Zambia found that the desire for children was one of the primary barriers to the use of condoms within the couple [24]. In summary, the desire to have children can co-exist with HIV infection and discordant relationships.

The Kenya AIDS Indicator Survey implemented in 2007 found that over 40% of HIV-infected individuals have HIV-uninfected regular partners [25]. The desire to have children may put the HIV-uninfected partners in discordant relationships at increased risk of HIV acquisition. We analysed data for HIV-discordant couples collected as part of the Partners in Prevention HSV/HIV Transmission Study to determine the magnitude of their risk of HIV transmission relative to whether or not they conceived during study follow-up.

Methods

The Partners in Prevention HSV/HIV Transmission Study was a randomized, placebo-controlled clinical trial of acyclovir for herpes simplex virus (HSV)-2 suppression to reduce HIV-1 transmission in HIV-discordant couples. Couples were enrolled in 14 sites in East and Southern Africa. The study protocol has been described in detail elsewhere [26]. Briefly, HIV-discordant couples were recruited through community HIV counselling and testing sites and local HIV clinics, and were referred to the study site for screening. Couples were eligible for enrolment if they were sexually active (defined as vaginal or anal intercourse at least three times in the last 3 months), were able to provide independent informed consent for participation in the study, planned to remain in the relationship for the duration of study follow-up (maximum 24 months), and provided locator information. Couples were ineligible if either partner was co-enrolled in another HIV-1 prevention or treatment trial, if the HIV-1-infected woman was pregnant based on self-report or urine testing at enrolment, or if the HIV-1-infected partner had a CD4 count <250 cells/μL, had a history of AIDS-defining diagnoses by World Health Organization (WHO) criteria or was on ART at the time of enrolment [26]. The University of Washington and the Kenya Medical Research Institute Ethical Review Committees and the University of California San Francisco Committee on Human Research approved the protocol. All participants provided written informed consent prior to enrolment.

All index partners were HIV-1 antibody and HSV-2 antibody positive. Couples were randomized to the acyclovir arm, wherein the index partner was treated with acyclovir 400 mg orally twice a day (bid), or the placebo arm. Of note, female index partners were advised to avoid pregnancy and all couples in the study were given access to condoms and hormonal contraception free of charge. Couples were followed prospectively for up to 2 years with an endpoint of HIV-1 seroconversion of the HIV-1-susceptible partner. Index participant follow-up visits occurred monthly and included a urine β-human chorionic gonadotropin (HCG) test (QuickVue™; Quidel Corporation, San Diego, CA, USA) to detect pregnancy. HIV-1-seronegative partner follow-up visits occurred quarterly, and included HIV-1 antibody testing and a urine β-HCG test.

Dual rapid HIV-1 antibody tests were performed with confirmatory HIV-1 enzyme immunoassay (EIA) for samples with discordant or dual positive rapid assays. HIV-1 serostatus at enrolment for all participants and during follow-up for all HIV-1 seroconverters was confirmed in batch testing conducted at the end of the study using HIV-1 EIA (Genetic Systems™ rLAV EIA; Bio-Rad Laboratories, Hercules, CA, USA) and western blot (Genetics Systems™ HIV-1; Bio-Rad Laboratories) at the University of Washington. CD4 testing for HIV-1-infected participants was performed at screening and 6-month

intervals using standard FacsCount (BD Biosciences, San Jose, CA, USA). HIV-1 RNA levels were determined at the University of Washington using the 96-test COBAS AmpliPrep/COBAS Taqman™ HIV-1 RNA assay version 1.0 (Roche Diagnostics, Indianapolis, IN, USA).

