XIV Conferencia Internacional sobre el SIDA. Barcelona, 7-12 de Julio 2002

Epidemiology*

Noel Gill[1]
Chris Archibald[2]
Tim Chadborn[1]
Julia del Amo[3]
Anatoli Kamali[4]
Tanarak Plipat[5]

[1]Communicable Disease Surveillance Centre, London, United Kingdom
[2]Centre for Infectious Disease Prevention and Control, Ottawa, Canada
[3]Miguel Hernandez University, Alicante, Spain
[4]Medical Research Council, Entebbe, Uganda
[5]Ministry of Public Health, Nonthaburi, Thailand

Correspondencia:
Noel Gill
E-mail:
ngill@phls.org.uk
Tim Chadborn
E-mail:
tchadborn@phls.org.uk

Knowledge of the epidemic in population terms

The XIV International AIDS Conference in Barcelona provided a platform to share knowledge of how best we can estimate the current and future burden of disease due to HIV and its impact on other infectious diseases. For example, enhanced sentinel surveillance in rural Kenya has improved HIV prevalence estimates and limitations of the detuned assay methodology for estimating incidence are being characterised. The conference also showed that prevalence and incidence estimates are increasingly enhanced by behavioural and STI surveillance, which provide information on the potential for HIV transmission in populations. Such information may identify populations for targeted interventions but there was also much data presented regarding biological factors that may affect HIV transmission and progression, such as HSV-2 infection, circumcision and virus sub-type.

Determinants of sexual transmission

Sexually transmitted infections result in genital ulceration and inflammation that disrupt mucosal integrity with a consequent increase in both the infectivity of HIV infected individuals and the vulnerability of HIV negatives. One explanation for the disappointing effect on HIV incidence of interventions that target curable STIs, is the high rate of HSV-2 disease in those at greatest HIV risk. Kamali presented data from a longitudinal cohort in Uganda that showed that the incidence of HIV infection was six times greater in the HSV-2 positives compared to the negatives[1].

Reynolds presented even more powerful data from a prospective study in India[2]. Over 200 HIV-1 and over 200 HSV-2 seroconversions were observed in a population with a 43% prevalence of HSV-2. The risk of HIV-1 seroconversion was 1.67 among HSV-2 prevalent cases, 1.92 among cases of incident HSV-2 infection over 6 months earlier and 3.81 in cases of HSV-2 infection within the last 6 months (Figure 1). Interventions to limit HSV-2 transmission, such as anti-HSV-2 therapy and vaccines, and studies of the consequences for HIV transmission are a priority.

Studies in non-human primates suggest that during acute infection the virus load in semen is closely related to changes of virus levels in blood. Using a calibrated model, Pilcher predicted that semen virus load peaked three weeks post infection, and that per act transmission probability was likely to be 20 times greater at this time compared to when the subsequent virus set point level was reached[3]. The effect of concurrent STIs on this difference in per act transmission is a potential subject for further research.

Reported associations of the protective effect of male circumcision against HIV infection may have been confounded as comparisons have rarely been within the same community. Agot surveyed over 800 men of the Luo ethnic group belonging to the same religious community[4]. Prevalence of HIV in uncircumcised men, at 30%, was 50% greater than in those circumcised and unchanged by adjustment for other risk factors.

Determinants of progression

Although ecological comparisons suggest that, so far, the progression of HIV-1 infection is not related to virus sub-type, data from the same location is sparse. A study from Cameroon and Senegal compared survival and CD4 count decline in 300 subjects between CRF-AG and other strains and found

*Publicado en: IAS Newsletter. 22, october 2002.

no difference[5]. In the United Kingdom a study followed 450 subjects and found a similar rate of CD4 decline and virological response to HAART between B and non-B subtypes[6]. These studies support the argument that differences in progression are predominantly due to factors other than virus subtype, such as age at infection.

