Barcelona Track C Overview – July 2002

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SLIDE 1

Knowledge of the epidemic in population terms was the topic of Track C, the epidemiology track. We approached our overview through looking for answers to the following questions:

1. What fresh information could we find on the determinants of HIV transmission in different populations?
2. What are population studies telling us about current HIV progression in individuals, and the impact of anti-retroviral therapy?
3. What more do we know about the interaction between the HIV infection and other infectious diseases especially tuberculosis and malaria?
4. How have our epidemiological methods improved and what have we learnt about their limitations?
5. Most of all, we wanted to know the good and bad news from surveillance systems around the world. Well-designed national and local surveillance systems inform policy makers about the success or failure of prevention programmes on HIV prevalence and incidence. Also when prevention is non-existent, we need to know the full impact of HIV related morbidity and mortality.

SLIDE 2

To assist me ascertain and interpret some of the new findings presented at the conference, I had a team of five co-rapporteurs from all parts of the globe: Chris Archibald from Canada, Tim Chadborn from Britain, Julia Del Amo from Spain, Anatoli Kamali from Uganda, and Tanarak Plipat from Thailand. I am grateful to them for the work they have undertaken on your behalf and for what I have learnt from each of them during the past few days.

Late last year, a few hundred of you volunteered to review 40 abstracts each, so the average number of reviews per abstract was only 1.8. With so few reviews per abstract, the 'attributable influence' of the scientific committee on the dividing line between oral and poster presentation is correspondingly increased. While we may have been successful at bringing the most important findings to your attention in the oral programme, I would nevertheless urge many more of you to act as reviewers for the next International AIDS Conference, thereby strengthening the peer review process. With the relevant experience you can review and report on 40 abstracts in three hours.

Determinants of sexual transmission

SLIDE 3

Sexually transmitted infections result in genital ulceration and inflammation that disrupts 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. A recently published meta-analysis of the risk for HIV infection in HSV-2 positive persons concluded that where HSV-2 prevalence reaches 50%, almost half the HIV infections can be attributed to HSV-2. This week Kamali presented data from a longitudinal cohort in Uganda (C1011) that showed HSV-2 prevalence was four times higher in HIV positive than HIV negative adults. Similarly, the incidence of HIV infection was six times greater in the HSV-2 positives compared to the negatives.

SLIDE 4

Reynolds presented even more powerful data from a prospective study in India. 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. 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.

SLIDE 5

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 model calibrated against concurrent blood and semen HIV RNA concentrations from 32 human subjects with acute infection, and 40 subjects with chronic infection, 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. Whether this difference in per act transmission would be as great in subjects with concurrent STIs would be interesting to know.

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. Prevalence of HIV in uncircumcised men, at 30%, was 50% greater than in those circumcised. The rate ratio was unchanged by adjustment for other measured risk factors.

Determinants of progression

SLIDE 6

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 (C2143) compared survival and CD4 count decline in 300 subjects between CRF-AG (the predominant strain in both countries) and other strains and found no difference. In the United Kingdom a study (C2144) followed 450 subjects (of whom 157 were infected with non-B subtypes) and found a similar rate of CD4 decline and virological response to HAART between B and non-B subtypes. These studies support the argument that differences in infection progression, when present, 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 indicate the need for programme changes. Cohn found by analysis of United States HIV/AIDS surveillance data (C1446) that the decreases in morbidity and mortality attributable to HAART, greatest between 1996 and 1997, were sustained through 2001. 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 (C1444), a finding which was also

reported by Perez-Hoyos in Spanish seroconverters (C4737). 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 (C1448).

Interaction with Tuberculosis

SLIDE 7

Whether tuberculosis accelerates the course of HIV infection is a subject of debate. 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 (C1100) compared virus load in 17 subjects who subsequently developed tuberculosis with 29 subjects without tuberculosis, matched on CD4 count at baseline and duration of follow. They 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.

Van Asten (C3384), in a study of 700 European injection drug users, showed the risk of tuberculosis increased with increasing time from HIV seroconversion, from three times greater in years 4 to 6, to 5 times greater at 9 years or more, compared to the baseline rate initially.

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Sonnenberg (C1102) reported on a retrospective cohort of 24000 South African gold miners from 1991 to 1997 that found the risk of tuberculosis doubled within the first year of HIV seroconversion compared to subjects who remained HIV negative, who were exposed to the same risk of tuberculous infection, and had the same opportunity of case ascertainment. 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.