This analysis used data collected from study participants enrolled in Kisumu, Kenya, one of the 14 trial sites. Participants' HIV-1 results, CD4 cell counts, urine pregnancy test results, and demographic information were extracted from the database and were used to compare couples who did and did not become pregnant. The two populations were compared using the χ^2 and Student's *t*-tests using SAS 9.0 for Windows (SAS Institute Inc., Cary, NC, USA) and EPI INFO 3.4.1 (Centers for Disease Control, Atlanta, Georgia, USA). The time of HIV-1 seroconversion was calculated as a range between the date of the last negative HIV-1 test and the first positive HIV-1 test. The date of conception was calculated by adding 2 weeks to the self-reported date of the last menstrual period. The timing of seroconversion and conception were compared to determine the temporal pattern, if any, of these events.

Results

Five hundred and thirty-two couples were enrolled in the study, including 532 men and 539 women; seven (1.3%) of the 532 men were enrolled with two female partners. Men and women made up 38.3 and 61.7% of the HIV-1-infected partners, respectively. The median age of male participants was 34 years [interquartile range (IQR) 29–47 years], and that of female participants was 27 years (IQR 23–34 years). Most participants were married (95.3%) and lived with their study partner (96.4%). The median duration of the relationship with the study partner was 5 years (IQR 2–11 years) and the median number of children with the study partner was 2 (IQR 0–3). Most of the participants (86.8%) self-identified as being from the Luo ethnic group and the median number of completed years of school was 8 (IQR 7–11 years). One hundred and eighty-nine (35.1%) of the 539 women had a positive pregnancy test at some point during participation in the study. There was no significant difference in the pregnancy rate among HIV-1-infected women (32.5%) and HIV-1-uninfected women (39.3%) ($P = 0.11$). At enrolment the median CD4 count of HIV-1-infected partners was 443 cells/μL (IQR 337–617 cells/μL), and the median HIV-1 viral load at enrolment was 18 225 HIV-1 RNA copies/mL (IQR 4210–72 682 copies/mL).

Forty-one seroconversions occurred during 888 person-years of follow-up, for an incidence of 4.6/100 person-years. Twenty seroconversions occurred among 186 HIV-uninfected individuals in partnerships in which pregnancy occurred (10.8% of HIV-1-negative partners in this group seroconverted), in comparison to 21 seroconversions among 353 uninfected individuals in partnerships in which pregnancy did not occur (5.9% of HIV-1-negative partners seroconverted), resulting in a relative risk of 1.8 [95% confidence interval (CI) 1.01–3.26; $P<0.05$]. Women who conceived and their male partners were younger, had been together for a shorter time, and had fewer children together than women and their male partners who did not conceive (Table 1). Of note, of the 20 seroconversions that occurred among partners in relationships in which pregnancy occurred, 12 occurred in women and eight in men. There was no significant difference between the CD4 cell counts (or HIV-1 viral loads) of HIV-infected individuals in the two groups (Table 1).

Of the 20 seroconversions that occurred in couples who became pregnant, 65% occurred within 6 months prior to conception and during the first 6 months of pregnancy and the remaining 35% occurred more than 6 months from conception (Fig. 1). In Figure 1, the women who seroconverted are denoted W1–W12 and the men M1–M8.

Discussion

In this cohort of HIV-1-discordant couples in Kisumu, Kenya, 35% of female participants became pregnant at some point during enrolment in the clinical trial despite a verbal agreement to delay pregnancy for the duration of the study and despite access to hormonal contraceptives and condoms free of charge. The women who conceived and their male partners were younger, had fewer children, and had been together for a shorter time than couples who did not conceive. While these data cannot distinguish between desired and undesired pregnancies, the demographic characteristics of couples who conceived during this study have been found in other studies of HIV-infected individuals in sub-Saharan Africa to correlate with desire for pregnancy at some point in the future [2,20].

