Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis

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Objectives: To synthesize the evidence on the risk of HIV transmission through unprotected sexual intercourse according to viral load and treatment with combination antiretroviral therapy (ART).

Design: Systematic review and meta-analysis.

Methods: We searched Medline, Embase and conference abstracts from 1996–2009. We included longitudinal studies of serodiscordant couples reporting on HIV transmission according to plasma viral load or use of ART and used random-effects Poisson regression models to obtain summary transmission rates [with 95% confidence intervals, (CI)]. If there were no transmission events we estimated an upper 97.5% confidence limit.

Results: We identified 11 cohorts reporting on 5021 heterosexual couples and 461 HIV-transmission events. The rate of transmission overall from ART-treated patients was 0.46 (95% CI 0.19–1.09) per 100 person-years, based on five events. The transmission rate from a seropositive partner with viral load below 400 copies/ml on ART, based on two studies, was zero with an upper 97.5% confidence limit of 1.27 per 100 person-years, and 0.16 (95% CI 0.02–1.13) per 100 person-years if not on ART, based on five studies and one event. There were insufficient data to calculate rates according to the presence or absence of sexually transmitted infections, condom use, or vaginal or anal intercourse.

Conclusion: Studies of heterosexual discordant couples observed no transmission in patients treated with ART and with viral load below 400 copies/ml, but data were compatible with one transmission per 79 person-years. Further studies are needed to better define the risk of HIV transmission from patients on ART.

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Keywords: highly active antiretroviral therapy, infectious, prevention of HIV infections, sexually transmitted diseases, transmission probability, viral load

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Introduction

The efficacy of antiretroviral drugs in the prevention of mother-to-child transmission of HIV is well documented [1] and there may also be a role of antiretroviral therapy (ART) in the prevention of sexual transmission of HIV [2]. Any reduction in the capacity of HIV to replicate is likely to reduce the risk of HIV transmission, unless the effect is offset by behavioural risk compensation [2,3]. HIV-infected men treated with zidovudine monotherapy in Italy were half as likely to transmit infection to their female partners than untreated men, after controlling for

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their more advanced disease [4]. Highly active antiretroviral combination therapy (ART) that can suppress HIV viraemia sustainably should have greater impact [2,3].

In January 2008 the Swiss Federal AIDS Commission stated that HIV-infected people on effective antiretroviral therapy and without other sexually transmitted infections were sexually noninfectious [5]. National public health bodies [6,7] have, however, reasserted existing guidance about the need for consistent condom use whereas some groups have supported the statement [8]. Our objective was to review the literature and obtain summary estimates of the risk of HIV transmission according to viral load, treatment with ART and presence of other sexually transmitted infections.

Methods

We included original articles and conference abstracts reporting on longitudinal studies of couples with one HIV-infected partner and documenting the number of HIV infections in previously seronegative sexual partners, and information about viral load in the HIV-seropositive partner, use of ART, or both. We excluded studies of preexposure prophylaxis and case-reports.

We searched the Medline and EMBASE databases from January 1996 to May 2008 and updated searches in February 2009. We used subject-heading terms for 'HIV infections' and 'disease transmission' and combined these with terms for either 'viral load' or 'antiretroviral therapy, highly active' (full search strategies available on request). We examined the reference lists of full text reports. We also searched the abstracts of the International AIDS Society conferences from 2001–2008 and the Conference on Retroviruses and Opportunistic Infections from 1997–2009 using key words 'HIV' and 'discordant', or 'discordant' and 'couple'. There was no restriction on the language of published articles.

Two reviewers independently assessed all titles and abstracts of published articles (S.A., M.M.) and conference abstracts (S.A., N.L.). If there was insufficient information in the title or abstract we retrieved the full text. We determined eligibility by consensus, with a third reviewer (M.E.) making a final decision in the case of disagreement. Two reviewers (S.A., M.M.) extracted the same information about each study. A third reviewer (N.L. or M.E.) resolved discrepancies. We extracted information about: study characteristics and population; the number of HIV transmission events and duration of follow-up; plasma viral load, use of ART and sexually transmitted infections in the seropositive partner; types and frequency of sexual intercourse; and condom use.

