# AIDS and Human Reproduction

## AIDS and Human Reproduction

Editor Francesco Mélica, Genoa

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#### Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Copyright 1992 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland) Printed in Switzerland on acid-free paper by Thur AG Offsetdruck, Pratteln ISBN 3-8055-5481-8

viewpoint, for the sudden rise and spread of a new highly pathogenic viral epidemic, attributed to a new strain, the HIV belonging to, but differing from, the variegated retrovirus family, known paradoxically for its harmlessness.

On the other hand; the MV epidenne is capitly expanding at Central

Over the span of the last 10 years, this newcomer has been responsible for a series of clinical syndromes, all serious and nearly all fatal, headed by AIDS itself, symbol and maximum expression of the epidemic's high mortality rate.

From its uncertain beginning only a few years ago up to the present time at the close of the 1980s, the natural history of AIDS has had a rapid evolution, and biological, epidemiological and clinical data continue to be amassed, as well as becoming increasingly pregnant with social implications.

The HIV, after having first attacked specific groups of the population, the so-called 'at-risk' categories, is today spreading indiscriminately.

Defences against the invader, rapidly prepared as soon as the viral nature had been identified, were insufficient to arrest its expansion, even if relatively efficient at reducing the mortal nature of the disease.

Since its dramatic onset, much has changed in the world panorama of HIV infection during the course of the last 10 years. Homosexuals, in the beginning the main social vehicles and spreaders of the virus, after having paid a heavy price for their sexual diversity very soon adopted opportune and vital corrective practices and tendencies. More moderate attitudes and lifestyles together with a more attentive hygienic surveillance have succeeded in significantly limiting the virus damage in this particular category.

The tragic toll of polytransfuser deaths caused by HIV-infected blood over the last few years has now been virtually extinguished, thanks also to more attentive screening, even if costly and lengthy, leading to a more

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careful selection of blood donors and thus offering a necessary safeguard to the many patients needing this indispensable and irreplaceable therapy: human blood transfusion.

On the other hand, the HIV epidemic is rapidly expanding in Central Africa. In those countries, AIDS daily takes on the dimension of an immense tragedy. There are many co-factors encouraging the rapid spread of this disease: a kind of racial 'predisposition' to the virus, the recent migrational upheaval of these peoples, forced to leave their villages in ever increasing numbers since the land is no longer capable of providing even subsistence level food, for the new large cities where they live massed together in squalid and unhygienic conditions, becoming rapidly infected with pathogenic agents on a scale quite unknown before now.

These unhealthy living conditions, new forms of social behavior, particular sexual promiscuity and above all prostitution, the old diseases (malaria, tuberculosis, sprue) mix with the new, sexually transmitted ones, and both the old and the new are the dominating factors leading to HIV acquisition and its increasingly widespread diffusion. Dominating the entire and desolate panorama is the extreme poverty existing in all African countries, making it almost impossible (at least for the moment) to carry out adequate health and AIDS prevention schemes, screening and disease controls and provide up-to-date therapy for those already infected since diagnostic screening instruments and the few drugs currently available capable of delaying viral replication are prohibitively costly.

The HIV epidemic is also on the increase in the vast universe of drug addicts, a dramatic social scourge in nearly all countries, preeminently so in the USA and some Western European countries (Germany, France, Switzerland, Italy, Spain). However, the more or less uniform abandonment by regular intravenous-drug users of certain forms of ritual group behavior (e.g. the 'shooting gallery'), which typified drug addict behavior in the years 1975-1985 has also led to a corrective trend in the last few years, comparable to that which has taken place on an international level in the homosexual world. It is of some slight comfort to be able to say that group infection, responsible for the initial HIV explosion and its rapid worldwide diffusion, is now no longer the case. The rapidly acquired and now firmly established use of the small, disposable insulin syringe and the use of drugs in small groups are the immediate result of behavioral adaptation by this particular category, even if unfortunately drug addiction is constantly increasing. However, it is a clear demonstration that intravenous-drug addicts, even if motivated only by survival instincts, are prepared to modify their habits along lines suggested by society in an attempt to safeguard, at least partially, their physical health and well-being, and will end bas visco if even garages evitants grown

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If this is cause for comfort, unfortunately there are many other considerations which do not give rise to optimistic forecasts. The majority of HIV-infected persons, particularly in Western European countries (Italy takes the lead!!), are drug addicts with a very poor sense of social responsibility, both towards themselves and other people; they come from all social backgrounds and work sectors, belonging to the youngest age groups who are more active in every sense, above all sexually.