As might be expected, however, anti-retroviral therapy could blunt this impact. In a study of over 700 HIV-infected subjects in South Africa, Badri reported (C4736) that the incidence of tuberculosis was reduced by more than 80% in the quarter who received HAART and that this protective effect was greatest in symptomatic patients and those with advanced immune suppression.

Interaction with Malaria

Further evidence of the impact of HIV on malaria came from two studies in South Africa. Grimwade (C7602) reported that the rate of severe malaria was doubled in HIV infected adults. Cohen (C7604) 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.

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A detailed prospective study of incident malaria in over a hundred HIV-infected adults in Malawi reported by Kublin (C1375) examined the effect of malaria on HIV. 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. 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

SLIDE 10

Application of new laboratory assays to detect recent HIV infection provides another way to estimate HIV incidence that does not require 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. Instead, HIV incidence can be estimated by testing a single serum sample. Each of the laboratory techniques for diagnosing recent infection exploits the slow maturing of the serological response over the course of the first year after infection. When two different assays with different sensitivities are used on the same specimen, a discordant result from the less sensitive method suggests recent infection.

SLIDE 11

The detuned assay approach was used to estimate an annual HIV incidence in a variety of settings worldwide. Rollins, in the second last example used antibody-negative RNA-positive methods to detect recent infections. In the last example, Hu (C4866) applied a new IgG capture enzyme immunoassay to diagnose recent infections in specimens collected from injection drug users in Bangkok in 1996 and the estimated HIV incidence was double the incidence measured at the same time in a local prospective cohort.

Despite the appeal of these methods, methodological problems and limitations remain. False positive results may be obtained if the person tested has AIDS or is on antiretroviral treatment, so some studies excluded those samples in which anti-retroviral drug residues were detected. The optimal techniques and appropriate window periods are still being worked out for non-B subtypes (C7603). The detuned method still has a certain rate of false positives even when the individual tested is not on treatment and does not have AIDS. McDonald (C1044) in Australia reported that 10% of non-AIDS, drug-naïve people with established infection were classified falsely as recent.

In situations where the technique is applied to diagnostic sera, Remis (C3457) 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. Interestingly, Kellog (C4869) used the technique in San Francisco to show that HIV incidence in homosexual men who had had three or more diagnostic HIV tests was three times that in men who had had fewer tests. Kaplan (C1308) 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.

Resistance and Sub-type surveillance

SLIDE 12

The surveillance of primary, or transmitted, drug resistance has two important purposes: firstly, to help develop initial treatment strategies since persons infected with drug-resistant variants of HIV may be at increased risk of drug failure despite never being on treatment, and, secondly to help evaluate prevention programs since the transmission of resistant virus may be viewed as a prevention failure.

Problems to be solved include reaching consensus on the list of resistance mutations that are relevant for surveillance, and the behaviour of drug-resistant non-B subtypes relative to wild-type non-B subtypes is limited. Moreover, as it is unknown how long resistance mutations remain detectable in patients not on treatment, surveillance of transmitted resistance in treatment-naïve patients must distinguish patients known to have been infected recently from those diagnosed recently, but with an unknown date of infection.

Ammaranond (C4741) studied 185 subjects with primary infection in Australia and found RTI resistance decreased from 29% in 92 – 95 to 15% in 96-01. PI resistance mutations were present in less than 2% and were not increasing. They postulated that effectively administered combination therapy may be associated with a fall in transmitted resistance.

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Bennett described a sentinel surveillance system in 10 cities in the United States (C1190). Between 1998 and 2000 over 900 specimens were collected from subjects newly diagnosed as infected, including almost 200 shown to have been infected recently using a detuned assay. Resistance to NNRTIs and to two or more drug classes was significantly greater in the recently infected compared with the rest.

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 that national initiatives can relate to.

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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. She argued for co-ordinated trials of similar vaccines in different countries to provide complete information about cross-subtype immunity.

Behavioural surveillance

SLIDE 15

There were a 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. On the other hand, in a rural district in Tanzania (C2058) where ´low key´intervention activities were implemented in rural and trading centres, including IEC, a school IADS programme, condom promotion, and syndromic STI management, HIV incidence rates increased to over 1% annually from 1990 to 2000 and consistent condom use has decreased.