We contacted authors of potentially eligible studies identified in the first search to confirm eligibility and to request additional information. We asked about numbers of HIV transmissions and follow-up time according to the viral load of the HIV seropositive partner (<400, 400–499, 500–9999, 10 000–49 999, 50 000 and more copies/ml) [9]. We defined an undetectable viral load as fewer than 400 copies/ml of blood viral load, according to the detection limit of tests used in most eligible studies. We asked for the lowest measured viral load at which transmission to a seronegative partner had occurred. We relied on published data if the authors were not contacted, could not be reached or additional data were not provided.

We also asked for data in the predefined viral load categories according to whether the seropositive partner had any other sexually transmitted infections. We defined any sexually transmitted infection as: positive serological tests or microscopy for syphilis, positive test results for *Neisseria gonorrhoeae*, or *Chlamydia trachomatis* from swabs or urine specimens, or positive genital ulcer swab results or serological tests for herpes simplex virus. We defined ulcerative sexually transmitted infections as syphilis and genital herpes. If this information was not available, or if diagnosis was based on self-report we categorized the status as unclear.

Statistical analysis

We aimed to estimate the risk of HIV transmission per unprotected act of sexual intercourse. In the absence of data about frequency of unprotected sexual intercourse we used the HIV transmission risk per 100 person years of follow-up. If the exact follow-up time was not available we estimated this from the reported mean or median. We used a random effects Poisson regression model to obtain a summary estimate of the transmission rate with 95% confidence intervals (95% CI). For each study or stratum, the total number of events was considered to be Poisson distributed for a given sum of person years. Poisson regression models were fitted with a logarithmic link function and total exposure time per study as an offset variable, and included γ-distributed random effects on the study or stratum level. If there were no events observed, we assumed that the number of events was Poisson distributed and obtained an upper 97.5% confidence limit based on exact Poisson probabilities. All analyses were conducted using STATA version 10 (Stata Corporation, College Station, Texas, USA).

Results

Our searches yielded 305 publications, including 56 conference abstracts. Figure 1 depicts the process of identifying studies. We contacted the authors of 21 of 26 potentially eligible studies: nine replied and four provided