We now know enough about the main body of regular intravenousdrug users. We do not, however, have sufficient knowledge as to the real entity of certain peripheral areas, e.g. periodic users (weekly, fortnightly, and so on) and sporadic users. And it is a fact that such drug users form the new vehicle of HIV infection which is now spreading among the general population through heterosexual relations and contacts. More so when the following risk factors are also present: preferential cocain use, certain racial characteristics, multiplicity of sexual partners and socioeconomic status. Thus, HIV infection, even if its diffusion among regular drug users has been somewhat hindered by recent corrective behavioral patterns, advances slowly but more constantly and is more widespread outside the regular drug users world. Thus the new path leading to HIV infection is mainly a heterosexual one; this applies as much to the poor countries of central Africa and the Caribbean Islands, where its rapid spread is helped by immunodepressive factors such as poverty, hunger, recurrent and chronic infection and disease, as it does to Western industrialized countries where its spread is facilitated by immunodepression caused by drug abuse, the use of other drugs (such as tranquillizers and sleeping pills), stress, poor alimentation and poverty.

Statistics carefully updated by the WHO and Center of Disease Control of Atlanta coldly document the new HIV infection routes. The increase in female prostitution, a trend seen in nearly all countries, reveals the role increasingly played by women, with female HIV statistics approaching that of men. This in turn presupposes an increase in pediatric AIDS. What is taking place is paradoxical: while on the one hand statistics show a drop in the number of neonatal HIV, on the other hand the overall number is growing. This seeming paradox can be explained as follows: the reduced number of pregnancies documented in advanced stages of the disease (CDC stages III and IV) is juxtaposed by a greater number of asymptomatic HIV-infected pregnancies, with a lower risk of virus transmission to the fetus. Thus, while the number of HIV-infected newborns is somewhat lower compared to that a few years ago, the overall number of neonatal HIV is actually on the increase. It will be possible only in the near future to verify if neonatal HIV can be even further reduced after azidothymidine antiviral action.

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The progressive increase in HIV in the young is accompanied, both within and outside the variegated world of drug users, by an enormous spread of many other infections and sexually transmitted diseases (viral: hepatitis B and C viruses, herpes simplex virus I and II, and non viral: various fungal and mycoplasma infections, Chlamydia trachomatis, Trichomonas vaginalis, Gardnerella vaginalis, Neisseria gonorrhoeae and syphilis). This results in increased anatomic damage and functional disorders as much among females as among males (in the former primarily chronic salpingitis and endometritis, and in the latter oligo-asymptomatic epididymitis, bladder and prostate infections). In this complex microcosm of genital pathogens, exposure to HIV is therefore extremely high, above all for women where the number of genital complications from saprophytic and pathogenic agents is higher and more variegated. These, together with HIV, find highly favorable conditions in that the mucosal surface is more extensive and consequently greater exposure to coital microlesions exists.

All these factors affect fertility in HIV-infected persons to a greater or lesser degree. Other, factors can be added to this picture which are all correlated to viral aggression. In particular, gametic damage to the spermatogenetic epithelium results from specific receptors for the virus (CD4<sup>+</sup>) on these cells known to be present as well as by intracytoplasmic particles interpreted as being proviral entities.

Other more general factors interact, such as malnutrition, as yet unclear neurohumoral effects, resulting from both the use of hard drugs and the often particular psychological state found in many HIV patients, as well as the need for stricter contraception controls and more frequent recourse to voluntary abortion.