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 this increase was corroborated by concurrent increases in reported syphilis and rectal gonorrhea. Similar STI increases in homosexual men have been reported from other cities, such as San Francisco. In the UK, there have been increases in reported STIs and unprotected anal intercourse among homosexual men.

Surveillance of injection drug users is necessary to discover behaviour changes and to modify prevention programmes appropriately. A study of drug users in Canada (C1394) showed HIV seroconversion was highly related to frequency of cocaine injection, and presumably the accompanying erratic and disorganized lifestyle. In these cocaine users, needle provision may not reduce risk and other forms of harm minimisation are of limited value. When drug users in Bangkok, who primarily injected heroin, began injecting midazolam, a behavioural study (C1396) showed the new drug was independently associated with needle sharing.

Prevalence and incidence surveillance

SLIDE 16

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

The epidemic in Botswana has intensified still further intensification so that prevalence in pregnant women in 2001 reached 36%. Compared with 2000, HIV prevalence increased in five of the six age groups of pregnant women.

Following the extension of sentinel surveillance in Kenya in 2001, Marum (C2056) reported that rural HIV prevalence was generally higher at an average of 11.5% than estimated by previous more limited sentinel surveillance. Estimates of the total HIV-infected in the population were revised upwards.

Badaru from Nigeria (C3325) reported a steady increase in the rate of HIV infections detected in diagnostic specimens by the public health laboratory in Lagos PHL – up from 1% in the early nineties to 29% in 2000.

Sentinel surveillance in China, presented by Ou Shuquan (C6072) has documented a steady diffusion of HIV infection through high risk groups. By end 2001, 22 of 25 sites had detected HIV in drug users and site prevalences ranged up to 77%. Also 15 of the 25 sites reported finding HIV in female sex workers.

Growing burden of orphans

SLIDE 17

Another tragic consequence of the HIV pandemic is the increasing number of orphaned children. By 2002, over 10 million children had lost their mother or both parents to AIDS and this number is predicted to double by 2010. By interviewing caretakers of orphans in 65 countries in 2000-2001, Monasch from UNICEF showed (C2140) orphans had less schooling and were more involved in child labour, compared to non-orphaned children. Using a large community cohort study from Uganda that overcomes the selection biases inherent in studies of hospital births, Nakiyingi (C2139) showed that both maternal HIV status and survival are strong predictors of childhood mortality and warned of the underestimation of HIV-related deaths in children when the

increased mortality in HIV-negative children, orphaned through maternal AIDS, is not taken into account.

Mobility and Migrants

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Over 150 million migrants currently live outside their country of citizenshipand more people are on the move than ever before. 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, reported by Isingo (C1485), of 11000 persons in rural Tanzania, 70% of the women and almost 60% of the men changed residence at least once between 1994 and 2000. The annual HIV incidence in the movers was 1.8%, over three times greater than in the non-movers. Lurie (C7451) 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.

Surveillance data on HIV/AIDS in migrants in the Europe were presented by Hamers (C2099). In seven Western European countries, selected because the data are available, the numbers of new HIV diagnoses in migrants from countries with a generalised epidemic doubled in the past four years.

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

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In conclusion, the recently released UNAIDS report is a monumental synthesis of the current and probable future of the pandemic that is both haunting and hopeful. Our worst fears of 10 years ago have inexorably come to fruition. The challenge presented in the report is as overwhelming as this Conference has been. At home last week as I opened the Report's global prevalence map, my daughter appeared at my shoulder and asked me to show her the countries her older sister was backpacking through. Her sister was moving from a low-prevalence country in South East Asia to one where the prevalence was much higher, so I felt the need to say that you don't get HIV just by visiting a country. 'I know Dad', Orla replied with all the patience a 10 year old requires when a father presumes her ignorance, 'you must exchange bodily fluids with someone who has HIV to get it yourself'. The effectiveness of that one to one communication is something I have held on to all week, as the loudspeakers boomed, the halls reverberated with noise, and the statistics overwhelmed. My co-rapporteurs and I experienced many one to one communications in the course of this week from many of you who contributed to Track C. We are grateful to you all for summarizing your findings so succinctly for us and your fellow conference attendees. Thank you.