Population impact of HAART

Monitoring population effectiveness of HAART is essential to show how clinical trial efficacy translates to given populations and to indicate the need for programme changes. In a study of 1800 seroconverters in Italy followed from 1980 to 2001, Pezzotti showed that the benefit attributable to HAART was less in drug users compared to homosexual men[7], a finding which was also reported by Perez-Hoyos in Spanish seroconverters[8]. Hubert found that in France, women and men had the same risk of AIDS and death at the same CD4 count, a finding that undermines the argument for gender specific therapeutic guidelines for treating HIV infection[9].

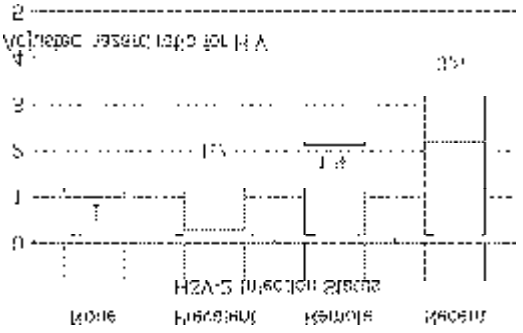

Figure 1.
Risk of HIV-1 by time of HSV-2 infection (Reynolds - C1012)

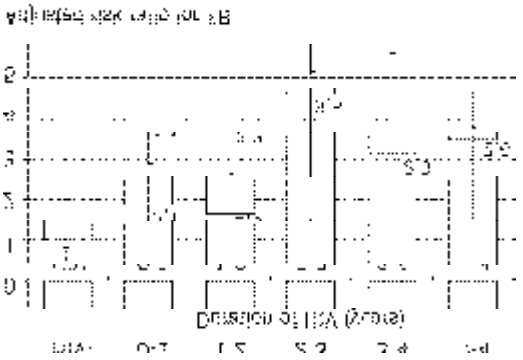

Figure 2.
Incidence of tuberculosis by duration of HIV (Sonnenberg - C1102)

Interaction with Tuberculosis

Tuberculosis enhances HIV replication in vitro and is associated with increased HIV virus load in co-infected patients, but the sequence of events is not clear. Day concluded that tuberculosis is not associated with a significant increase in viral load and that high viral load may be a risk factor for, rather than a consequence of, the onset of tuberculosis[10].

Sonnenberg reported on a retrospective cohort of 24000 South African gold miners that found the risk of tuberculosis doubled within the first year of HIV seroconversion compared to subjects who remained HIV negative[11] (Figure 2). This recognition of the very early effect of HIV infection on tuberculosis suggests that estimates of the impact of the HIV pandemic on tuberculosis incidence may need to be revised upwards.

Interaction with Malaria

Further evidence of the impact of HIV on malaria came from Cohen in South Africa who showed that the proportion with severe malaria in the HIV-infected increased with decreasing CD4 count, from 6% in the HIV-negative, to over 20% in those with a CD4 count of less than 200[12].

A detailed prospective study of incident malaria in HIV-infected adults in Malawi reported by Kublin showed that HIV RNA levels increased 0.25 - 0.35 logs over baseline in those with malaria parasitaemia and returned to baseline levels after adequate malaria treatment[13]. This increase in viral load, especially if sustained, could lead to increased HIV transmission and more rapid disease progression with substantial implications for public health consequences.

Surveillance Methods

New laboratory assays to detect recent HIV infection on a single serum sample allow estimations of HIV incidence without the costly and time-consuming follow-up of HIV-negative individuals over time, or the tracking of repeat visits by the same individual at health care facilities. However, optimal techniques and appropriate window periods are still being worked out for non-B subtypes[14] and this method still has a certain rate of false positives even when the individual tested is not on treat-

ment and does not have AIDS. McDonald in Australia reported that 10% of non-AIDS, drug-naïve people with established infection were falsely classified as recent[15].

In situations where the technique is applied to diagnostic sera, Remis used simulations to show that incidence can be severely overestimated if the interval between repeat diagnostic tests is related to risk of infection, or the probability of diagnostic testing is closely related to episodic high risk behaviour[16]. Kaplan presented methods that attempt to adjust for the bias inherent in diagnostic specimens, based upon the collection of additional test history data and reasons for the current HIV test in those shown to have recent infection[17].