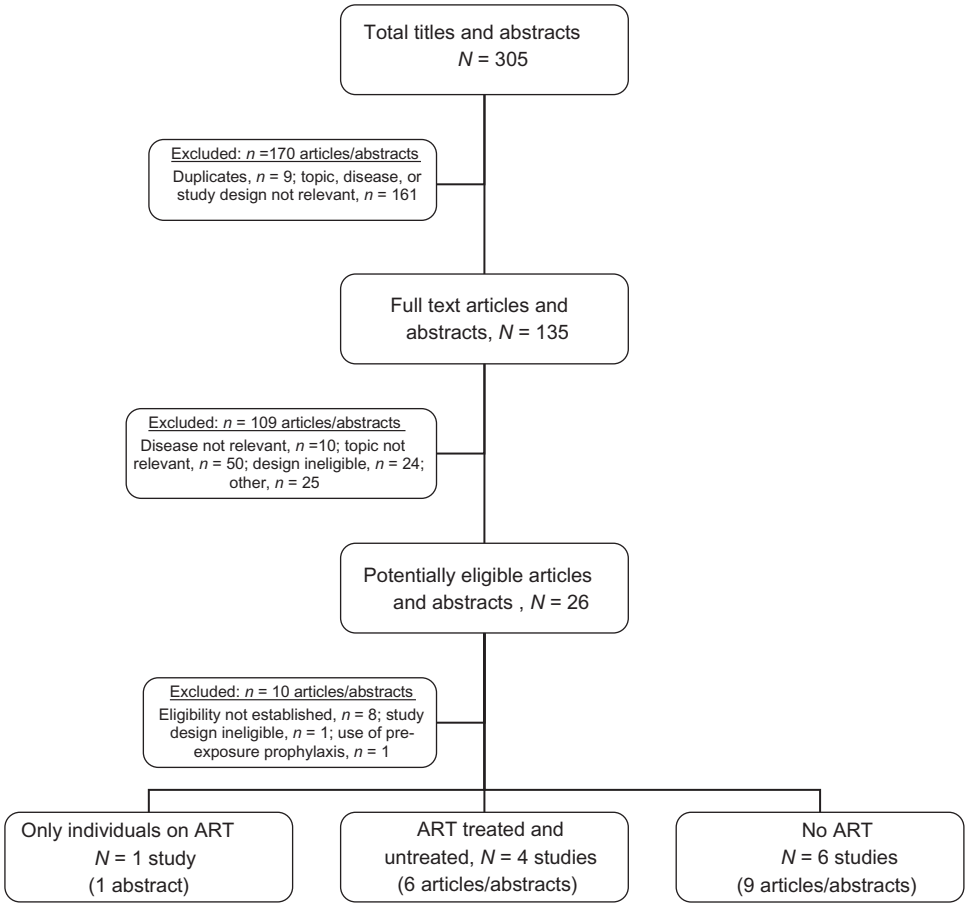

Fig. 1. Identification and selection of eligible studies. When there was more than one publication for a study, we used data from the one with the largest number of participants for whom relevant data could be extracted; studies reporting only individuals on antiretroviral therapy (ART), one abstract [18]; studies reporting on both ART treated and untreated individuals, four studies [10,11,23,24], two additional linked abstracts [20,22]; studies reporting only on individuals not on ART, six studies [9,12–14,17,21], two additional linked articles [15,16], one additional linked abstract [19].

additional information [10–13]. We identified 11 eligible cohorts reporting on 5021 couples and 461 HIV transmission events in 16 publications or abstracts from eight countries [9–24] (Table 1). The largest number of serodiscordant couples was reported in five studies from sub-Saharan Africa [9,17,18,23,24]. All included studies were conducted amongst heterosexual couples. There were insufficient data to allow estimation of summary rates of transmission through sexual intercourse without condoms, or to separate female–male and male–female transmission.

We analysed the risk of HIV transmission per 100 person-years of follow up because we only identified one study reporting on HIV transmission per coital act and stratified by viral load [15,16]. Data about coital frequency and transmission events were collected from the same population of untreated HIV-infected individuals in Rakai, Uganda. The estimated probability of HIV transmission per coital act, after controlling for age, ranged from 0.0001 when viral load was below 1700 copies/ml (sexual intercourse 10.4 times per month) to 0.0023 when viral load was greater than 38 500 copies/ml (sexual intercourse 7.9 times per month) [15].

HIV transmission and highly active antiretroviral therapy

Five studies included couples in which the HIV-seropositive partners used antiretroviral therapy, with 1098 person years of follow-up [10,11,18,23,24] (Table 1). One study reported specific antiretroviral regimens [10]. We did not identify any studies that reported on both viral load and all microbiologically diagnosed sexually transmitted infections.

The overall HIV transmission risk from antiretroviral-treated patients to heterosexual partners, irrespective of viral load and other sexually transmitted infections, was 0.46 (95% CI 0.19–1.09) per 100 person-years, based on five episodes of HIV seroconversion (Fig. 2) [10,11, 18,23,24]. Information on the lowest measured viral load at which transmission had occurred while

Table 1. Characteristics of eligible studies.