HIV-uninfected individuals in this cohort who were in partnerships in which conception occurred had a 1.8-fold increased risk of HIV acquisition compared with couples who did not conceive. Within discordant couples, HIV viraemia is the strongest single risk factor for HIV transmission [27]. The HIV-infected partners in this cohort were not on highly active antiretroviral therapy (HAART) at the time of enrolment and most were viraemic, putting the HIV-uninfected partner at significant risk of HIV acquisition through unprotected sexual intercourse. Sixty-five percent of HIV seroconversions occurred within 6 months of conception or the first 6 months of pregnancy. If these pregnancies occurred as a result of purposeful unprotected intercourse with the goal of conception, then the desire for pregnancy may put HIV-discordant couples

Table 1 Comparison of individuals and couples in HIV-1-serodiscordant relationships in which pregnancy did and did not occur

	Pregnancy occurred ($n = 373$)	No pregnancy occurred ($n = 698$)	*P*-value
Individual level; all participants (men, women, index, and partners)			
Age (years) [median (IQR)]			<0.01
Total (overall)	27 (24–32)	34 (27–44)	
Men	31 (27–36)	38 (30–49)	
Women	24 (22–28)	30 (24–39)	
Number of children with study partner [median (IQR)]	1 (0–3)	2 (0–4)	0.01
Number of years with study partner [median (IQR)]	4 (2–7)	6 (2–7)	<0.01
Individual level; index participants only (men and women)			
CD4 count of HIV-1-infected partner (cells/μL) [median (IQR)]	477 (349–615)	429 (331–623)	0.12
HIV-1 viral load (copies/mL) [median (IQR)]	16 700 (3555–60 770)	19 045 (4915–79 890)	0.21
Individual level; partner participants only (men and women)			
Incidence of HIV-1 seroconversion/100 person-years	10.8	5.9	0.046
Couple level			
Percent of couples who were female HIV positive and male HIV negative	56.7	64.3	0.10

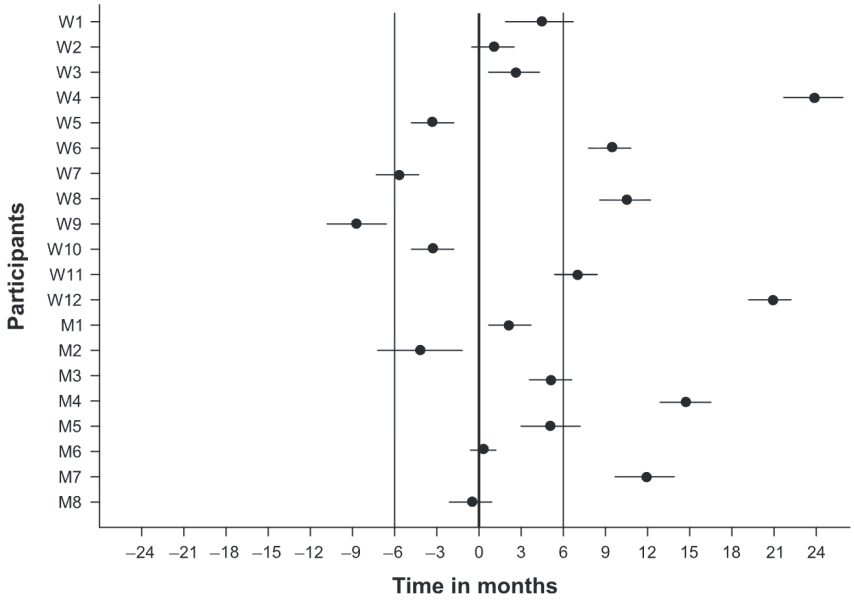

Fig. 1 Timing of seroconversion relative to conception in individuals who seroconverted. Conception is the vertical bar at time = 0. The 12 female participants are W1–12 and the eight male participants are M1–8. Seroconversion is represented by the dots with the range from last negative HIV test to first positive. For men, seroconversion is timed relative to their partner's pregnancy.

at increased risk of HIV transmission. Alternatively, pregnancy itself may increase HIV transmission risk to an uninfected male partner [28] and/or enhance susceptibility of the female genital tract to HIV-1 infection [29].