It is necessary to carefully and regularly check the genital picture of HIV patients, which has an inflammation-dysplasia-cancer evolution unknown in the general population. The immediate consequences are already evident: in the younger age groups there is an increase in genital cancer, of the penis and above all of the cervix uteri, where other co-factors (sexual precocity, multiplicity of partners, voluntary abortions) have already led to a certain increase in HIV patients.

Last, but by no means least, however, is the problem of caring for HIV patients. The category of health care workers has clearly become more at risk than others, and is moving towards an even higher rating in the classification. Unfortunately we still do not know, nor will we know in the immediate future, the real nature and precise mechanism involved, how the healthly host organism reacts and resists on the one hand in the face of an exiguous infective vital load on the other and the mechanisms of interaction which take place, delaying the onset of symptoms in the early stages of infection and seroconversion.

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Health care workers in labor wards and operating theaters where vaginal and pelvic operations of every kind are performed are clearly in the front rank of professionals at risk. This picture is even further aggravated by the lack of updated instruments and obstetric protective measures and procedures, the inevitability of repeated contact with infected blood, amniotic liquid and vaginal secretions. All these elements increase the generally accepted risk involved in inadvertent skin puncture.

The First International Symposium on AIDS and Reproduction has been held to clarify the multiple aspects correlating this new sexually transmitted viral infection to the anatomofunctional state of both male and female and reproductive apparatuses, as well as to the health of the

newborn exposed to HIV infection.

My deepest thanks are due to Dr. Sandra Chiodi, Dr. Paolo Cristoforoni, Dr. Vincenzo Maritati, Dr. Franco Diani, Dr. Paolo Repetto, Dr. Tiziana Calcagno and the Scientific Secretariat for their boundless enthusiasm and tireless collaboration in organizing the Symposium.

Finally, my special thanks to Dr. Oliviero Varnier for his invaluable liaison work with several important speakers, and to Thelma Eyden Barone for her translations and helpful consultancy at all stages of the Symposium's organization in support of our shaky knowledge of the English language.

Francesco Mélica

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## AIDS Epidemiology: The Past 10 Years, The Next 10 Years

Paolo R. Crocchiolo

Clinical Research and Drug Development, Global Programme on AIDS, World Health Organization, Geneva, Switzerland

The WHO regularly receives reports of AIDS from its member states. As of November 1, 1990, a cumulative total of 298,914 reports of AIDS have been received from 157 countries. Based on HIV seroprevalence data from these countries, WHO estimates that there have been over 8 million persons infected with HIV since the early 1980s. Based on a progression rate of HIV infection to AIDS of 5% per year, WHO further estimates that over 800,000 cases of AIDS have occurred as of November 1, 1990: approximately 400,000 more than actually reported. Approximately 54% of HIV infections are thought to have occurred in Africa, 35% in the Americas and 8% in Western Europe. The remaining infections have occurred in Eastern Europe, the Middle East, the Pacific Basin and Southeast Asia.

Three means of transmission of HIV have been identified: sexual intercourse with an infected partner; HIV-infected blood and blood products including blood-contaminated needles and syringes and organ transplants, and perinatal transmission from an infected mother to her infant. Sexual intercourse is responsible for the majority of infections worldwide, while transfusion of HIV-infected blood is the most efficient means of transmission (table 1). Based on the predominant means of transmission and the year or time period when HIV was introduced, the WHO has described several epidemiological patterns of HIV infection and AIDS.

Australia and New Zealand, HIV infections began to spread extensively shortly before or after 1980 among men who had sex with men and intravenous-drug users (pattern I).

In the Caribbean and Latin America, extensive spread of HIV probably began in the early 1980s; population groups initially infected were predominantly homosexual or bisexual men and intravenous drug users

Table 1. HIV transmission: Global summary 1990

Exposure and and and		Percent of total
Blood transfusion	>90	5
Perinatal	20 40	10
Sexual intercourse 21E9 Y O.I.	OCC VO.1 1.0 Past	mobia de de la
Vaginal		Y 01 1xe (60) dT
Anal		(15)
Intravenous drug use	0.5-1.0	10
Needle type exposure	< 0.5	Papinos Croechiolo
Other ZGIA in a minimum	Fig. Dovelap 0.0 nr Global Pr	Chroningers? -0.0-11

residing in large cities (pattern I). During the latter half of the 1980s there was a shift to heterosexual transmission of HIV, thought at present to be the major means of transmission (pattern I/II).