Study	Location	Risk groups of index case	Viral load limit of detection (copies/ml)	Frequency of HIV tests	Sexually transmitted infections tested for (or by history or examination)	Total enrolled	Analysed	Total follow-up (person-years)	Index case on ART	HIV transmission on ART	HIV transmission not on ART	Lowest viral load at transmission copies/ml	Overall HIV transmission rate (per 100 person-years)
Studies including only individuals receiving ART													
Bunnell [18]	Uganda	Heterosexual	Not stated	6 monthly	Not stated	928	62	184	62	1	Not applicable	Not stated	0.5 (0.01, 3.0)[a]
Studies including both individuals receiving ART and not receiving ART													
Castilla[b,c] [11,22]	Spain	IDU, heterosexual	50	Not stated	Syphilis (any STI, dysuria, discharge, ulcer, warts)	Not stated	393	1481	60	0	5	362[d]	0.3 (0.1, 0.8)[a]
Melo[b,c] [10]	Brazil	IDU, heterosexual	50	6 monthly	Gonorrhoea, HPV, HSV, syphilis	93	93	1108	41	0	6	1497[d]	5.7 (2.1, 12.3)
Reynolds[b,e] [24]	Uganda	Heterosexual	400	12 monthly	(Genital ulcer disease)	205	205	421	20	0	34	Not stated	8.1 (5.6, 11.3)[a]
Sullivan[f,g] [20,23]	Rwanda, Zambia	Heterosexual	No viral load data	3 monthly	Not stated	Not stated	2993	5609	Not stated	4	171	Not measured	3.1 (2.7, 3.6)[a]
Studies on individuals not receiving ART													
Fideli[f,h] [17,19]	Zambia	Heterosexual	400	3 monthly	Syphilis, trichomonas	1022	317	1829	0	Not applicable	129	2000	7.1 (5.9, 8.3)[a]
Mehendale [21]	India	Not stated	Not stated	3 monthly	Not stated	242	242	68	0	Not applicable	1	Not stated	1.5 (0.001, 8.1)
Operskalski [14]	USA	Blood transfusion	400	6 monthly	Not stated	38	16	21.2	0	Not applicable	3	8000	14.1 (2.9, 41.4)[a]
Quinn[e] [9,15,16]	Uganda	Heterosexual	400	10 monthly	Chlamydia, gonorrhoea, trichomonas, syphilis	415	415	778.1	0	Not applicable	90	1500	11.6 (9.3, 14.2)[a]
Ragni[c] [12]	USA	Blood products	400	Not stated	Not stated	39	39	388.2	0	Not applicable	5	600	1.3 (0.4, 3.0)[a]
Tovanabutra[c] [13]	Thailand	Not stated	50	6 monthly	(Chlamydia, gonorrhoea, HSV, syphilis, warts)	310	246	224.7	0	Not applicable	12	10 318	5.3 (2.8, 9.3)[a]

ART, highly active antiretroviral therapy; HPV, human papillomavirus; HSV, herpes simplex virus; IDU, injecting drug use; NGU, nongonococcal urethritis; STI, sexually transmitted infection. Not stated – information not provided and could not be estimated from published report.

[a]Transmission rate and confidence intervals estimated from published data or data provided by authors.

[b]Study includes both treated and untreated individuals, with seroconversions occurring only in partners of untreated patients.

[c]Additional data provided by authors.

[d]Seroconversion in partner of a person not on ART.

[e]Studies report on same study population but on couples enrolled during different time periods.

[f]Studies report on same study population, but on couples enrolled during different time periods.

[g]Total of six seroconversions documented, but two excluded because they could have occurred prior to ART initiation.

[h]Study reported 162 seroconversions and analysed 129 epidemiologically linked pairs (109 with laboratory data) and 208 consecutive nontransmitting pairs.