Pregnancy intention is difficult to define and therefore difficult to measure even in prospective studies. Intention includes elements of wantedness and timing which may not be captured in the interview question or the respondent's answer [30]. A pregnancy can also change from undesired to desired or vice versa depending on whether the question is posed before or after the birth [31]. In addition, conception requires joint action of two individuals who may have differing desires. In the case of couples, especially couples in parts of sub-Saharan Africa where women may not have full autonomy to make reproductive choices, reproductive behaviour may reflect the desire of only one member of the couple [32]. One major limitation of this study is that pregnancy intention or desire was not directly measured. It could be that pregnancy is a marker of unprotected intercourse rather than the motivation for engaging in unprotected intercourse. Behavioural data such as frequency of unprotected intercourse or use of long-acting birth control may have helped to differentiate between desired and undesired

pregnancies. Our analysis is limited by the lack of consistent behavioural data of this kind and by the lack of data on pregnancy outcome, often because participants exited the study prior to delivery of the infant. To our knowledge, there have not been any published studies that have assessed pregnancy intention prospectively in an HIV-discordant couple cohort and measured the effect of desired pregnancy on HIV transmission. Our results suggest that a study of this nature is an important next step in understanding high-risk behaviour in HIV-discordant couples.

If some of the pregnancies that occur in HIV-discordant couples are intentional, a harm reduction approach should be adopted in counselling about reproductive choices. It is clear that HIV-discordant couples will conceive even in the absence of safe methods to reduce their risk of HIV transmission and may therefore benefit from the most basic education about risk reduction. Counselling tailored specifically to female-positive and male-positive couples should be provided, including instructions about feasible practices such as timed unprotected intercourse, home insemination, or confirmation of viral suppression; all of which are outlined in the British HIV Association Guidelines for Management of Sexual and Reproductive Health [33]. Further study of this population is required to assess whether strategies to reduce the risk of HIV transmission while allowing conception would have an impact on the HIV epidemic in sub-Saharan Africa.

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References

1 World Health Organization. AIDS epidemic update: November 2009. Available at http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf (accessed 21 June 2010).

2 Guthrie BL, de Bruyn G, Farquhar C. HIV-1-discordant couples in sub-Saharan Africa: explanations and implications for high rates of discordancy. *Curr HIV Res* 2007; **5**: 416–429.

3 Lingappa JR, Lambdin B, Bukusi EA *et al.* Regional differences in prevalence of HIV-1 discordance in Africa and enrollment of HIV-1 discordant couples into an HIV-1 prevention trial. *PLoS One* 2008; **3**: e1411.

4 Painter TM. Voluntary counseling and testing for couples: a high-leverage intervention for HIV/AIDS prevention in sub-Saharan Africa. *Soc Sci Med* 2001; **53**: 1397–1411.

5 Allen S, Meinzen-Derr J, Kautzman M *et al.* Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS* 2003; **17**: 733–740.

6 Allen S, Tice J, Van de Perre P *et al.* Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *BMJ* 1992; **304**: 1605–1609.

7 Caselli GVJ, Wunsch G. *Demography: Analysis and Synthesis.* London: Academic Press, 2006.

8 Westoff C, Cross R. *The Stall in the Fertility Transition in Kenya. DHS Analytical Studies No 9 2006.* Calverton, MD: ORC Marco.

9 Kenya National Bureau of Statistics. Kenya Demographic and Health Survey 2008–9. MEASURE DHS 2009. Available at www.measuredhs.com/pubs/pub_details.cfm?ID=1008&ctry_id=20&SrchTp (accessed 1 September 2010).

10 Askew I, Ezeh A, Bongaarts J, Townsend J. Kenya's Fertility Transition: Trends, Determinants and Implications for Policy and Programmes. Population Council 2009. Nairobi. Available at www.popcouncil.org/pdfs/2009_KenyaFertilTrans.pdf (accessed 21 June 2010).

11 Magadi MA, Agwanda AO. Investigating the Association between HIV/AIDS and Recent Fertility Patterns in Kenya. *Soc Sci Med* 2010; **71**: 335–344.

12 Baek C, Rutenberg N. Addressing the family planning needs of HIV-positive PMTCT clients: Baseline findings from an operations research study. Horizons Research Update 2005. Population Council. Available at www.phishare.org/files/3633_FPMTCT_RU.pdf (accessed 1 September 2010).