Though HIV appears to have been present in Africa several decades earlier, extensive spread of HIV in Eastern and Central Africa is not thought to have begun until the late 1970s, and heterosexual transmission is the major means of transmission (pattern II). Extensive spread of HIV in West Africa began sometime in the mid-1980s.

In areas in which HIV was introduced in the mid-1980s or later (pattern III), the predominant modes of HIV transmission have not yet been determined because of low prevalence of infection. These areas include North Africa, the Middle East, Eastern Europe, Asia and the Pacific excluding Australia and New Zealand.

In areas where heterosexual transmission is the predominant means of HIV transmission, perinatal transmission has also become important. Transmission rates from HIV-infected women to their children are approximately 30%, and appear to increase with increasing immunosuppression of the mother. At the beginning of this decade it was estimated that more than 3 million females were infected with HIV.

Based on known fertility and HIV transmission rates, it is estimated that these women gave birth to about 2 million infants of whom 500,000 were likely to have been infected with HIV. The 1.5 million uninfected children will inevitably be left without a mother, and often without both parents, the social consequences of which are already being felt in certain African counties where traditionally orphaned children were absorbed in the extended family, no longer possible because of the large numbers of orphaned children.

Virtually all short-term (less than 5 years) projections predict that AIDS cases will at least double or triple in most areas of the world.

Projections more than 5 years in the future are difficult to make but WHO Delphi projections (the average of expert estimates) indicate that by the year 2000 there may be a cumulative total of 15–20 million HIV-infected adults and from 5 to 6 million cumulative AIDS cases among adults.

During the 1990s over 3 million AIDS cases will occur in adults infected prior to 1990; another 1-2 million adult AIDS cases will develop as a result of unprevented HIV infections acquired in the 1990s, and about 1 million adult AIDS cases may be prevented by public health programs.

AIDS during the 1990s will have a very selective and severe impact on adult and child mortality rates in many areas of the world. In most pattern I countries, during the 1990s HIV-related deaths will become one of the leading, if not the leading cause of death in young adults aged 20–40 years. Homosexual men and intravenous drug-users will continue to be the most affected population groups in these countries through the 1990s.

During the 1990s, the impact of AIDS will be greatest in large urban areas of sub-Saharan African countries – especially Central and Eastern Africa. Expected infant and child deaths due to AIDS may increase child mortality rates in these areas by as much as 50% during the 1990s, thus reversing the gains in child survival achieved over the past decade. AIDS deaths in young children and in those aged 15–49 will reduce expected population growth in urban centers by over 30%, and the adult mortality rate will more than triple. However, population growth for these countries is expected to remain positive during this decade.

Orphaned children of HIV-infected mothers will increase as their HIV-infected mothers die of AIDS so that more than 10 million uninfected children less than 10 years of age are expected to be AIDS-related orphans in Africa during the 1990s. Caring for these orphans and for HIV-infected persons worldwide will present great demands on health systems and a major challenge in the 1990s.

wheeted populations were homosexual and bisexual men and intravenousling users, and pattern II of altered as Zaire and Hatti where the smootpal mode of transmission was through interosexual intercourse. The last interest experience has shown this system to be concewhat of

n oversimplification. The HIV pandemic is includely present and growing, apidly in Asia and substituted for areas, and there is evidence that in one of these countries are epides for much more along the lines of the Wrigant pattern II are dunic is a nerging. Today I shall cover the current.

Paolo R. Crocchiolo, MD. Clinical Research and Drug Development, Global Programme on AIDS, World Health Organization, CH-1211 Geneva 27 (Switzerland)

## Heterosexually Transmitted HIV Infection in Asia

George W. Rutherford

Department of Epidemiology and Biostatistics, the Center for AIDS Prevention Studies, and Department of Pediatrics, School of Medicine, University of California, San Francisco, Calif., USA

Of the 298,914 cases of AIDS reported to the WHO through October 31, 1990, 804 (0.3%) have occured in Asia. Thus, while the AIDS epidemic is still young in the World's most populous continent, it is present, and it is being increasingly recognized as a significant public health problem in all parts of Asia.