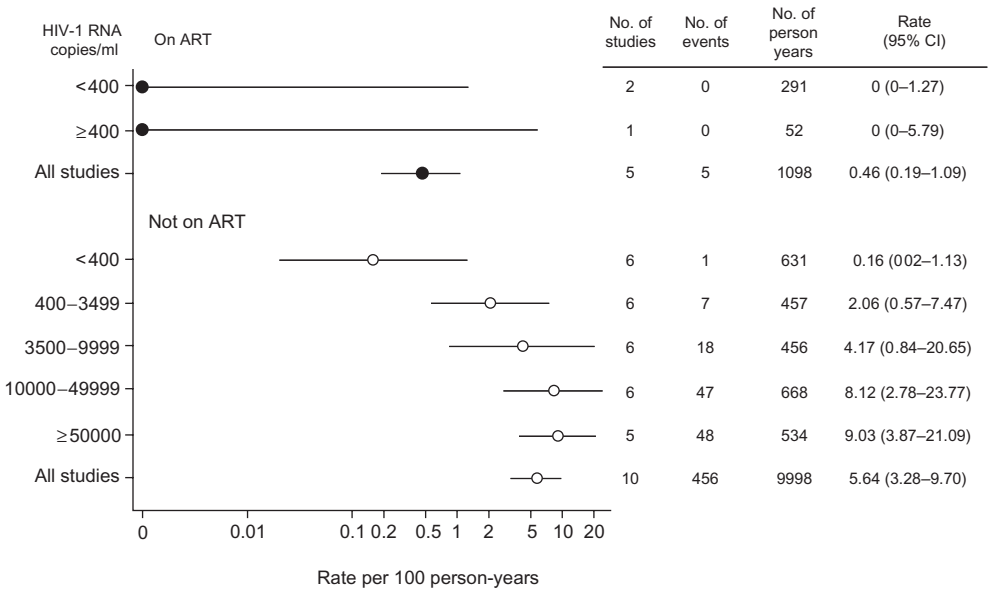

Fig. 2. Forest plot of summary HIV transmission rates, per 100 person-years, according to use of antiretroviral therapy and plasma viral load. ART, antiretroviral therapy; CI, confidence interval; the meta-analysis of couples where the HIV-infected partner received ART included two studies with viral load data [10,11] and three studies without viral load data [18,23,24]; the meta-analysis of couples with the HIV-infected partner not receiving ART included seven studies with viral load data in at least one category [9,10,11–14,17] and three studies without viral load data [21,23,24]. Note that not all studies with viral load data contributed to all viral load strata.

taking antiretroviral therapy was not available for either of the studies in which new HIV infections occurred [18,23]. In the two studies with information stratified according to viral load there were no reported episodes of HIV transmission from HIV seropositive people with undetectable viral load in 291 person years of follow-up (upper 97.5% confidence limit 1.27 per 100 person years) [10,11]. Three studies did not report on associations between HIV transmission and other sexually transmitted infections [18,23,24]. Melo *et al.* [10] and Castilla *et al.* [11] reported no association with the infections assessed in their studies (Table 1).

HIV transmission from people not on antiretroviral therapy

Ten studies included HIV seropositive people not receiving antiretroviral therapy with 9998 person years of follow up [9–14,17,21,23,24]. The overall HIV transmission rate, irrespective of viral load category and sexually transmitted infections, was 5.64 (95% CI 3.28–9.70) per 100 person years (Fig. 2). Amongst people with viral load below 400 copies/ml, irrespective of sexually transmitted infections, the transmission rate was 0.16 (95% CI 0.02–1.13) per 100 person years, based on one episode of HIV transmission in six studies [9,11–14,17]. The transmission rate increased with increasing viral load to 9.03 (95% CI 3.87–21.09) per 100 person years amongst individuals with viral load at least 50 000 copies/ml (Fig. 2).

The lowest measured viral load values around the time of HIV-transmission events were available for seven studies (Table 1). Three values, all in untreated individuals, were below 1500 copies/ml: at 362 copies/ml (Castilla J, 17 July 2008, personal communication), 600 copies/ml (Ragni M, 21 July 2008, personal communication) and 1497 copies/ml [10].

Discussion

This systematic review did not identify any study from which the risk of HIV transmission per act of unprotected sexual intercourse amongst persons with suppressed viraemia following ART could be quantified directly. The available studies found no episodes of HIV transmission in discordant heterosexual couples if the HIV-infected partner was treated with ART and had a viral load below 400 copies/ml, but the data were also compatible with one transmission per 79 person-years. There were insufficient data to stratify rates according to the presence or absence of sexually transmitted infections, use of condoms, direction of transmission, or practise of vaginal or anal intercourse. The comparison of overall rates in patients on ART and not on ART nevertheless indicate that heterosexual transmission was reduced by 92%, from 5.64 to 0.46 per 100 person-years. Of note, our review did not identify any study with data on ART and transmission risk in homosexual men.

The main strengths of this study were that we searched systematically for published and unpublished literature and attempted to quantify statistical uncertainty around

the transmission rate. Additional information from several authors allowed us to combine data in consistent viral load categories to increase the precision of estimated transmission risks [10–13] and to report the minimum viral load at which HIV transmission occurred. The main limitations of the study relate to the lack of data that could be combined statistically. Four included studies were only available as conference abstracts with limited details [18,21,23,24]. Precision was also limited by small or zero numbers of events in each viral load category and short follow-up times. There are recognized difficulties in obtaining confidence intervals when no events have been observed [25]. The interpretation of the lower limit of zero and upper 97.5% limit obtained using exact Poisson distribution probabilities differs from the standard 95% confidence interval. However, they demonstrate the uncertainty about the true HIV transmission rate by describing a range of values for the true quantity of interest that are compatible with the observed data. Describing the likelihood function about the true value of the parameter is an alternative but the results obtained would not alter our conclusion.