Resistance and Sub-type surveillance

The surveillance of primary, or transmitted, drug resistance should help develop initial treatment strategies for persons infected with drug-resistant variants of HIV and help evaluate prevention programs since the transmission of resistant virus may be viewed as a prevention failure.

It is unknown how long resistance mutations remain detectable in patients not on treatment and therefore surveillance must distinguish patients known to have been infected recently from those diagnosed recently but with an unknown date of infection. Bennett described a sentinel surveillance system in 10 cities in the United States[18]. In a sample of over 900 specimens collected between 1998 and 2000, resistance to NNRTIs and to two or more drug classes was significantly greater in the recently infected compared with the rest (Figure 3).

Larger and more representative surveillance systems for monitoring primary drug resistance are needed. The WHO-IAS programme for global HIV drug resistance surveillance, HIV Res-Net, should provide a framework for national initiatives.

In low-income countries surveillance of viruses is focusing on estimating the proportions of HIV-1 subtypes and recombinants circulating in potential vaccine trial sites. McCutcheon analysed over 150 strains from Uganda, Kenya, and Tanzania and showed how these countries differ markedly in the composition of strains in circulation[19]. She argued for co-ordinated trials of similar vaccines in different countries to provide complete information about cross-subtype immunity.

Behavioural surveillance

There were many valuable examples of the strengths of behavioural surveillance. For example, significant increases in condom use and in the age at first sex in Uganda have provided corroborating evidence regarding the success of prevention programs in reducing HIV prevalence[20,21]. On the other hand, in a rural district in Tanzania where “low key” intervention activities were implemented, HIV incidence rates increased and there was little change in risk behaviour[22].

Data presented at this conference remind us that the epidemic is not under control in all transmission groups in high-income countries. HIV incidence in homosexual men attending STI clinics in Amsterdam increased during 1991-2001, and there were concurrent increases in syphilis and rectal gonorrhoea[23]. In the UK, there have been increases in reported STIs and unprotected anal intercourse among homosexual men[24,25].

Surveillance of injection drug users is necessary to discover behaviour changes and to modify prevention programmes appropriately. A study of drug users in Canada showed HIV seroconversion was highly related to frequency of cocaine injection[26]. In these cocaine users harm minimisation strategies are of limited value. When drug users in Bangkok, who primarily injected heroin, began injecting midazolam, a behavioural study showed the new drug was independently associated with needle sharing[27].

Prevalence and incidence surveillance

There was much evidence of the mounting impact of HIV from a variety of surveillance systems or special studies in different countries.

- The epidemic in Botswana has intensified still further so that prevalence in pregnant women in 2001 reached 36%[28].
- Following the extension of sentinel surveillance in Kenya in 2001, Marum reported that rural HIV prevalence, at an average of 11.5%, was generally higher than previously estimated[29].
- Badaru from Nigeria reported a steady increase in the rate of HIV infections detected in diagnostic specimens in Lagos from 1% in the early nineties to 29% in 2000[30].
- Sentinel surveillance in China, presented by Shuquan Ou has documented a steady diffusion of HIV infection through high risk groups with site prevalence up to 77% among drug users in 2001[31].

Growing burden of orphans

Another tragic consequence of the HIV pandemic is the increasing number and plight of orphaned children. Using a large community cohort study from Uganda that overcomes the selection biases inherent in studies of hospital births, Nakiyingi showed that both maternal HIV status and survival are strong predictors of childhood mortality and warned of underestimating HIV-related deaths in children when not taking into account the increased mortality of HIV-negative AIDS orphans[32]. By interviewing caretakers of orphans in 65 countries in 2000-2001, Monasch from UNICEF showed that orphans had less schooling and were more involved in child labour than non-orphaned children[33].

Mobility and Migrants

Over 150 million migrants currently live outside their country of citizenship and mobility is increasing. Mobility facilitates sexual mixing and a link between mobility and risk of HIV infection is evident in many parts of the world.