During the 1990s, the impact of AIDS will be greatest in large urban

The recognition of AIDS and HIV infection as significant problems in Asia has not always been the case. In 1987, WHO proposed a system of geographical classification of HIV infection. In this system, Asia, the Near and Middle East, North Africa, the Soviet Union and parts of Eastern Europe were said to be pattern III countries, countries in which HIV infection was introduced in the early to mid-1980s, with the principal infected populations being homosexual and bisexual men, sex workers who had contact with persons from endemic areas, and recipients of blood and blood products imported from endemic areas. In pattern III countries, HIV seroprevalence was felt to be very low in the overall population. This was in contrast to pattern I countries, such as the US, where the principal infected populations were homosexual and bisexual men and intravenous-drug users, and pattern II countries, such as Zaire and Haiti, where the principal mode of transmission was through heterosexual intercourse.

The last 3 years' experience has shown this system to be somewhat of an oversimplification. The HIV pandemic is indeed present and growing rapidly in Asia and other pattern III areas, and there is evidence that in some of these countries an epidemic much more along the lines of the African pattern II epidemic is emerging. Today, I shall review the current state of knowledge regarding HIV and AIDS in Asia (exclusive of the Soviet Union), focusing on its epidemiology in and potential for future spread among heterosexual populations.

Table 1. AIDS cases by continent and year of report! but some AIDA synthamical & share

incidence	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
Africa - (	0	2	14	82	0 283	3,350	11,982	20,921	31,651	7,357
Americas	387	1,130	3,283	6,536	12,473	20,674	32,216	39,909	42,968	21,087
Asia 0.0	1	2	8	6	31	56	120	148	242	176
Europe	48	86	279	687	1,743	3,566	6,627	9,766	11,621	5,103
Oceania	0	1	6	46	129	240	403	550	571	347
Total 1.0	436	1,221	3,590	7,357	14,659	27,886	51,348	71,294	87,053	34,070

<sup>1</sup> Cases reported to WHO as of October 31, 1990.

#### Epidemiology of AIDS in Asia

As I mentioned earlier, 804 cumulative cases of AIDS had been reported to WHO from Asian countries through October 31 of this year (table 1). The number of reported AIDS cases in Asia has grown from fewer than 10 cases per year from 1981 through 1984 to 242 in 1989. Recently, the number of reported cases has increased by 23% between 1987 and 1988 and by 64% between 1988 and 1989.

I want to begin by reviewing what is known about AIDS cases and rates in Asia. Of 37 Asian countries, 25 (68%) have reported cases to WHO. Twelve (32%) countries have reported no cases, including Afghanistan, Bahrain, Bangladesh, Bhutan, the Democratic People's Republic of Korea, Iraq, Macao, the Maldive Islands, Mongolia, Myanmar (formerly Burma), Vietnam and Yemen. Of the 804 cumulative cases reported through October 31, 1990, 280 (35%) were from countries in the Near and Middle East, 147 (18%) were from countries in South and Southeast Asia, and 377 (47%) were from countries in the Far East.

Among Near and Middle Eastern countries, the largest numbers of cases were reported from Israel (116, 41%), Turkey (37, 13%) and Lebanon (31, 11%; table 2). Among Southern and Southeastern Asian countries, the largest numbers were from India (48, 33%), Thailand (45, 21%) and Singapore (21, 14%; table 3). Among Far Eastern countries, the largest numbers were from Japan (290, 77%), the Philippines (37, 10%) and Hong Kong (27, 7%; table 4). The highest incidence of AIDS has been in Qatar with 1.4 cases per 100,000, followed by Cyprus with 0.5 cases per 100,000, and Brunei Darussalam, Israel, Nepal and Oman, each with 0.4 cases per 100,000. In comparison, AIDS case incidence through 1988 was 3.0 cases per 100,000 in Italy, 1.4 per 100,000 in Austria and 0.3 per 100,000 in Finland.