We found no direct evidence that, as stated by the Swiss Federal AIDS commission [5], the HIV transmission risk through unprotected sexual intercourse from an infected individual taking ART consistently under medical supervision, with blood viral load below 40 copies/ml and without any other sexually transmitted infection was 'much lower than one per 100 000 acts of sexual intercourse.' We found that there is considerable uncertainty about this risk: first, although there were no observed episodes of HIV transmission from people with undetectable viral load on highly active antiretroviral therapy, data are compatible with one new HIV infection for every 79 person-years of follow-up (one per 7900 sex acts if the yearly average is 100 contacts [15] and transmission probability is constant). Second, episodes of HIV transmission were found to have occurred at viral load levels lower than reported in earlier studies [9]. There might therefore be no transmission threshold or a lower threshold than previously believed [5,26].

Mathematical models have been developed to predict the effects of antiretroviral therapy on HIV transmission but variability in assumptions based on epidemiological and biological data makes them difficult to interpret [27]. The reduction in HIV transmissibility due to antiretroviral therapy includes estimates from two to 100 times [28], two to 10 times [29], and 100 times [30]. Our meta-analysis should be useful in this context and inform future modelling studies.

There is also uncertainty about the role of sexually transmitted infections. Focusing on ulcerative conditions and symptoms as a proxy for lower genital tract inflammation [5] is problematic. First, symptoms in women correlate poorly with clinical signs of inflammation or diagnosed infections [31]. Second, HIV transmission appears to be enhanced by bacterial vaginosis [32], a vaginal infection characterized by an absence of inflammation [31]. Third, sexual transmission of herpes simplex virus, the most common cause of genital ulcer disease in many countries, can occur during asymptomatic virus shedding [33]. Suppressing clinical recurrences with acyclovir does not reduce the risk of HIV transmission [34,35]. Furthermore, adherence to recommendations for regular testing for sexually transmitted infections in HIV-infected people would have to improve from current levels [36].

The risk of HIV transmission from people on highly active antiretroviral therapy is likely to be very low but it is nevertheless important that statements on transmission risk are based on thorough evaluation of the available data [37,38]. The need for systematic searches and clear documentation about the design, quality and consistency of evidence, and the availability or absence of direct evidence to address important clinical and public health questions is well recognized [38]. The users of recommendations can then distinguish between statements based on appraisal of evidence by experts and those based on systematic methods. The results of our systematic review show where there is a lack of direct evidence and where further research is required.

Greater precision about the HIV transmission rate per sexual act on highly active antiretroviral therapy can be obtained from empirical studies. An upper 95% confidence interval of one in 100 000 per unprotected sex acts would be obtained if the observed HIV transmission rate were one in 550 000 sex acts. This is equivalent to 5500 person years of observation with an average of 100 unprotected sex acts per year, or 1100 couples followed for 5 years having unprotected sex and free of sexually transmitted infections, assuming a constant transmission probability and each act as an independent event. An ongoing randomized trial to follow 1750 HIV serodiscordant heterosexual couples for a median of 5.75 years with the infected partner receiving highly active antiretroviral therapy will help to provide this information [39]. Studies to determine HIV transmissibility through insertive and receptive anal intercourse when viraemia is fully suppressed are needed to provide direct evidence for men who have sex with men. The implications of differences between antiretroviral agents in drug levels in plasma and genital tract, and of intermittent viral 'blips' also need to be clarified [3].

In conclusion, our study supports the World Health Organization's view [2] that at present there is insufficient evidence to formulate guidance on the role of ART in HIV prevention, both at the level of the individual and the population. Further studies quantifying transmission risk in different patient groups and under different conditions are required to inform such recommendations.

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Author contributions: S.A. did the literature searches, study selection, data extraction, and wrote the first draft; M.E. obtained funding, designed and supervised the study, and revised the paper; M.M. contributed to study selection, data extraction, and revision of the paper, M.Z. provided statistical advice and revised the paper; N.L. designed and supervised the study, conducted the analysis, and revised the paper.

Conflicts of interest: N.L. became a member of the Swiss Federal AIDS Commission on 1 January 2008. M.Z. was employed at the Swiss Federal Office of Public Health from 1998–2000 and head of the office of the Swiss Federal AIDS Commission at the Swiss Federal Office of Public Health from 1988–1989. The views expressed here are those of the authors.

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