13 Heys JKW, Jhangri GS, Alibhai A, Rubaale T. Fertility desires and infection with the HIV: results from a survey in rural Uganda. *AIDS* 2009; **23** (Suppl 1): S37–S45.

14 Hoffman IF, Martinson FE, Powers KA *et al.* The year-long effect of HIV-positive test results on pregnancy intentions, contraceptive use, and pregnancy incidence among Malawian women. *J Acquir Immune Defic Syndr* 2008; **47**: 477–483.

15 Homsy J, Bunnell R, Moore D *et al.* Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study. *PLoS One* 2009; **4**: e4149.

16 Baylies C. The impact of HIV on family size preference in Zambia. *Reprod Health Matters* 2000; **8**: 77–86.

17 Feldman R, Maposhere C. Safer sex and reproductive choice: findings from ''positive women voices and choices'' in Zimbabwe. *Reprod Health Matters* 2003; **11**: 162–173.
18 Myer L, Morroni C, Cooper D. Community attitudes towards sexual activity and childbearing by HIV-positive people in South Africa. *AIDS Care* 2006; **18**: 772–776.
19 Oladapo OT, Daniel OJ, Odusoga OL, Ayoola-Sotubo O. Fertility desires and intentions of HIV-positive patients at a suburban specialist center. *J Natl Med Assoc* 2005; **97**: 1672–1681.
20 Nattabi B, Li J, Thompson SC, Orach CG, Earnest J. A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery. *AIDS Behav* 2009; **13**: 949–968.
21 Cooper D, Harries J, Myer L, Orner P, Bracken H, Zweigenthal V. ''Life is still going on'': reproductive intentions among HIV-positive women and men in South Africa. *Soc Sci Med* 2007; **65**: 274–283.
22 Smith DJ, Mbakwem BC. Life projects and therapeutic itineraries: marriage, fertility, and antiretroviral therapy in Nigeria. *AIDS* 2007; **21** (Suppl 5): S37–41.
23 Ujiji OAE, Ilako AM, Indalo F, Rubenson DB. ''I will not let my HIV status stand in the way.'' Decisions on motherhood among women on ART in a slum in Kenya-a qualitative study. *BMC Women's Health* 2010; **10**: 13.
24 Hageman KVC, Haworth A, Henderson F *et al* Condom use among HIV discordant couples in Zambia: barriers to consistency. *4th Annual International AIDS Society Conference*. Sydney, Australia, July 2007 [Abstract WEPEC028].
25 National AIDS and STI Control Programme MoH K. Kenya AIDS Indicator Survey 2007: Preliminary Report. 2008.
26 Lingappa JR, Kahle E, Mugo N *et al*. Characteristics of HIV-1 discordant couples enrolled in a trial of HSV-2 suppression to reduce HIV-1 transmission: the partners study. *PLoS One* 2009; **4**: e5272.
27 Quinn TC, Wawer MJ, Sewankambo N *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000; **342**: 921–929.
28 Royce RA, Sena A, Cates W Jr., Cohen MS. Sexual transmission of HIV. *N Engl J Med* 1997; **336**: 1072–1078.
29 Quinn TC, Overbaugh J. HIV/AIDS in women: an expanding epidemic. *Science* 2005; **308**: 1582–1583.
30 Klerman LV. The intendedness of pregnancy: a concept in transition. *Matern Child Health J* 2000; **4**: 155–162.
31 Santelli J, Rochat R, Hatfield-Timajchy K *et al*. The measurement and meaning of unintended pregnancy. *Perspect Sex Reprod Health* 2003; **35**: 94–101.
32 Dudgeon MR, Inhorn MC. Men's influences on women's reproductive health: medical anthropological perspectives. *Soc Sci Med* 2004; **59**: 1379–1395.
33 Fakoya A, Lamba H, Mackie N *et al*. British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.