In a longitudinal study in rural Tanzania, reported by Isingo, 70% of the women and almost 60% of the men changed residence at least once between 1994 and 2000[34]. The annual HIV incidence in the movers was over three times greater than in the non-movers. Lurie described how migrant men in South Africa were 26 times more likely to be infected from outside their regular relationship than their regular female partners[35].

Surveillance data on HIV/AIDS was presented by Hamers showing that in seven Western European countries the numbers of new HIV diagnoses in migrants from countries with a generalised epidemic doubled in the past four years[36] (Figure 4).

As the pandemic progresses, mobile and migrant people are likely to be disproportionately affected and the need for appropriate public health responses that recognize the vulnerability of migrants will increase.

Conclusion

The recent UNAIDS report is a monumental synthesis of the current and probable future of the pandemic that is both haunting and hopeful (http://www.unaids.org/barcelona/presskit/barcelona%20report/contents_html.html). Generations are growing up that will be profoundly affected by AIDS as the impact of the pandemic intensifies. Strengthened surveillance is necessary to monitor the full conseqences for populations of continuing HIV transmission and to ensure HIV prevention efforts continue to have the highest priority in every society. At the same time many in the affected generations will put into practice current prevention messages and future surveillance must reveal how successful these efforts are.

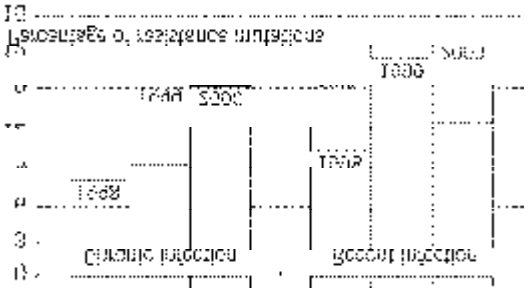

Figure 3.
Resistance in newly diagnosed HIV infections (Bennett - C1190)

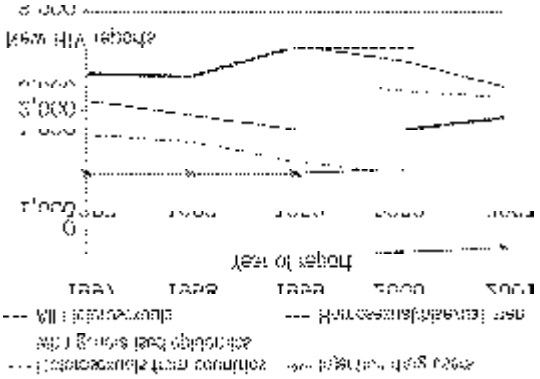

Figure 4.
New reports of HIV in seven Western European Nations (Hamers - C2099)

Prevention interventions to support behavioural change should also take account of the prevalence of HSV-2 and lack of circumcision as facilitators of HIV transmission. For those infected with HIV, it will be important to respond to the immediate risk of TB, to monitor the prevalence of resistance in newly diagnosed cases, and to recognise that IDUs have gained less benefit from HAART than MSM.

References

1. Kamali A, *et al.* Association between prevalence and incidence of Herpes Simplex Virus-2 (HSV-2), syphilis and HIV-1 infection in rural Uganda. C1011.
2. Reynolds SJ, *et al.* Recent Herpes Simplex Virus Type 2 Infection and the Risk of HIV Acquisition in Pune, India. C1012.