Table 2. Cumulative AIDS cases and incidence by country: Near and Middle East<sup>1</sup> 1 sides T

Country					Cases				Incidence
Israel	128,1	150 05	199,11	L- F-Te	82 116 283	-41		0	0.4
Turkey					871 37 822.8				< 0.1
Lebanon					15 31 0		19		0.2
Qatar '					23				L4monds
Cyprus					PS 17 31				0.5
Oman					14				0.4
Pakistan					Ped.43				< 0.1
Jordan									< 0.1
Iran (Isla	amic Re	public)			DUCK 19 15 3010		OHW.o		< 0.1
Syrian A	rab Rep	oublic			9				< 0.1
Kuwait					1				< 0.1
Afghanis	tan				0				0.0
Bahrain					0				0.0
Iraq					0.5				0.0
nau					0				0.0

<sup>&</sup>lt;sup>1</sup> Cases reported to WHO as of October 31, 1990. Incidence = reported cases per 100,000 population.

Table 3. Cumulative AIDS cases and incidence by country: South and Southeast Asia

Country of the countr	Cases Cases	Incidence
ldive Islands, Viorgolia, Wyanaibn		
Phailand Vitalian of the Sun to Har	urmaj. Vietnom and41 eu	< 0.1mmol
Singapore month area (Alizz Va		
Malaysia no sommara mon ejev	15	< 0.1
Sri Lanka da da da na benjanga man	SIA, AID TO (4 TO SETE TO	< 0.1
Vepal odmun targest numbe large	Near and Middle Hystern	0.4
Brunei Darussalam	por ed from bras! El 16, 41'	0.4 20083
d Southeastern Asian coundeshing b		
	bors were from India (48	
Maldistac		
Myanmar (Burma)	groupe it stort the it.	0.0
Vietnam (Vietnam Vietnam Vietn	e from Japan (200, 70%). (	0.0

<sup>&</sup>lt;sup>1</sup> Cases reported to WHO as of October 31, 1990. Incidence = reported cases per 100,000 population.

Table 4. Cumulative AIDS cases and incidence by country: Far East! 1 to amount of should

Country bold bas rasid	stoubo Cases and bas boold	Incidence
Japan tamasyM	290	< 0.1
Philippines	37	< 0.1
Hong Kong Israel	nam turxasi27bms buuxazamed	- 0.1 fauxo
China (Taiwan) arba1	. 14 Prices pages refolds	< 0.1
Republic of Korea	6	< 0.1
China soniqual'i	3	< 0.1
Democratic People's Republic of K	orea 0	0.0
Macao	0	0.0
Mongolia	0	0.0

the Asign epidemics of sexually 775 asmitted and parenterally (conslated

The Patterns of HIV Infection is 12 II VIII tada work benefits T at 200155 and

I now want to move to describing what is known about the prevalence and distribution of HIV infection in Asia, focusing on three heterosexual epidemics. In general, we recognize four basic patterns of HIV infection in Asia (table 5). Parentally transmitted infection through infected blood and blood products accounts for a large percentage of HIV infection in much of Asia, especially in areas where other newer patterns of infection have not yet emerged, such as much of the Near and Middle East. In highly westernized countries, such as Israel but also Japan and Hong Kong, sexual transmission among homosexual and bisexual men accounts for a large percentage of the infected population. Homosexual and bisexual men are infected elsewhere in Asia, as well, and data among persons of Asian and Pacific Islander ancestry living in San Francisco, Calif., indicate that sexual transmission among homosexual and bisexual men of Asian ancestry can reach epidemic proportions.

However, despite these patterns of spread, the rapidly emerging HIV epidemics in many parts of Asia involve heterosexuals who have acquired infection either sexually or through sharing needles. These two types of epidemics can exist side by side, as has occurred for instance in Thailand, but, unlike the North American and European epidemics where intravenous drug use and heterosexual transmission of HIV are closely linked,

<sup>&</sup>lt;sup>1</sup> Cases reported to WHO as of October 31, 1990. Incidence = reported cases per 100,000 population.