3. Pilcher C.D, *et al.* Semen viral dynamics in acute HIV infection: implications for sexual transmission C1487.
4. Agot K, *et al.* HIV-1 prevalence in circumcised versus uncircumcised Luo men from African instituted churches in rural Kenya. C1486.
5. Bourgeois A, *et al.* The predominance of HIV-1 CRF02_AG in west and west central Africa is not related to difference in pathogenesis: a four-year prospective multicentre study. C2143.
6. Easterbrook P.J, *et al.* Impact of HIV-1 viral subtype on disease progression. C2144.
7. Pezzotti P, *et al.* Factors associated with survival and progression to AIDS before and after the introduction of HAART. C1444.
8. Perez-Hoyos S, *et al.* Effectiveness of HAART in Spain. Transmission category and gender differences in the population from GEMES cohorts. C4737.
9. Hubert J.B, *et al.* Gender, disease progression and response to HAART. C1448.
10. Day J.H, *et al.* Does tuberculosis increase HIV viral load? C1100.
11. Sonnenberg P, *et al.* How soon after HIV infection does the risk of TB start to rise? A retrospective cohort study in South African gold miners. C1102.
12. Cohen C, *et al.* Increase in severe malaria in HIV-positive adults in South Africa. C7602.
13. Kublin J.G, *et al.* Malaria infection elevates HIV-1 viral load. C1375.
14. Withum D.G, *et al.* Serological testing algorithm for recent HIV seroconversion (STARHS): CDC's investigational new drug program and uses of a testing strategy to detect early HIV-1 Infection. C7603.
15. McDonald A, *et al.* Monitoring HIV transmission in Australia using a detuned testing strategy. C1044.
16. Remis R.S, *et al.* Estimates of HIV incidence based on detuned assay results may be strongly biased: Evidence from a simulation study. C3457.
17. Kaplan E.H, *et al.* Proposals for estimating HIV incidence in the United States from HIV reporting data and the detuned assay. C1308.
18. Bennett D.E, *et al.* Prevalence of mutations associated with antiretroviral drug resistance among newly diagnosed, drug-naïve men and women with HIV in ten U.S. cities, 1997-2000. C1190.
19. McCutcheon F.E, *et al.* Coordinated vaccine trials in Kenya, Uganda, and Tanzania will be required to define cross protective immunity among HIV-1 subtypes A, C, and D. C1193.
20. Mwaluko G, *et al.* Sexual behaviour trends and HIV during 1994-2000 in a longitudinal study in rural Tanzania. C1230.
21. Urassa M, *et al.* Continuing spread of HIV in rural Tanzania: prevalence and incidence trends in Kisesa during 1994-2000. C2058.
22. Bessinger R.E, *et al.* Trends in AIDS prevention behaviour in Uganda during the nineties. C1227.
23. Dukers N.H.T, *et al.* HIV incidence on the rise among homosexual men in Amsterdam: using a novel approach for detecting recent infections. C1144.
24. Fenton K.A, *et al.* The resurgence of infectious syphilis in England and its implication for HIV transmission and prevention. C1013.
25. Mercer C.H, *et al.* Changing patterns of homosexual partnership in Britain: Evidence from the 1990 and 2000 National Surveys of Sexual Attitudes and Lifestyles (Natsal). C1145.
26. Tyndall M.W, *et al.* Intensive injection cocaine use as a primary risk factor for HIV seroconversion in a cohort of poly-drug users in Vancouver, Canada. C1394.
27. van Griensven F, *et al.* The emergence of midazolam injection and its association with needle sharing among injecting drug users (IDUs) in Bangkok, Thailand. C1396.
28. Masupu K, *et al.* HIV prevalence among pregnant women attending antenatal clinics in Botswana, 2001. C6070.
29. Marum L.H, *et al.* Estimating rural seroprevalence using rural sites and women's residence in sentinel surveillance for HIV-1 in Kenya. C2056.
30. Badaru S.O.S, *et al.* Seroprevalence of Hiv-1 and 2 antibodies in Lagos, Nigeria over a 10-year period. C3325.
31. Qu S, *et al.* National sentinel surveillance of HIV infection in China from 1995 to 2001. C6072.
32. Nakiyingi J.S, *et al.* Child survival and mother's HIV status in a rural Ugandan cohort. C2139.
33. Monasch C.R, *et al.* Monitoring the situation of orphans, a global assessment. C2140.
34. Isingo R, *et al.* Mobility is an important risk factor for HIV infection in rural Tanzania. C1485.
35. Lurie M.N, *et al.* Who infects who? HIV discordance and the directionality of spread among migrant and non-migrant couples in South Africa. C7451.
36. Hamers F.F, *et al.* HIV among migrant populations in Europe. C2099.